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Published since 3 January 1920

Małgorzata Kalicińska-Buraczewska's reminiscences about her family, friends and Ujazdowski Hospital

The potential of viruses as a biological weapon.

Severe adverse drug reaction with eosinophilia in a patient taking nonsteroidal anti-inflammatory drugs

Thoracic sympathectomy in the treatment of primary palmar hyperhidrosis

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1) On the first page: main title in Polish and English, Author's or Authors' (max. 10 people) first and last names, including academic degrees, full name of affiliated institute (institutes), head of the institute (academic degree, first and last name), below an abstract (up to 15 lines) with keywords in Polish and another abstract with keywords in English, corresponding author, his/her postal address with postal code, telephone (fax) and e-mail address.

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Original articles should be prepared according to the following structure: introduction, aim, material and methods, results, discussion, conclusions, references; case reports: introduction, case description, discussion, summary (conclusions), and references.

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3) References should be presented according to the order they appear in the text. If the article has no more than four authors, all of them should be named, if there are more – a maximum of first three, followed by "et al.". References should be numbered using the keyboard, please do not use automatic numbering. Examples of citations:

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7. The paper should be accompanied by: a) author's request to publish the paper with a declaration that the article has not been published before and not simultaneously submitted to any other journal b) approval of the head of the clinic, head of the department or head of the institute in which the research has been conducted, and in case of a study carried out in several centres - approval of all of them, c) Declaration of Conflict of Interest, d) acknowledgements, if applicable.

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Animus Fortis award

Editorial note

We are delighted to announce that yet another Animus Fortis Gala was held on 4 June in the Military Institute of Medicine. The gala drew Animus Fortis 2019 winners invited by the chairman for the award committee, Maj Gen Grzegorz Gielerak, Professor MD, PhD.

There were two first prizes (statuettes) and two honourable mentions (diplomas).

- The individual first prize was presented to **Grzegorz Ramotowski,** a paramedic coordinator and first aid trainer. His courage and composure saved a mother and her baby from drowning. It was half way through his running workout when he noticed a pram rolling straight into a river, followed by a woman who threw herself into the water to save her child. Unfortunately, she could not swim, and the baby was not breathing after being pulled out. Mr Ramotowski managed to save them both.

Photo. 1. This year's Animus Fortis Award Laureates
Fot. 1. Tegoroczni laureaci Nagrody Animus Fortis

Photo. 2. Grzegorz Ramotowski, a paramedic coordinator and first aid trainer – 1st prize winner in the individual category
Fot. 2. Grzegorz Ramotowski, koordynator ratownictwa medycznego, szkoleniowiec pierwszej pomocy - laureat nagrody w kategorii indywidualnej

Photo. 3. Street Medical Patrol – winner in the institutional category
Fot. 3. Uliczny Patrol Medyczny - laureat nagrody w kategorii instytucjonalnej

- The first prize in the institutional category was awarded to the **Street Medical Patrol.** This pioneering project was launched with the cooperation of the Warsaw Municipal Police, Caritas Polska and the Doctors of Hope Association. Several times a month, a marked car patrols the most remote and unapproachable areas of the capital city to provide the homeless with necessary supplies and aid.
- **Senior Fireman Michał Klugowski** received an honourable mention in the individual category for extending first aid at a car accident on 6 July 2019 while not on duty. He initiated the appropriate rescue operation, opened the airways of the injured and began to reduce their blood loss, eventually saving their lives.
- In the institutional category, an honourable mention was granted to the **Warsaw Youth Rescue Team.** This is an independent group at the ANIKAR Fund, where 30 young people pursue their passions and personal interests in first-aid training.

We would like to express our respect and admiration to all the award winners for their remarkable achievements.

We wish them much continued success in their efforts and endeavours in the area which is so vital for the society.

Editorial Board of "Military Physician",

Thoracoscopic sympathectomy in treatment of primary palmar hyperhidrosis - personal experience

Sympatektomia piersiowa jako metoda leczenia nadpotliwości pierwotnej dłoni - doświadczenia własne

Edyta Santorek-Strumiłło,[1] Marcin Włodarczyk[2]

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Abstract. The aim of our study was to evaluate the effectiveness of thoracoscopic sympathectomy. The authors paid particular attention to the presence of side effects after surgery. A conclusion from the study is that thoracoscopic sympathectomy is a safe treatment of primary palmar hyperhidrosis, with satisfactory and long term results.
Key words: primary palmar hyperhidrosis, thoracic sympathectomy

Streszczenie. Celem pracy była ocena skuteczności sympatektomii piersiowej w leczeniu nadpotliwości pierwotnej dłoni. W pracy zwracaliśmy szczególną uwagę na występowanie działań niepożądanych po zabiegu operacyjnym. Na podstawie pracy wyciągnęliśmy wniosek, że sympatektomia piersiowa w leczeniu nadpotliwości pierwotnej dłoni jest zabiegiem bezpiecznym, dającym dobre i długotrwałe efekty. **Słowa kluczowe:** sympatektomia piersiowa, pierwotna nadpotliwość dłoni

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Introduction

Hyperhidrosis, even mild, is troublesome for the patient. This problem is associated with aesthetic, social and psychological burdens. It significantly increases shame and reduces self-esteem. According to different sources, hyperhidrosis affects 1 to 3% of the population. It is defined as excessive sweating, above the level required to maintain thermal homeostasis [1, 2].

Sweating is a physiological process necessary for thermoregulation. Various exogenous and endogenous factors determine the quantity of secreted sweated, including ambient temperature, stress or foods consumed. In physiological conditions, approximately 500 ml of sweat is secreted daily, up to a few litres with intensive exercise.

Hyperhidrosis can be classified as primary or secondary, or as focal or generalised. Primary hyperhidrosis is not associated with any pathological condition, and sweating usually occurs in one or multiple areas of the body (palms, soles and armpits). Secondary hyperhidrosis is associated with underlying conditions (e.g. Diabetes, hyperthyroidism, tuberculosis or obesity), and pharmacotherapy (e.g. ciprofloxacin, acyclovir or antidepressants). Primary hyperhidrosis is diagnosed based on the guidelines of the Canadian Hyperhidrosis Advisory Committee, stating that the symptoms must persist for at least 6 months, and at least 4 criteria must be met [3-5]:

- persists for at least 6 months,
- affects the area with increased number of eccrine glands,
- bilateral and symmetrical,

- symptoms do not occur during sleep,
- episodes are experienced at least once a week;
- onset is observed at 25 years of age or earlier,
- positive family history;
- adversely affects everyday activities.

Treatment options for primary hyperhidrosis include pharmacotherapy (e.g. anticholinergics) and local treatment (products containing aluminium chloride, ionophoresis or botulinum toxin), as well as surgical therapy (thoracoscopic sympathectomy). Surgical treatment is associated with a risk of typical complications in the perioperative period. The patient should also be informed about a potential adverse effect in the form of compensatory sweating, i.e. excessive perspiration in other body regions [6-9].

Aim of the study

The aim of the study was to assess the outcomes of surgical treatment (thoracoscopic sympathectomy) of primary palmar hyperhidrosis, with the emphasis on the adverse effects of the procedure.

Material and methods

The study subjects were patients operated in the Department of Thoracic, General and Oncological Surgery in the years 2015-2019 due to primary palmar hyperhidrosis. They received planned thoracoscopic sympathectomies (T2-T4 sympathetic ganglia were dissected and removed). All subjects were qualified to a follow-up in the hospital's General Surgery Clinic (visits took place 14 days after the surgery and 3, 6 and 12 following the procedure). They all received perioperative prophylactic treatment against infections (a single dose of 1.0 g of cefazolin, administered before the surgery). The study group comprised the patients who attended a follow-up visit after a thoracoscopic sympathectomy in the General Surgery Clinic, i.e. 49 patients (37 females and 12 males).

The available medical records from the hospital (regarding the hospitalisation period) and from the General Surgery Clinic were analysed.

The intensity of symptoms was evaluated before and after the surgery, using a subjective Hyperhidrosis Disease Severity Scale (HDSS). In the Post-operative period, the intensity of compensatory sweating was also assessed (HDSS), as well as occurrence of complications and intensity of pain symptoms.

HDSS uses four degrees of symptom intensity:

1 - perspiring is never noticeable and never interferes with daily activities,

2 - perspiring is tolerable but sometimes interferes with daily activities,

3 - perspiring is barely tolerable and frequently interferes with daily activities,

4 - perspiring is intolerable and always interferes with daily activities [4].

The statistical analysis was performed using Statistica 6 software, and the calculations were based on Shapiro-Wilk W test, t-Student test, Friedman's ANOVA and Kruskal-Wallis test. In all the analyses p value (probability) of < 0.05 was considered statistically significant.

Results

Group characteristics by sex, age and comorbidities

The study group included 37 female (75.5%) and 12 male (24.5%) subjects. Mean age was 34 years. 89.80% of the patients in the study group did not have any comorbidities. Three subjects (6.12%) suffered from arterial hypertension, one subject (2.04%) had atopic dermatitis and one patient (2.04%) had psoriasis. No statistically significant differences were found between the sex and outcomes of thoracoscopic sympathectomy. No statistically significant correlations were observed between the comorbidities in the study group and the effects of the study treatment.

Group characteristics by post-operative complications

No fatalities were observed in the study group. Post-operative complications were found in 4 patients (8.16%); in all cases the complication was pneumothorax not requiring pleural drainage, and resolving within 24 hours after the procedure.

Group characteristics by post-operative pain symptoms

The analysis included subjects examined during the hospitalisation and follow-up visits in the General Surgery Clinic. Post-operative pain symptoms (pain in the intercostal area) persisting for up to 4 days after the surgery were observed in 40 patients (81.63%). They were successfully treated with NSAIDs. In 5 (10.2%) subjects the pain persisted for 28 days, and in 3 (6.12%) patients up to 3 months after the surgery; treatment with NSAIDs was effective. Only in 1 (2.04%) subject the pain persisted for more than 3 months following the surgery; however, the patient considered it acceptable compared to the benefits of the thoracoscopic sympathectomy. No statistically significant correlations between the duration of post-operative pain and other studied factors were found.

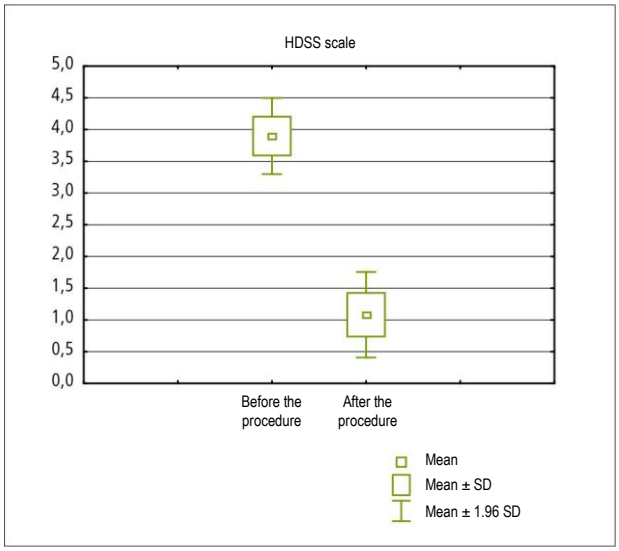

Figure 1. Intensification of primary palmar hyperhidrosis (HDSS scale) before and 14 days after thoracoscopic sympathectomy

Rycina 1. Nasilenie dolegliwości (pocenie dłoni) w skali HDSS przed zabiegiem i do 14 dni po zabiegu

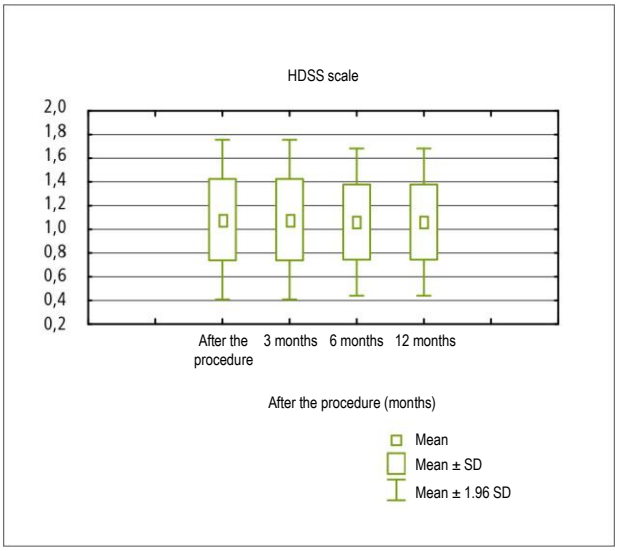

Figure 2. Intensification of primary palmar hyperhidrosis (HDSS scale) up to 14 days after and 3, 6 and 12 months after thoracoscopic sympathectomy

Rycina 2. Nasilenie dolegliwości (pocenie dłoni) w skali HDSS do 14 dni po zabiegu, po 3, 6 i 12 miesiącach

Group characteristics according to palmar hyperhidrosis following the surgery (HDSS)

The surgery resulted in a statistically significantly reduced HDSS scores (palm sweating after the procedure): 3.89 ±0.031 *vs.* 1.08 ±0.34; p < 0.001. The effect was visible already on the first day after the surgery (when it was assessed). The reduction of palmar HDSS scores after the procedure was permanent and remained at a stable level. No statistically significant differences were observed between subsequent palmar HDSS scores 3, 6 and 12 months following the surgery (1.08 ±0.34 *vs.* 1.08 ±0.34 *vs.* 1.06 ±0.32 *vs.* 1.06 ±0.32, p = 0.392). The intensity of symptoms (palmar hyperhidrosis) assessed by HDSS before and after the procedure is presented in Figure 1, while Figure 2 shows symptom (palmar hyperhidrosis) intensity assessed by HDSS up to 14 days following the procedure and 3, 6 and 12 months after the procedure.

Group characteristics according to compensatory hyperhidrosis following the surgery (HDSS)

After the procedure, HDSS scores for compensatory sweating remained at similar levels for the first 3 months (2.16 ±0.47 *vs.* 2.12 ±0.44, p = 0.538). A statistically significant difference in the reduction of HDSS scores for compensatory sweating was found within 6 months after the procedure (2.16 ±0.47 *vs.* 2.08 ±0.43; p = 0.037). This level remained unchanged at 12 months following the surgery (2.16 ±0.47 *vs.* 2.08 ±0.43, p = 0.037).

Compensatory sweating in the study group was observed in the armpits, on the thoracic wall and abdomen.

Figure 3 presents the intensity of compensatory sweating assessed by HDSS at 14 days following the procedure and after 3, 6 and 12 months following the procedure.

Discussion

Hyperhidrosis significantly reduces patient's social life and results in limitations in professional and social functioning. An increasing number of people are noticing the problem, as well as becoming aware of possible treatment options.

Our study presents thoracoscopic sympathectomy as a method of treating palmar hyperhidrosis. It is a minimally invasive procedure, associated with few potential complications. Patients are satisfied with the cosmetic effect of the procedure (local). All subjects in the study group positively assessed the cosmetic effect of

their surgery. It is an important aspect, as young women were the dominant population in the study group (37 patients, 75.5%), and the mean age was 34 years old. During the medical interview subjects were asked about the onset of symptoms and they all reported childhood or adolescence. In the subject literature the condition also affects mostly females, and the mean age of patients varies between 25 and 38 years, depending on the author. It is consistent with the diagnostic criteria for primary hyperhidrosis, according to which the onset occurs in childhood or puberty [10-12].

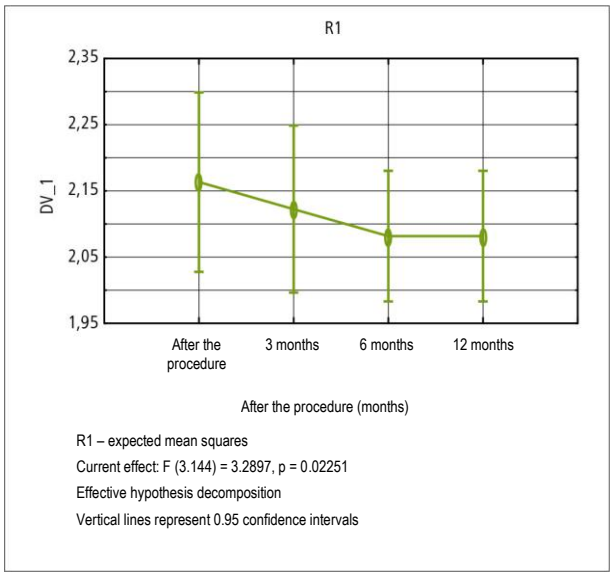

Figure 3. Intensification of compensatory sweating (HDSS scale) up to 14 days after and 3, 6 and 12 months after thoracoscopic sympathectomy

Rycina 3. Nasilenie dolegliwości pocenia kompensacyjnego w skali HDSS do 14 dni po zabiegu, po 3, 6 i 12 miesiącach po zabiegu

No fatalities were observed in the study group, and the only post-operative complication was pneumothorax (8.16% of patients) that did not require pleural drainage and was absorbed after 24 hours following the surgery. Other authors observed in their studies complications such as Horner syndrome, subcutaneous emphysema and pneumothorax [4, 8, 13]. Stefaniak reports pneumothorax in 2.1% of patients, with 0.35% requiring drainage [4].

Our study also analysed the duration of pain symptoms. In majority of subjects (81.63%) pain subsided after up to four days following the surgery (81.63%); only 2.04% of patients experienced pain for more than 3 months after the sympathectomy. They all reported pain of minor intensity, described as tolerable compared to the benefits of the procedure (reduction or elimination of palmar hyperhidrosis). Other authors presented similar outcomes [1, 4, 5].

No statistically significant correlations between the duration of post-operative pain and other studied factors were observed [4, 5, 9]. All subjects reported a significant reduction of palmar HDSS scores after the procedure. The result was permanent, and remained at a stable level at 3, 6 and 12 months following the surgery. The effect was statistically significant. Staniśić also demonstrated very good early results of surgical procedure and elimination of symptoms in all the subjects [8]. It should be emphasised that patients undergoing thoracoscopic sympathectomy may experience compensatory perspiration, i.e. increased sweating in areas previously unaffected by the problem, such as armpits, back, lower abdomen, but also face and scalp. The degree of compensatory sweating is measured using HDSS score. In the study group we also observed this phenomenon. A week after the surgery, insignificant and mild compensatory perspiration (HDSS 1 and 2) was found in 83.7% of the subjects, moderate sweating (HDSS 3) in 14.3%, and significant compensatory perspiration in 2%. 12 months after the sympathectomy, the number of subjects with barely tolerable compensatory sweating (HDSS 3) decreased to 10.2%, and none of the patients met the criteria of significant compensatory perspiration. Compensatory sweating in the study group was observed in the armpits, on the thoracic wall and abdomen. All the subjects stated that the benefits from the procedure considerably outweigh the temporary pain symptoms and compensatory sweating.

Other authors report similar outcomes of their studies. The compensatory sweating assessed as HDSS 3 and 4 is reported in 17-34% of patients, whereas compensatory sweating of any intensity is observed in 73-100% of patients undergoing the surgery [4, 11, 14, 15]. Based on our study and the available literature, thoracoscopic sympathectomy can be considered an effective method of therapy for primary palmar hyperhidrosis. However, patients should be carefully selected (only those with primary hyperhidrosis) and informed about the potential compensatory sweating.

Conclusions

- Thoracoscopic sympathectomy is an effective method of treatment for primary palmar hyperhidrosis.
- Reduction or complete elimination of excessive sweating occurs immediately after the procedure, it is permanent and remains at a stable level.
- Compensatory sweating following thoracic sympathectomy is tolerable for patients.

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Stevens-Johnson syndrome as a severe adverse drug reaction – a case report

Zespół Stevensa-Johnsona jako ciężka reakcja na stosowane leki - opis przypadku

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Abstract. Toxic epidermal necrolysis (TEN) and Stevens-Johnson Syndrome (SJS) are severe adverse drug reactions that involve the skin and mucous membranes. They are expressed by hemorrhagic erosions, erythema and more or less severe epidermal detachment presenting as blisters and areas of denuded skin. Drugs are assumed or identified as the main cause of SJS/TEN in most cases. Diagnosis relies mainly on clinical signs together with the histological analysis of a skin biopsy showing typical full-thickness epidermal necrolysis due to extensive keratinocyte apoptosis. To reduce the high risk of mortality, management requires prompt diagnosis, determination and removal of the cause, assessment of prognosis (e.g. using the SCORTEN scale), rapid implementation of appropriate care and treatment (using immunomodulatory drugs, such as intravenous immunoglobulin) and sometimes treatment in the intensive care unit.
Key words: drug eruptions, Stevens-Johnson syndrome, toxic epidermal necrolysis

Streszczenie. Toksyczna nekroliza naskórka (TEN) i zespół Stevensa-Johnsona (SJS) są ciężkimi niepożądanymi reakcjami dotyczącymi skóry i błon śluzowych. Charakteryzują się erozjami krwotocznymi, rumieniem i mniej lub bardziej ciężkim odwarstwieniem naskórka, przedstawiającym się w postaci pęcherzy i obszarów ogołoconej skóry. W większości przypadków przyczyną SJS/TEN są leki. Rozpoznanie opiera się głównie na występowaniu objawów klinicznych oraz wyniku biopsji skóry, w której stwierdza się typową nekrolizę naskórka na całej grubości w wyniku rozległej apoptozy keratynocytowej. Aby zmniejszyć duże ryzyko śmiertelności, konieczne są: szybka diagnoza, ustalenie i wyeliminowanie przyczyny, ocena rokowania (np. za pomocą skali SCORTEN), szybkie wdrożenie odpowiedniej pielęgnacji i leczenia (z użyciem leków immunomodulujących, takich jak dożylna immunoglobulina) oraz niekiedy specjalistyczna opieka na oddziale intensywnej terapii.
Słowa kluczowe: zespół Stevensa-Johnsona, toksyczna nekroliza naskórka, osutka polekowa

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Introduction

Many drug-induced reactions, potentially serious or life-threatening, have been reported in the literature, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). In both cases erythematous eruptions, blisters and mucosal lesions are observed, so the clinical presentation resembles that of severe burns. Erythema multiforme, SJS and TEN are severe bullous skin diseases [1]. Presented below is a case of SJS with an unexpectedly mild course.

Case study

A 50-year-old male, otherwise healthy, was urgently admitted to the Department of Infectious Diseases and Allergology from the HED of the Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine in Warsaw, due to skin lesions diffused across the whole body.

The medical history revealed that two weeks prior to the occurrence of the lesions the patient had developed fever of up to 40°C, severe pharyngeal pain and cough, articular and muscular pain, and general malaise. Based on these symptoms, the patient was diagnosed with bronchitis, and received antibiotic therapy with amoxicillin and clavulanic acid (6 days), and azithromycin (3 days); the drugs were administered simultaneously. Additionally, he received antipyretic and anti-inflammatory medications (paracetamol, ibuprofen). On the fifth day of treatment, non-pruritic erythematous-bullous lesions were observed, initially on the skin of the palms, as well as purulent secretion from the urethra and dysuria. The problems prompted the patient to report to HED. Generalised loud wheezing was found over the left lung field, and, to a lesser degree, over the right lung. Thoracic X-ray demonstrated perihilar interstitial-parenchymal consolidations in the lower field of the left lung, and traces of fluid in the left pleural cavity. The patient was diagnosed with community-acquired pneumonia and urethritis, and discharged with recommendation to use clarithromycin 500 mg BID and triamcinolone 12 mg QD.

Due to deterioration of the clinical status, the patient returned to the HED 5 days later. The following imaging tests were performed: thoracic X-ray, which revealed a partial regression of consolidations in the lower field of the left lung, compared to the previous image, and abdominal ultrasound, which was difficult to interpret due to a significant quantity of gas in the small intestine. The jejunum was largely filled with gas and liquid content, its lumen was moderately dilated to 16-17 mm, no effective peristalsis was observed, the wall was partially swollen, and no free fluid was found between loops. Hydrops of gallbladder of 50 mm was demonstrated, with unchanged walls and without any deposits. Particulate echoes within the urine in the urinary bladder indicated the presence of blood cells.

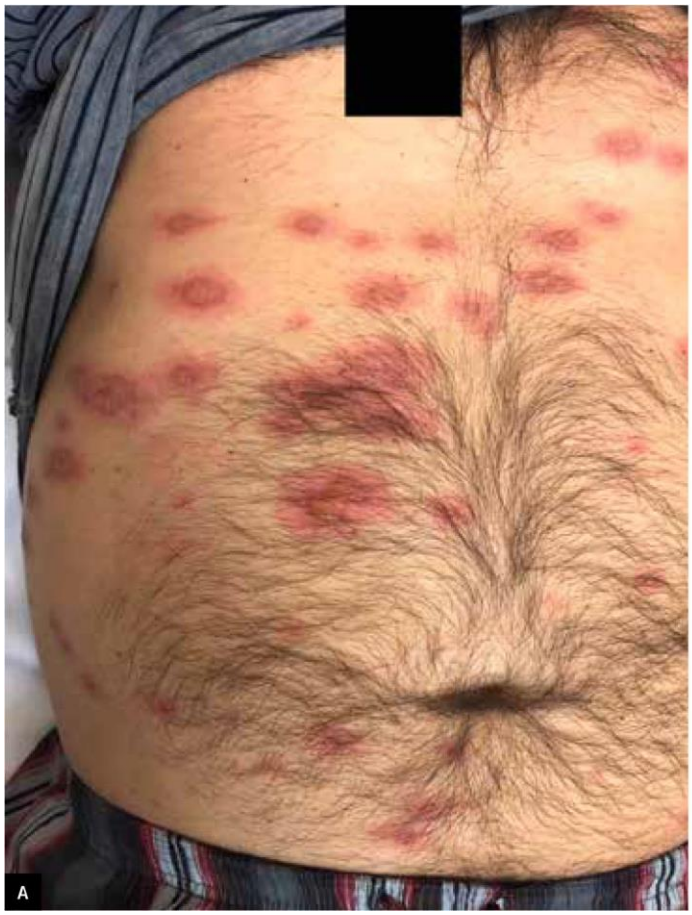
The patient was admitted to the Department of Infectious Diseases and Allergology. The patient's general condition at admission was moderately good. Verbal contact was impeded by extensive lesions in the oral mucosa. The physical examination revealed diffused skin lesions of the body trunk (Fig. 1), limbs (Fig. 2) (erythematous-papular, flat, elevated lesions with erosion in the centre), vermilion (Fig. 3), oral mucosa, pharyngeal mucosa and genitals (primarily erosions covered by a haemorrhagic scab). In the right parietal area a pigmented lesion of 3 x 3 cm was observed. The abdomen was soft, not painful upon palpation, and the peristalsis was audible and normal. In the rectal area a small quantity of fresh blood was found, without signs of bleeding in *per rectum* examination. According to the patient, the last stool was passed the day before, it was of normal colour, without any pathological elements.

The patient reported occurrence of similar skin lesions, although less pronounced, approximately 2 years before, also during therapy with antibiotics and paracetamol. He also informed about occurrence of viscous secretion in the eye area a few days before, which resolved spontaneously, with only minor lacrimation remaining.

Laboratory tests revealed the following clinically relevant abnormalities: elevated CRP – 5.8 mg/dL (N: <0.8 mg/dL), ESR – 77 mm/h (N: <8 mm), APTT – 45.2 s (N: 23.0 – 35.0 s), leukocytosis – 15.59 x 10^9/L (N: 4.0 – 10.0 x 10^9/L) and lymphopaenia 9% (N: 19 – 48%, absolute values within the normal range), neutrophilia 13.41 x 10^3/µL, 86.1% (N: 1.9 – 8.0 x 10^3/µL, 40 – 74%), eosinopaenia 0 (N: 0.05 – 0.50 x 10^3/µL) and thrombocytosis 721 x 10^9/L (N: 150 – 400 x 10^9/L). General urinalysis showed signs of urinary tract infection.

Due to the specific skin lesions, biopsy was not performed, and initial diagnosis of SJS was established. Samples from the atypical pigmented lesion in the right parietal area were collected, and histopathological examination revealed seborrhoeic verruca.

Following the initial diagnosis, the patient received intravenous methylprednisolone at the initial dose of 250 mg BID. Since the admission to the hospital, due to extensive erosions, prophylactic antibiotic therapy was also introduced, including 100 mg of intravenous doxycycline QD for 14 days, and 500 mg of intravenous acyclovir QD for 10 days. The skin lesions were treated topically with Oxycort. To prevent gastric and duodenal ulceration during therapy with glucocorticoids, intravenous pantoprazole was administered at 40 mg QD. Due to the presence of ulcerations and haemorrhagic scabs on the lips, the patient could not open the mouth to enable examination of the oral cavity. Therefore, the maxillo-facial surgeon was asked for consultation. Intraoral examination revealed blisters, erosions in the buccal mucosa, palatal mucosa, fundus of the oral cavity and tongue. Additionally, bad oral hygiene, caries and tartar were found. Improved oral hygiene was introduced, including rinsing with chlorhexidine-based mouthwash 3 – 4 times a day, and rinsing with flax seed rinse (covering effect), as well as using lanolin ointment on the lips. The patient received blended meals without hot and spicy foods. The consulting urologist recommended using Octenisept on the lesions in the genital area. During the



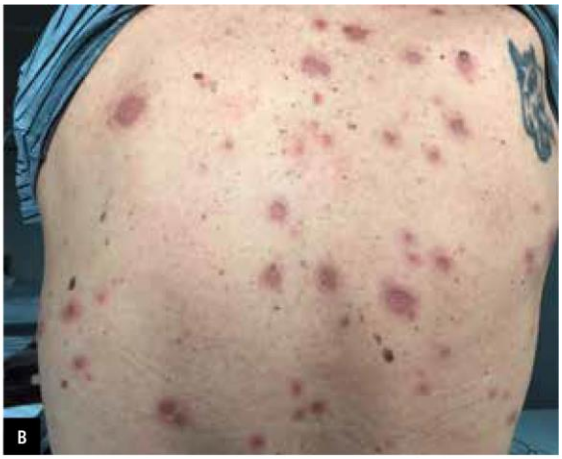


Figure 1. A-B. Red macular lesions with dusky centre mimicking target-like lesions on trunk skin

Rycina 1. A-B. Wykwity rumieniowe z ciemnym zabarwieniem w centrum, przypominające tarcze strzelnicze na skórze tułowia

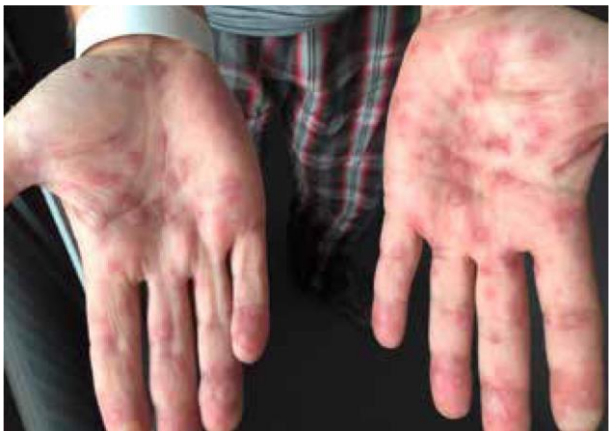


Figure 2. Red macular lesions with dusky centre mimicking target-like lesions on limb skin

Rycina 2. Wykwity rumieniowe z ciemnym zabarwieniem w centrum, przypominające tarcze strzelnicze na skórze kończyn

hospitalisation, lacrimation and stinging in the eyes persisted. Ophthalmological examination demonstrated only a lesion in the upper left eyelid (suggested planned assessment with a slit lamp), and no other significant abnormalities. Using eye drops and observation were recommended.

After two days of therapy, the mucosal lesions were reduced, and after 5 days, also the manifestations on the skin of the trunk and limbs started gradually subsiding (skin eruptions were paler, blisters were drying up). From the moment no new cutaneous and mucosal lesions were observed, the dose of methylprednisolone was gradually reduced, and finally replaced by 30 mg/day of oral prednisone.

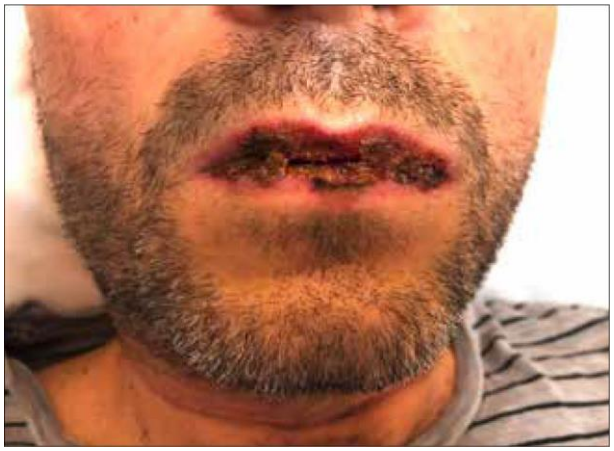


Figure 3. Erosions of oral mucosa
Rycina 3. Nadżerki na błonie śluzowej jamy ustnej

After 2 weeks of treatment, the patient was discharged in a generally good condition, with light pink erythematous lesions on the skin of the trunk and limbs, and with minor epidermal exfoliation. The erosions in the oral mucosa were healed. CRP was reduced to 0.3 mg/dL.

The patient was advised to continue oral prednisone (30 mg/day, with dose reduction by 10 mg every 5 days) and doxycycline (100 mg QD for the following 4 days), and to avoid exposure to the sun. In addition, topical administration of mometasone ointment on the skin lesions on the trunk and limbs was recommended, as well as using emollients. A follow-up visit at the Clinic of Allergology in 14 days was suggested. As the eruptions were healing, systemic corticosteroids were discontinued, the patient was instructed to use emollients and improve oral hygiene.

Discussion

Based on the clinical picture, medical history and good response to the treatment, an initial diagnosis of SJS was suggested, and further confirmed by the clinical course and reaction to the therapy. In the presented case, SJS was probably an adverse reaction to pharmacotherapy (antibiotics and non-steroidal anti-inflammatory drugs), although the concurrent infection could also be a contributing factor. The courses of the disease was not severe, the patient responded well to the therapy with corticosteroids, and the condition did not evolve into TEN.

SJS and TEN are sudden, life-threatening necrotic skin reactions. The general incidence of SJS is estimated to be 1.2 – 6.0/million, and in the case of TEN it is 0.4-1.2/million. The frequency is similar in men and women [2]. Numerous authors consider the two conditions to be the same disease (in the spectrum of erythema multiforme), varying only in intensity of skin, mucosal and systemic lesions. The principal criterion distinguishing SJS and TEN is the extent of skin/mucosal lesions expressed as the percentage of the affected tissue area (body surface area, BSA). In SJS, acute necrosis of the epidermis and mucosa is found in less than 10% BSA. If the disease affects over 30% of the skin/mucosa surface, it suggests TEN, associated with higher mortality. Necrosis affecting 10-30% of the skin/mucosa surface points to overlap Stevens-Johnson syndrome-toxic epidermal necrolysis (Fig. 4) [3].

The pathophysiology of SJS has not been fully understood. It is believed that the disease develops as a result of a delayed type IV hypersensitivity reaction (in Coombs and Gell's classification; subtype IVc according to Pichler) [4]. In this reaction, cytotoxic CD8+ lymphocytes, through perforin and granzymes, activate the intracellular system of caspases responsible for cell death (apoptosis) [5 – 7]. Excessive expression of Fas ligand on the necrolytic epidermis plays an important role in this process.

The development of the syndrome may also be determined by genetic factors. It has been postulated that in patients demonstrating slow internal acetylation and using medications such as azoles, protease inhibitors, serotonin re-uptake inhibitors and quinolones, the risk of SJS is increased [8 – 11]. Slow acetylation can contribute to pathological skin reactions [11]. A reduced rate of acetylation results in the accumulation of reactive metabolites, such as glutathione transferase, which trigger cellular cytotoxicity reactions affecting the epidermis, and causing apoptosis of keratinocytes [12]. CD8 cells participate in this process. There are two mechanisms of apoptosis: the first one involves binding of the Fas membrane receptor in keratinocytes (CD95) with its ligand FasL (CD95L), whereas the second one involves activation of perforin and granzyme B pathways [13].

It is believed that pharmacotherapy is the most common cause of SJS (50% – 80% of cases) and TEN (approx. 80% of cases), although these conditions may also be due to malignant diseases and infections. The latter are the principal causes of SJS and TEN in children; it is estimated that half of the patients diagnosed with SJS have recently had an upper respiratory tract infection [14].

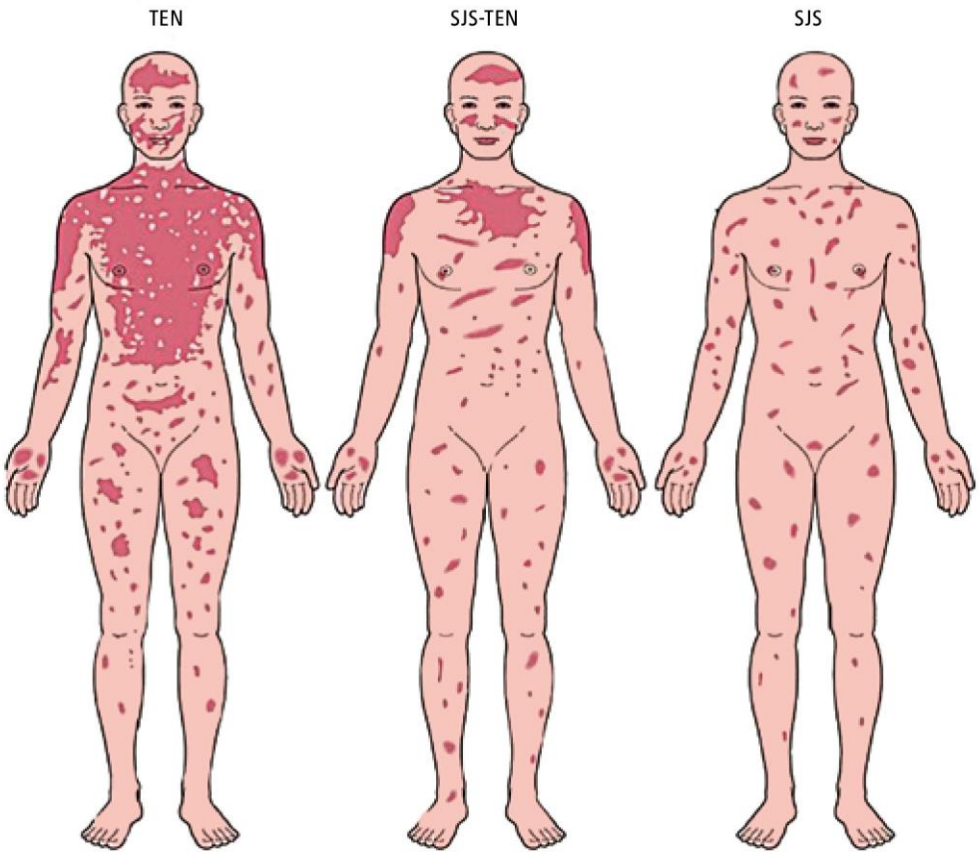


Figure 4. Pictorial representation of body surface involvement in SJS, SJS-TEN overlap and TEN syndrome (adapted from Fig. 21.9 Bologna and Bastuji-Garin S. et al. Arch Derm, 1993; 129: 92)

Rycina 4. Obrazowe przedstawienie zajęcia powierzchni ciała w SJS, zespole nakładania SJS-TEN i TEN (na podstawie ryc. 21.9 Bolonia i Basti-Garin S. et al. Arch Derm, 1993; 129:92)

The most common microorganism causing SJS is *Mycoplasma pneumoniae.* 25 – 33% of infected patients may present with skin symptoms, especially eruptions, urticaria and SJS. Moreover, *Mycoplasma pneumoniae* was found to cause erythema multiforme (EM) and "atypical SJS", manifesting as severe mucositis without skin lesions. SJS associated with *Mycoplasma pneumoniae* is mostly observed in children and young adults [15].

SJS and TEN typically occur following the administration of antibiotics (sulfonamides, fluoroquinolones, minocycline, cephalosporins, tetracyclines, doxycycline and penicillin), anticonvulsants (lamotrigine, carbamazepine, phenytoin, phenobarbital), allopurinol, certain non-steroidal anti-inflammatory drugs, nevirapine and sertraline [16]. It should also be emphasised that the immunological changes in patients infected with HIV or suffering from systemic lupus increase the risk of these reactions [17].

SJS is characterised by pronounced lesions on the mucosa, concurrent with lesions on the trunk, described as atypical target-like lesions, erythematous lesions or changes resembling erythema multiforme. These lesions have irregular outlines and darker centre. Prior to eruptions, prodromal symptoms may occur, including fever, rhinitis, conjunctivitis and dysuria. Patchy rash starts at the trunk, face and limbs; it spreads rapidly and becomes confluent. Small vesicles or large, fragile blisters may form. If eyelids are affected, haemorrhagic lesions may occur. Simultaneously, conjunctivitis with a tendency

for adhesions is observed. Within less than 24 hours, adhesion between conjunctiva and cornea may develop, potentially resulting in vision loss. Similar lesions in the form of erosions, ulcerations and haemorrhagic scabs can be found of the oral and genital mucosa, causing stenosis and problems with eating, urination and defecation [1].

The diagnosis is based mainly on clinical symptoms and histological analysis of a skin biopsy demonstrating a typical full-thickness epidermal necrolysis due to extensive keratinocyte apoptosis. Differential diagnosis should include *Herpes simplex*, staphylococcal scalded skin syndrome *(*SSSS), Behcet's disease (pustular skin lesions), Kawasaki disease (primarily in children), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), drug-induced erythroderma, certain bullous autoimmune diseases and, in the case of high-risk patients, also graft-versus-host disease (GVHD).

Mortality rates in SJS are 1 – 5%. SJS/TEN overlap is associated with higher mortality rates of 25%, and TEN with 45%. The skin lesions do not leave scars, although post-inflammatory discolouration or altered pigmentation may persist for months or years [1]. The most important factors in the treatment of SJS include early diagnosis, prognostic assessment with the use of SCORTEN (SCORe of Toxic Epidermal Necrolysis), quick identification and withdrawal of the drug inducing the reaction, therapy and careful wound care.

SCORTEN evaluates 7 parameters listed in Table 1. One point is assigned for each factor identified in a patient. The total score allows to determine the prognosis regarding mortality (0 – 1 points: mortality 3.2%; 2 points: 12.1%, 3 points: 35%, 4 points: 58.3%, > 5 points: 90%). Patients with SCORTEN score of 3 or higher should be treated at intensive care units, if possible [18, 19].

Topical treatment involves application of chlorhexidine, octenidine or polyhexanide on the erosions. Non-adherent gauze could also be used to prevent rapid drying of the skin surface. Erosions in the oral cavity should be treated with oral disinfectants, and mild ointments can be applied on those on the vermilion. If lesions are located on the urethra, supervision of an urologist is recommended. If they are found in the area of female genitalia, properly placed moist dressings and hip baths are indicated to prevent adhesions and stenoses. If eyes can be affected, consultation with an ophthalmologist is necessary; the treatment may involve using anti-inflammatory eye drops. Use of systemic glucocorticoids in SJS is controversial, as their immunosuppressive effect may intensify the disease symptoms and increase the risk of sepsis [20, 21]. However, there is evidence that sometimes glucocorticoids are associated with good clinical results [1], as in the case of the presented patient. If inflammatory lesions are observed (pronounced oedema), early therapy with high doses of glucocorticoids for a short time is applied. Another option is administration of high doses of intravenous immunoglobulins (IVIG) to inhibit necrosis of keratinocytes. IVIG is usually administered at 2 – 3 g/kg b.w. in divided doses for 2 to 4 days [22, 23]. There are also reasons to consider using cyclosporine A as immunomodulatory agent. This therapy has been demonstrated to reduce the length of hospitalisation and mortality rates in severe SJS [24, 25]. However, the study on the effectiveness of the above methods is ongoing.

Table 1. SCORTEN (according to [19])
Tabela 1. Skala SCORTEN (wg [19])

Parameter	Criterion
Age	≥40 years old
Malignant neoplasm	present
Heart rate	≥120/min
Affected body surface area	≥10%
Serum urea concentration	>10 mmol/L
Serum bicarbonate concentration	<20 mmol/L
Serum glucose concentration	>250 mg% >14 mmol/L

Conclusions

In conclusion, the role of symptomatic treatment in the management of patients should be emphasised, including fluid therapy with electrolytes and albumins, analgesic therapy, treatment of affected skin and mucosa, use of emollients to increase epidermisation, monitoring and prevention of urinary tract infections and respiratory infections, and antibiotic therapy if infection is suspected. All these measures significantly reduce the severity of disease and increase the chances of cure without complications.

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Diffuse malignant epithelioid mesothelioma of the pleura with breast metastasis - a case report

Rozlany międzybłoniak epitelioidny opłucnej z obecnością zmiany przerzutowej do piersi - opis przypadku

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Abstract. Malignant mesothelioma is a cancer of a human body serous membranes. It is uncommon and frequently causes diagnostic and therapeutic problems. Common clinical symptoms include shortness of breath, cough and chest pain. Loss of appetite and fatigue appear in late-stages of the disease. A key element of the diagnosis involves biopsies with sampling. In some cases, receiving a satisfactory microscopic examination result can be a great challenge. Asbestos exposure is a proven risk factor for mesothelioma. Mesothelioma is an aggressive cancer with short survival time and poor prognosis. Breast metastases of malignant mesothelioma are extremely rare. The diagnostic and therapeutic path was analysed, taking into account the difficulties and limitations of the therapy. In most cases treatment is palliative and limited to managing pleural effusion.
Keywords: asbestosis, breast tumor, mesothelioma, metastasis, pleural effusion

Streszczenie. Międzybłoniak opłucnej jest złośliwym nowotworem błon surowiczych. Występuje rzadko i często przysparza trudności diagnostyczno-terapeutycznych. Najczęstsze objawy kliniczne choroby to duszność, kaszel i ból w klatce piersiowej. W późnych stadiach pojawiają się utrata apetytu i ogólne osłabienie. Kluczowym elementem diagnostyki jest biopsja z pobraniem materiału do badania. W niektórych przypadkach uzyskanie wiarygodnego wyniku mikroskopowego może stanowić duże wyzwanie. Udowodnionym czynnikiem ryzyka zachorowania na międzybłoniaka jest narażenie na azbest. Międzybłoniak jest agresywnym nowotworem o krótkim czasie przeżycia i niekorzystnym rokowaniu. Przerzuty międzybłoniaka do piersi należą do wyjątkowo rzadko występujących. Przeanalizowano szlak diagnostyczno-terapeutyczny z uwzględnieniem trudności i ograniczeń terapii. U większości chorych z międzybłoniakiem leczenie ma charakter paliatywny i ogranicza się do działania w celu opanowania wysięku w jamie opłucnowej.
Słowa kluczowe: międzybłoniak, guz piersi, przerzuty, azbest, wysięk opłucnowy

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Introduction

Pleural mesothelioma is a neoplasm originating in serous membranes of the human organism. It develops most frequently in the pleural cavity. In most cases, mesothelioma demonstrates a high potential for malignancy, and tends to be aggressively expansive. As the disease progresses without any specific early clinical symptoms, the final diagnosis is difficult to establish and often delayed. In Poland, approximately 120 cases of pleural mesothelioma are reported, which qualifies it as a rare neoplasm. The disease affect people over 60 years of age and 70 – 80% of patients are male [1]. Late clinical symptoms include dyspnoea, cough, impaired respiratory

efficiency and non-specific symptoms, such as body weight loss and general weakness. The majority of patients attending the hospital show signs of generalised disease, which prevents causative treatment and limits the management options to palliative therapy. If the disease is detected early, extensive surgical procedures can be performed, but they do not guarantee full recovery. Long-term survival is observed only in patients with histopathologically confirmed lesions of mesothelial origin, characterised by positive prognosis (localised mesothelioma, well-differentiated papillary mesothelioma).

Diagnostics

The diagnostic algorithm includes laboratory, imaging and endoscopic tests, in accordance with the relevant standards regarding the oncological diagnostics of respiratory neoplasms. Every patient receives a contrast-enhanced computed tomography examination to assess the presence and stage of lesions in both pleural cavities or potential invasion of lymph nodes. At an early stage, focal pleural thickening may occur, with heterogeneous enhancement; typically, diffuse pleural thickening and pleural effusion are observed [2]. The key element in the treatment of patients with any neoplasm is the result of a histopathological test and immunohistochemical profile [3]. Reliable material can be obtained from samples of the lesions with suspected neoplastic transformation. They may be collected during surgical procedures including transthoracic core-needle biopsy, thoracoscopy or video-assisted thoracoscopic surgery (VATS). If the patient's general status prevents using anaesthesia or when urgent procedure is required, the aspirate acquired through thoracentesis can be used. However, it should be noted that in some cases cytological analysis does not suffice to confirm the diagnosis [4].

Another important step in the diagnostic process is mediastinoscopy to assess the mediastinal lymph nodes [5]. This examination determines further management by selecting candidates for a radical surgical procedure.

Professional exposure

Exposure to asbestos is an established predisposing factor for the disease, frequently mentioned in the subject literature. However, considering the low incidence and the development of advanced industrial technologies, at present most patients with confirmed diffuse mesothelioma has never been in contact with asbestos. Therefore, a majority of people working with this material at some point in their lives will never develop diffuse mesothelioma. It is possible that due to increased used of radiotherapy in medicine (especially considering the progress in paediatric oncology) its negative effects and delayed reactions will contribute to the formation of neoplasms, including diffuse mesothelioma.

Qualification for a surgical procedure

Surgical management of diffuse pleural mesothelioma is limited. Only in stages I and II of the disease can radical treatment be considered. This involves extrapleural pneumonectomy with mediastinal lymphadenectomy and resection of half of the diaphragm and pericardium, followed by their reconstruction. Alternatively, radical pleurectomy/decortication can be performed. Significant differences in the quality of life and increased mortality rates were confirmed in patients receiving pneumonectomy, compared to those undergoing lung-sparing procedures. Therefore, in the past twenty years, the percentage of patients receiving pneumonectomy has been decreasing, with a shift towards less invasive procedures [6].

There are a few highly specialised centres in Poland with sufficient experience in performing these procedures. The most popular surgery in the treatment of diffuse pleural mesothelioma is thoracoscopy with talc pleurodesis. It is intended as a palliative procedure, but although it does not offer a curative effect, it provides a significant clinical and functional improvement, in a minimally invasive manner.

Distant metastases

Distant metastases of diffuse pleural mesothelioma are usually found in the liver (55.9%), adrenal glands (31.3%), kidneys (30.1%) and the contralateral lung (26.8%). Less frequently they are observed in the CNS (3%) [7].

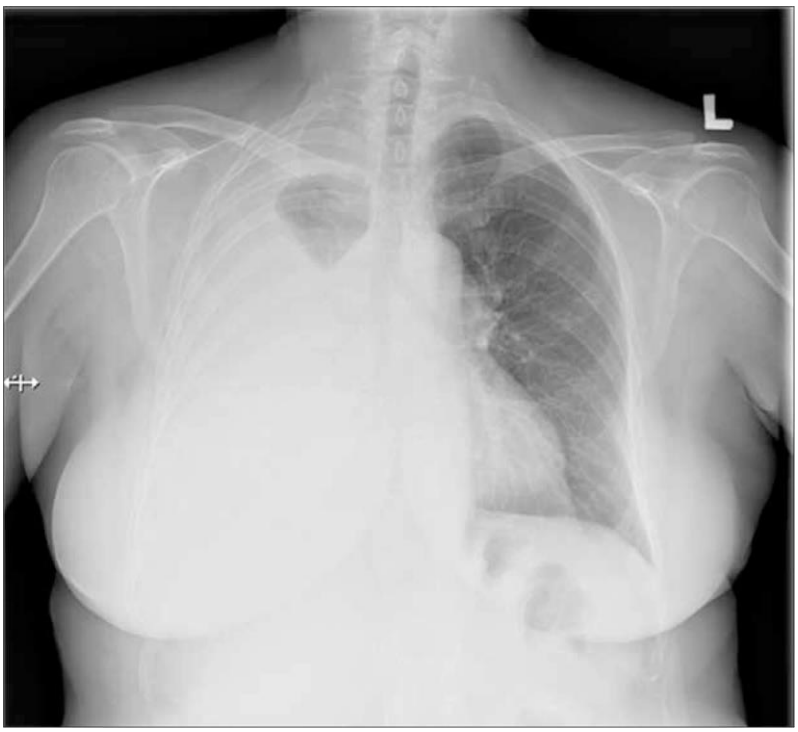


Figure 1. Chest X-ray (28.12.2019). Almost complete opacification of right hemithorax - large amount of fluid in right pleural cavity. Atelectatic lung parenchyma consolidation over effusion (WIM Radiology Unit).
Rycina 1. RTG klatki piersiowej PA (28.12.2019). Niemal całkowite zacienienie płuca prawego - bardzo duża ilość płynu w prawej jamie opłucnowej. Zagęszczenia niedodmowe miąższu płucnego nad płynem (Zakład Radiologii Lekarskiej WIM).

Combination therapy

Adjuvant radiotherapy or chemotherapy with cisplatin and gemcitabine are additional elements in the multi-stage treatment of patients with diffuse pleural mesothelioma.

Prognosis

Diffuse pleural mesothelioma is aggressive and associated with poor prognosis. The highest survival rates are observed in patients undergoing radical surgery [8]. With combined therapy, the median survival is 12 months, and the 5-year survival rates are up to 5.6% [9].

Case study

A 65-year-old woman, receiving long-term treatment due to primary arterial hypertension, reported to the HED of the Military Institute of Medicine due to exercise-induced dyspnoea and dry cough. She denied chest pains, haemoptysis, fever, respiratory infection, body weight loss or nicotinism. At the admission the patient was in a generally good condition and in a stable respiratory status. The physical examination revealed reduced vesicular murmur on the right side. Imaging diagnostics confirmed pleural effusion in the right pleural cavity (Fig. 1). During the hospitalisation, right-sided thoracentesis was performed three times, resulting in 4250 ml of effusion fluid collected. The clinical status was gradually improved, and the episodes of dyspnoea resolved. To extend the diagnostics, thoracic X-ray was performed. It demonstrated a considerable amount of fluid in the right pleural cavity (Fig. 2) and nodular pleural thickening (Fig. 3). A solid nodule of 17 mm in diameter was found in the upper external quadrant of the left breast (Fig. 4).

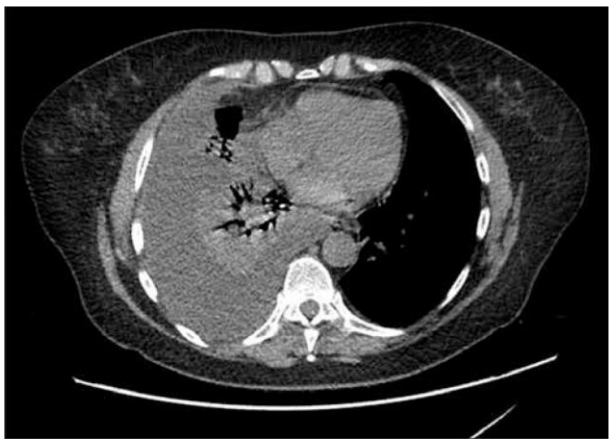


Figure 2. Thoracic CT image (02.01.2020). Large right pleural effusion and large right atelectatic changes (WIM Radiology Unit).
Rycina 2. TK klatki piersiowej (02.01.2020). Widoczna duża ilość płynu w jamie opłucnej prawej, rozległe zmiany niedodmowe w płucu prawym (Zakład Radiologii Lekarskiej WIM).

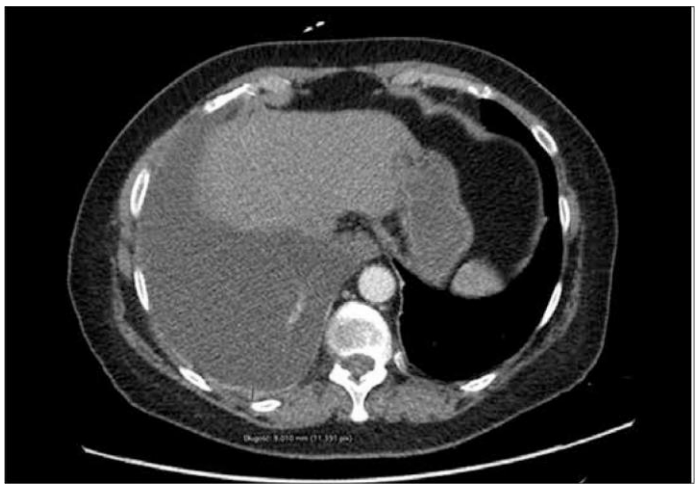


Figure 3. Thoracic CT image (02.01.2020). Large quantity of fluid in right pleural space with minor nodular pleural thickening up to 9 mm, enhanced post-contrast (WIM Radiology Unit).

Rycina 3. TK klatki piersiowej (02.01.2020). Widoczna duża ilość płynu w prawej jamie opłucnowej z niewielkim guzkowym pogrubieniem opłucnej do 9 mm, ulegającym wzmocnieniu po dożylnym podaniu kontrastu (Zakład Radiologii Lekarskiej WIM).

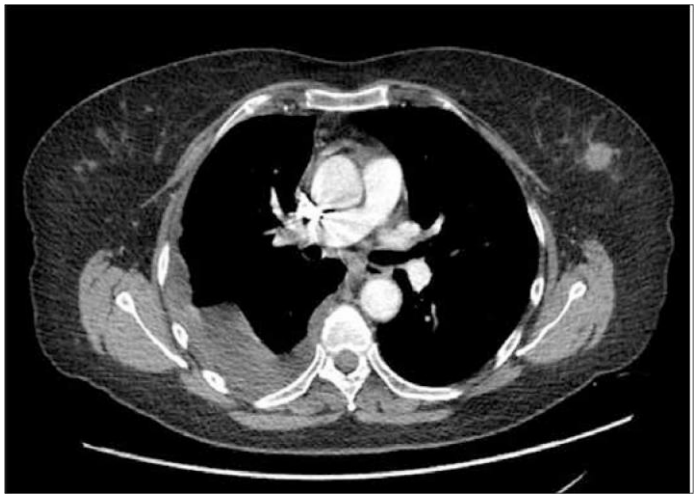


Figure 4. CT scan showing left breast focal lesion (WIM Radiology Unit)

Rycina 4. Na skanie tomografii komputerowej widoczna zmiana ogniskowa w lewej piersi (Zakład Radiologii Lekarskiej WIM)

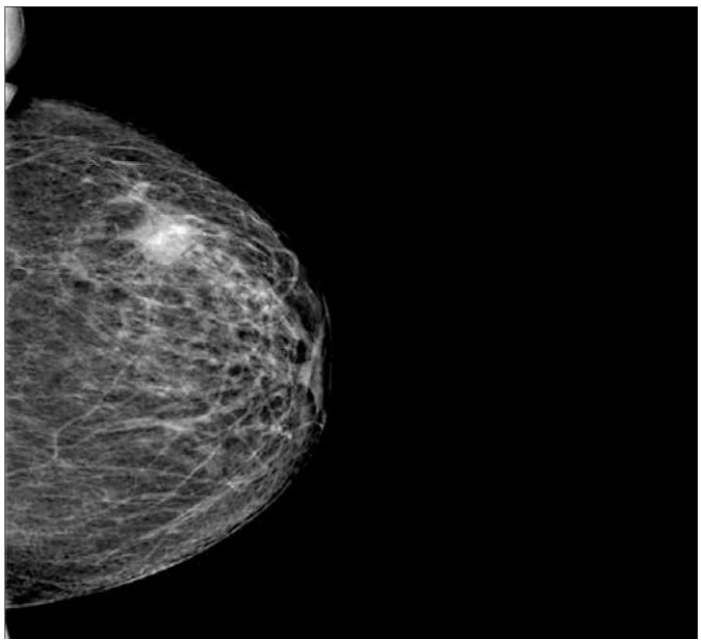


Figure 5. Mammography (08.01.2020) shows 24 x 22 mm condensation with blurry margins located in upper outer quadrant of left breast (WIM Radiology Unit)

Rycina 5. Mammografia (08.01.2020). W badaniu widoczne w piersi lewej w kwadrancie górnym zewnętrznym nieostro odgraniczone zagęszczenie o wymiarach 24 x 22 mm (Zakład Radiologii Lekarskiej WIM).

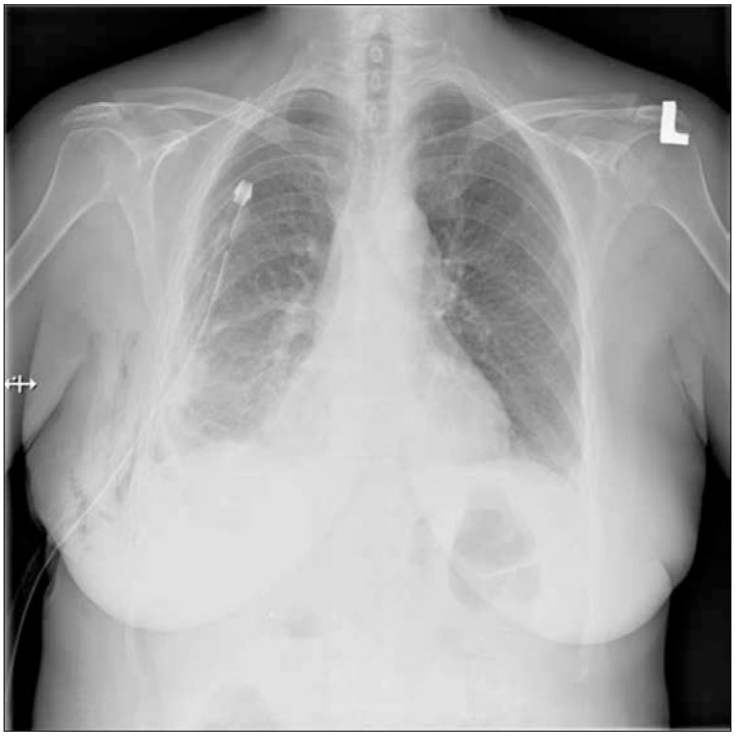


Figure 6. X-ray of the chest with suction drainage (12.02.2020). Visible subcutaneous right side emphysema. Right side pleural effusion (much less than in previous radiographs) with atelectatic lung parenchyma consolidation in right lower lobe. Small amount of fluid in left pleural cavity. Pleural thickening (WIM Radiology Unit).
Rycina 6. Obraz RTG klatki piersiowej z drenażem ssącym (12.02.2020). Widoczna rozedma podskórna po stronie prawej. Obecny płyn w prawej jamie opłucnowej (znacznie mniej niż w badaniach poprzednich) z zagęszczeniami niedodmowymi miąższu płucnego w polu dolnym płuca prawego. Niewielka ilość płynu w lewej jamie opłucnowej. Pogrubienie opłucnej (Zakład Radiologii Lekarskiej WIM).

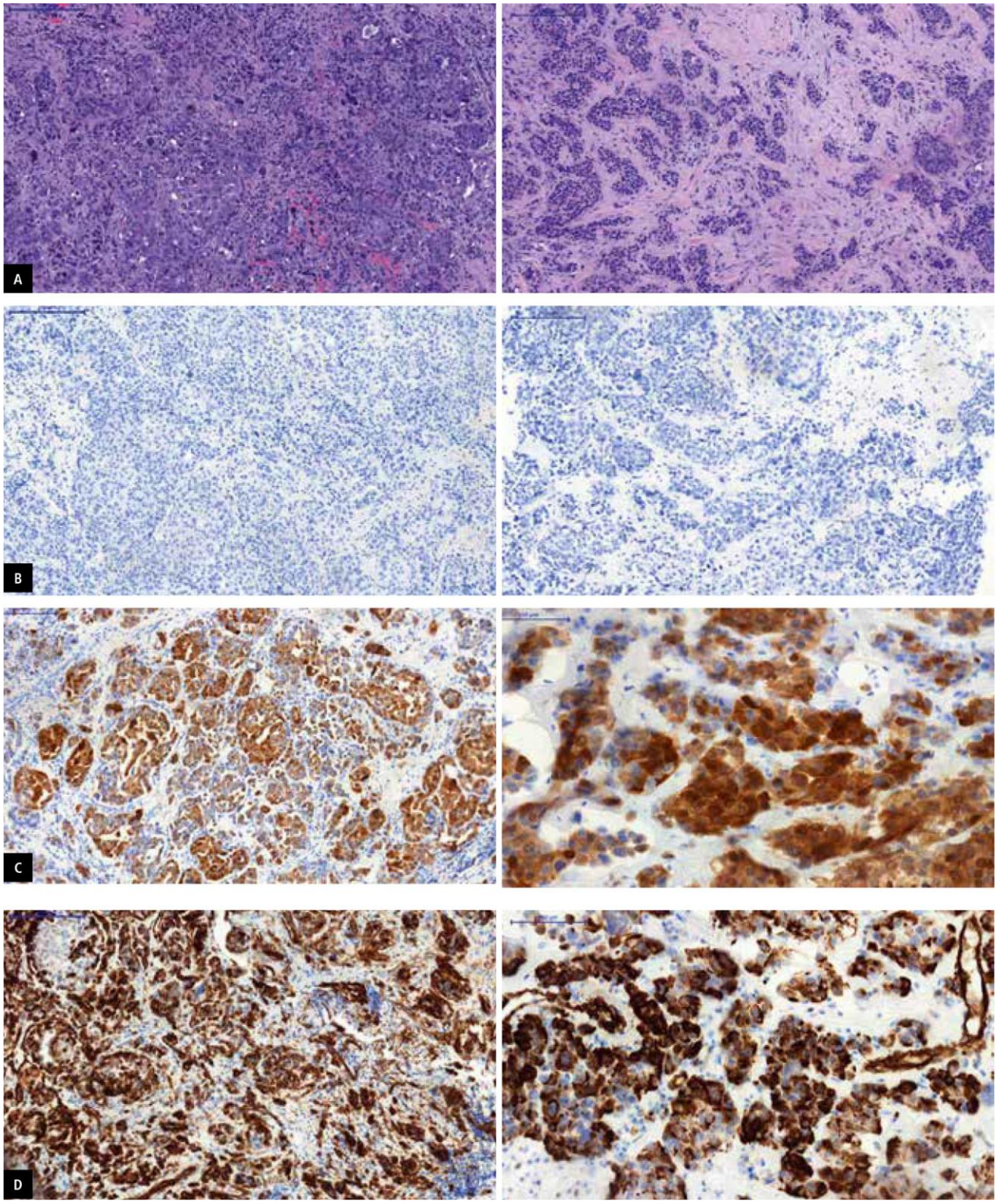
The newly detected focal lesion in the left breast was further examined in a mammography (Fig. 5). The cytological preparations from the thoracentesis aspirate revealed inflammatory effusion cells, including numerous, diffused in large groups, large cells demonstrating suspicious nuclear polymorphism. Immunocytochemical staining tests did not reveal expression of steroid receptors (ER or PR). This cytological picture did not support an unambiguous diagnosis.

The material from core-needle biopsy of the focal lesion in the left breast standard histopathological assessment revealed a moderately differentiated invasive carcinoma of no special type (NST). Immunohistochemical analysis demonstrated a triple-negative immunophenotype (ER, PR and HER2) with a high proliferation index (Ki-67 60%). At that stage of the diagnostic process, there were no premises suggesting other type of neoplasm than primary breast cancer.

As the histopathological diagnosis of the pathology in the pleural cavity had not been established, a diagnostic thoracoscopy with pleurodesis was performed. During a surgical procedure on 6 February 2020, the pleural fluid was evacuated and talc pleurodesis was performed (Fig. 6). Samples of the pleura were collected for histopathological examination. Initial results of the pleural samples, based only on the basic hematoxylin and eosin stains, revealed cancer infiltration. However, immunohistochemical examination demonstrated an immunophenotype that did not support the initial diagnosis, but suggested epithelioid mesothelioma.

Based on the clinical picture, two interpretations of the test results were possible. Coincidence could explain a co-existence of two independent neoplasms, especially taking into account that breast cancer is the most common neoplasms in women. However, due to absence of hormonal receptors and overexpression of HER2 in the cancer cells (despite the fact that triple-negative status is found in 10 – 15% of breast cancer cases) in the BGI test, it seemed doubtful that the patient suffered from two independent diseases.

The collected tissue material was re-analysed. The microscopic preparations from the core-needle biopsy of the breast lesion and the samples from the pleura were compared. Importantly, both proliferative lesions were morphologically similar. Immunohistochemical examinations revealed the same phenotype with expression of mesothelial markers (WT1, calretinin, HBME-1), and absence of markers typical for breast cancer (mammaglobin, GCDFP-15) (Fig. 7). The final histopathological interpretation, together with the clinical data, supported the conclusion that the lesion in the breast was a metastasis of the diffuse epithelioid pleural mesothelioma. Due to the generalised nature of the disease preventing radical resection of the lesion, considering the clinical status and potential complications, the patient was qualified for symptomatic management.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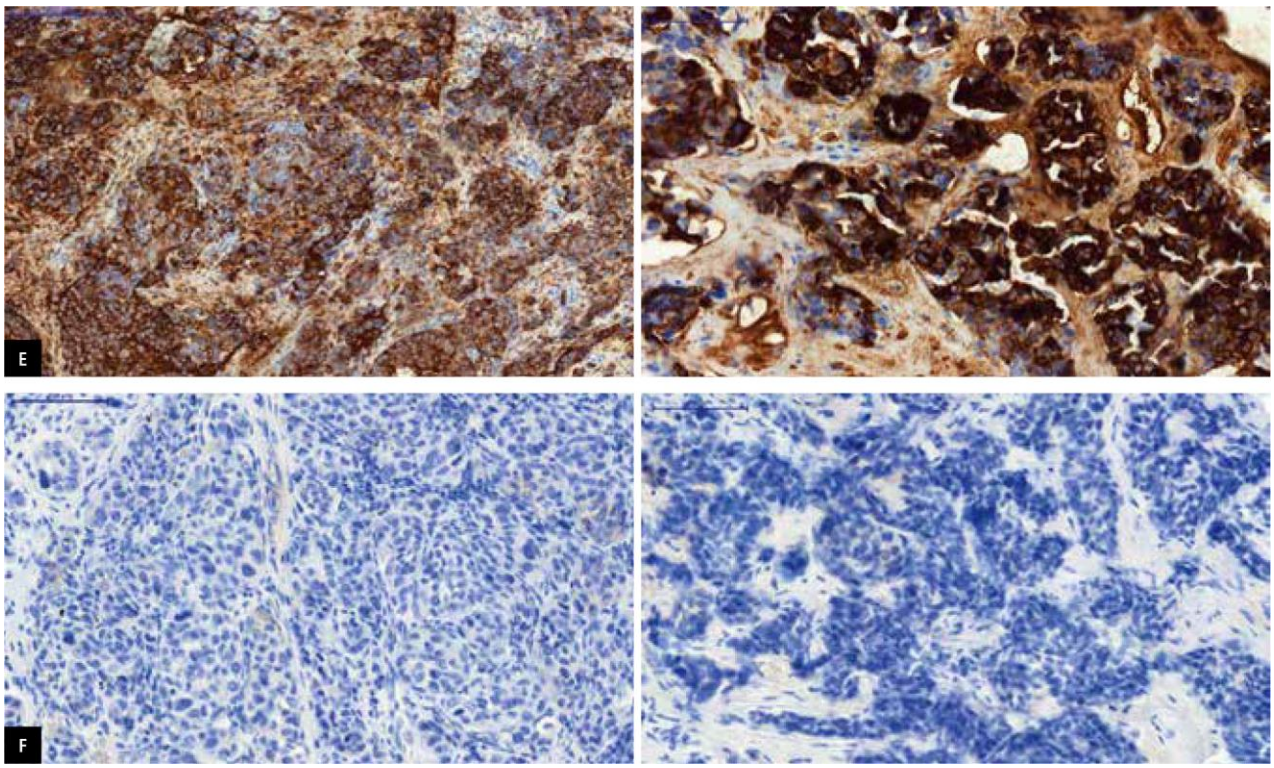

Figure 7. Comparison of microscopic images. Breast tumour tissue analysis (right). Pleural cavity tissue samples (left). Similar immunophenotype found in both lesions. A. Haematoxylin and eosin staining. B. Immunohistochemical staining: ER. C. Immunohistochemical staining: calretinin. D. Immunohistochemical staining: WT1. E. Immunohistochemical staining: HBME-1. F. Immunohistochemical staining: mammoglobin (WIM Pathomorphology Unit).

Rycina 7. Porównanie obrazów mikroskopowych - po stronie prawej analizowano wycinki z guza piersi, po stronie lewej wycinki z jamy opłucnowej. Ujawniono analogiczny immunofenotyp obu zmian. A. Barwienie hematoksyliną i eozyną. B. Badanie immunohistochemiczne: ER. C. Barwienie immunohistochemiczne: kalretynina. D. Barwienie immunohistochemiczne: WT1. E. Badanie immunohistochemiczne: HBME-1. F. Badanie immunohistochemiczne: mammoglobina (Zakład Patomorfologii WIM).

Conclusion

Diffuse pleural mesothelioma still poses a therapeutic challenge. It affects a small percentage of population, but most patients die from the disease within a year from the diagnosis [10]. None of the developed treatment methods is successful. Neither surgery nor chemotherapy, radiotherapy or immunotherapy are effective. The major therapeutic problem is associated with excessive accumulation of fluid in the pleural cavity, and progressing respiratory failure [11]. In order to improve the quality of life, various methods of evacuation and prevention of effusion are implemented, such as thoracentesis, drainage, chemical and talc pleurodesis. Despite ongoing efforts, no method ensuring sustained clinical improvement has been developed. In most cases, respiratory impairment prevents palliative chemotherapy and results in fatal complications.

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Severe Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome in a patient taking nonsteroidal anti-inflammatory drugs – a case report

Ciężka reakcja polekowa z eozynofilią (zespół DRESS) u pacjentki przyjmującej niesteroidowe leki przeciwzapalne - opis przypadku

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Department of Infectious Diseases and Allergology, Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine in Warsaw; head: Assoc. Prof. Andrzej Chciałowski MD, PhD

Abstract. The article presents the case of a 36-year-old obese female with hypertension in whom, after a 4-week treatment with nonsteroidal anti-inflammatory drugs due to upper respiratory tract infection, the Drug Reaction with Eosinophilia and Systemic Symptoms syndrome (DRESS) developed in form of skin urticaria, oedema and multi-organ dysfunction. Differential diagnosis and treatment methods are discussed.
Keywords: DRESS, drug eruptions, eosinophilia

Streszczenie. W pracy przedstawiono przypadek 36-letniej kobiety z otyłością i nadciśnieniem tętniczym, u której po 4-tygodniowej terapii niesteroidowymi lekami przeciwzapalnymi z powodu infekcji górnych dróg oddechowych rozwinął się zespół ogólnoustrojowej reakcji polekowej z eozynofilią (zespół DRESS) pod postacią pokrzywki skórnej, obrzęków oraz dysfunkcji wielonarządowej. Omówiono diagnostykę różnicową i sposoby leczenia.
Słowa kluczowe: DRESS, reakcje polekowe, eozynofilia

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Introduction

DRESS (drug rash with eosinophilia and systemic symptoms) is a general systemic type IV hypersensitivity reaction to drugs, accompanied by eosinophilia [1 –3]. It is diagnosed in 1/1,000 – 1/10,000 patients using pharmacotherapy [2, 3], regardless of their age or sex. It is associated with high mortality rates [4, 5], primarily due to hepatic or renal failure [2, 6, 8, 12].

This article presents a case of a 36-year-old female who developed the syndrome during therapy with non-steroidal anti-inflammatory drugs due to an upper respiratory tract infection.

Case study

A 36-year-old female with obesity and arterial hypertension was admitted to the Department of Infectious Diseases and Allergology, Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine, with suspected severe intolerance reaction to non-steroidal anti-inflammatory drugs (NSAIDs).

Based on the medical history, the onset of the disease in mid-July 2019 was manifested by rhinitis and fever of 39.5°C, followed 5 days later by severe pharyngeal pain and confluent, macular rash, initially on the face, later also

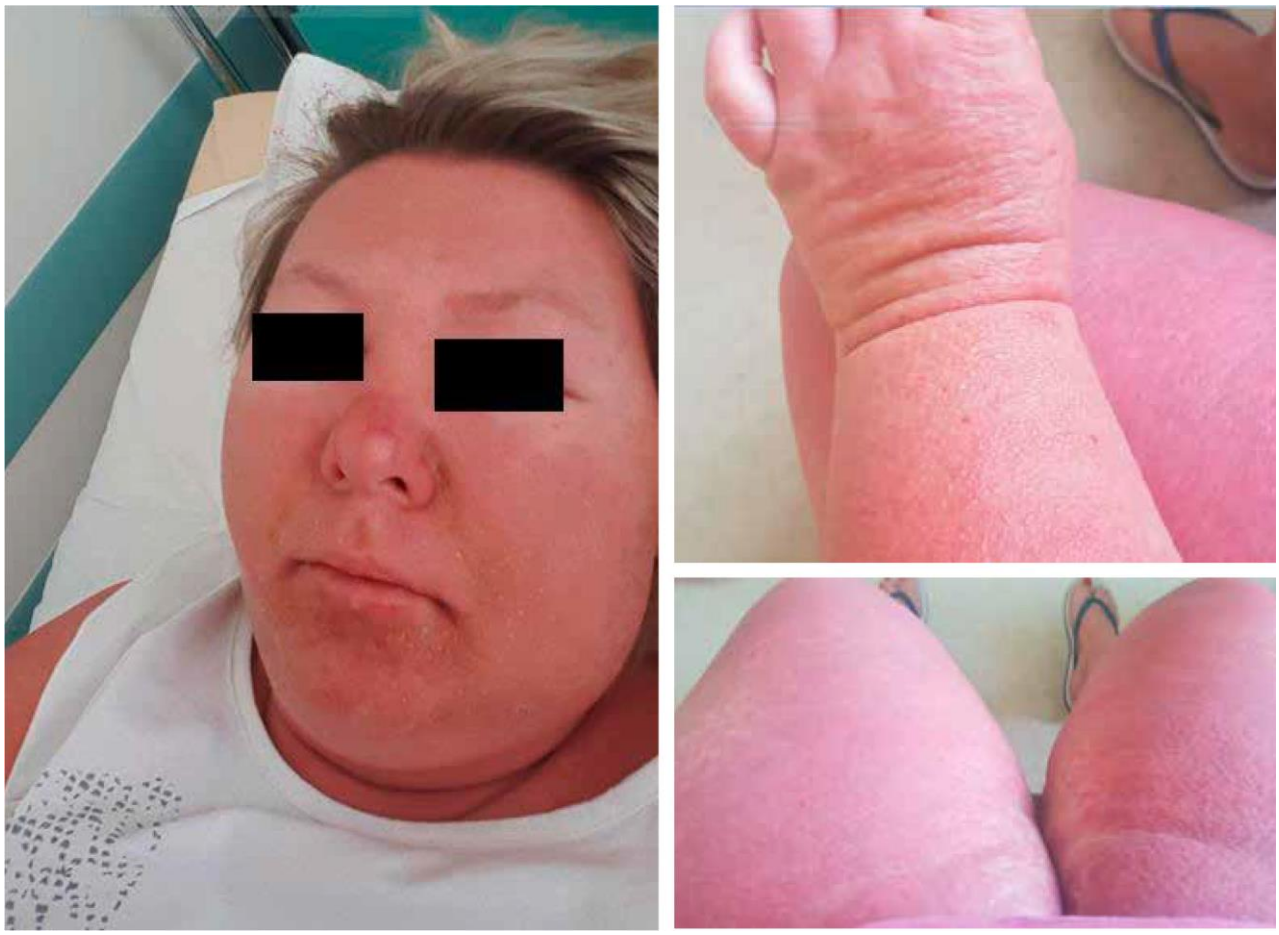

Figure 1. Confluent patchy rash with subcutaneous oedema on face and limbs. Epidermis peeling trait and honey-coloured crusts on face.
Rycina 1. Zlewna plamista wysypka skórna z obrzękiem tkanki podskórnej w obrębie twarzy i kończyn. Cechy łuszczenia się naskórka i miodowożółte strupy na twarzy.

on the trunk and limbs. The physician at an outpatient clinic prescribed NSAID and cefuroxime, but due to exacerbation of the skin lesions, he referred the patient to the hospital with suspected scarlet fever. At the hospital therapy with antibiotics (ceftriaxone, clindamycin) and antipyretic drugs was continued, but without success. The oedema of the face and limbs increased, and the next day pruritus of the vermilion and difficulty with swallowing occurred. A month after the onset of symptoms, following a phone consultation, the patient was transferred to the Department of Infectious Diseases and Allergology, Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine.

At the admission, the patient's condition was serious. She reported skin burning and stinging in the feet, as well as pain in the upper abdomen and nausea. The patient denied dyspnoea. Pronounced inflammatory lesions were found on the palate and in the pharynx, as well as generalised subcutaneous oedema, primarily of the face, confluent macular rash on the abdomen, thorax and face, with signs of epidermal exfoliation on the face and neckline. Honey-coloured crust was observed around the mouth and nose (Fig. 1). The cardiac activity was regular ~100/min, arterial pressure of 110/70 mm Hg. The abdominal ultrasound revealed clear hepatomegaly and splenomegaly. No significant abnormalities were found in the echocardiographic examination.

Laboratory tests revealed significant leukocytosis – 51.3 x 10^9/L (N: 3.9 – 9.5 x 10^9/L) and significant eosinophilia – 7100/µl (N: 0.03 – 0.29/µl), abnormal peripheral blood smear (atypical lymphocytes: 15%, granulocytes with dysplastic features), hypoglycaemia – 65 mg/dL (N: 74 – 106 mg/dL), elevated hepatic markers: ALT to 513 U/L (N: <33 U/L), AST to 287 U/L (N: <31 U/L), GGTP to 208 U/L (N: 5 – 36 U/L) and inflammatory markers: CRP to 7.9 mg/dL (N: <0.8 mg/dL), PCT to 0.65 ng/mL (N: <0.05 ng/mL), abnormal coagulation profile: D-dimers – 4.54 µg/mL (N: <0.5 µg/mL), APTT to 43.7 s (N: 23 – 35 s). *Escherichia coli* was grown in urine cultures.

The patient was initially diagnosed with DRESS.

Due to persistent refractory fever of up to 39°C, broad spectrum antibiotics (vancomycin 1 g b.i.d., imipenem 500

mg b.i.d.) were administered while waiting for the results of the antibiogram. The therapy also included systemic steroids (prednisone 50 mg q.d., human immunoglobulin 50 g q.d. [200 g administered in total]) and low-molecular-weight heparin for anticoagulation prophylactics, which probably cause the transient thrombocytopaenia – 40 x 10^9L (N: 153 – 368 x 10^9/L).

Due to suspected myeloproliferative syndrome, FISH cytogenetic testing was performed, but as it did not reveal translocation of *FIP1L1* and *PDGFRA* genes, deletion of *CHIC2* gene or rearrangement involving the *PDGFRB* gene, including translocation t(5;12)(q33;p13), myeloproliferative process was excluded.

The applied treatment resulted in a gradual clearance of the cutaneous lesions, and normalisation of laboratory test results: leukocytes reduced to 7.67 x 10^9/L, eosinophilia reduced to 990/μL. Hepatic markers and coagulation profile were normal. CRP values remained slightly elevated to 3.8 mg/dL.

After two weeks of treatment, with a slight maculopapular rash, the patient was discharged with diagnosis of DRESS and instructions to continue prednisone at a dose of 50 mg/day. The dose was to be gradually reduced and a periodic follow-up at an outpatient setting was recommended.

At home the patient discontinued prednisone completely, and after three days she was re-admitted to the hospital due to pronounced exacerbation of the cutaneous lesions. Increased dose of prednisone (up to 60 mg/day) did not provide the expected results, so cyclosporine (300 mg/day) was introduced after 12 days of treatment. In addition, due to inflammation of the skin and subcutaneous tissue (probably resulting from a mechanical injury) complicated with abscess in the right inguinal area, empirical antibiotic therapy was introduced (ceftriaxone 2 g/day). After the results of cultures from the abscess were obtained (*Escherichia coli, Enterococcus faecalis*), targeted therapy with piperacillin 4 g + tazobactam 500 mg t.i.d. and metronidazole 500 mg t.i.d. was applied.

After 30 days of treatment (including 17 days of antibiotic therapy and over 20 days of cyclosporine therapy), the cutaneous lesions and local skin inflammation resolved (Fig. 2).

After the discharge, the patient was instructed to use prednisone (20 mg/day) and cyclosporine (300 mg/day). She continued treatment as a patient of the outpatient clinic, which she regularly attended for follow-up visits.

Due to improved clinical status, the doses of the prescribed medicines were gradually reduced. The prednisone therapy was discontinued after 3 months, and cyclosporine after 5 months following the hospital discharge.

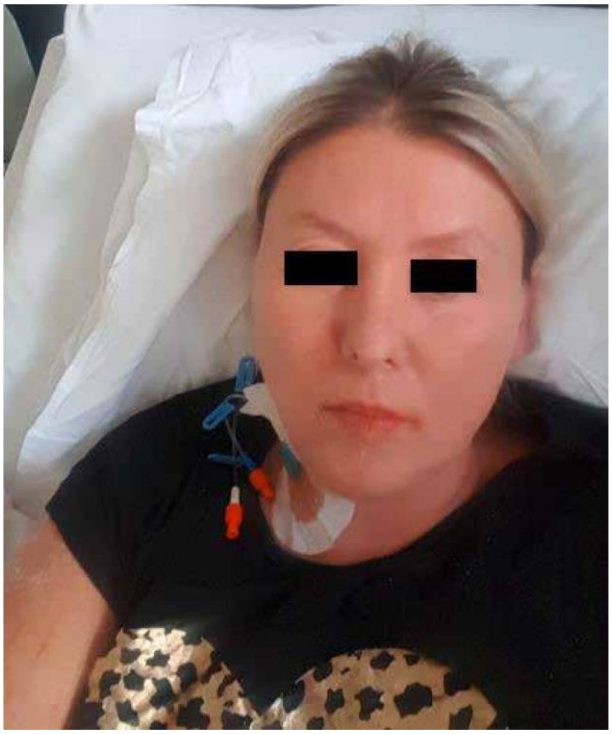

Figure 2. Condition upon resolution of lesions
Rycina 2. Stan po ustąpieniu zmian skórnych

Discussion

The number of products that may induce DRESS is constantly growing (over 50 have been identified) and although originally only anticonvulsants were associated with the risk, currently the list includes also antibiotics, antivirals, anti-inflammatory drugs, antidepressants, allopurinol, diltiazem and mexiletine [3, 6-9]. In the presented case the reaction was caused by an antibiotic or NSAID.

The syndrome results from dysfunction of the enzymes responsible for metabolism of drugs and the presence of toxic compounds in the blood [5, 7] that trigger the inflammatory cascade [3, 6], frequently including reactivation of latent viruses (e.g. HHV-6, HHV-7, EBV, CMV) [2, 3, 6, 7, 10]. There have been reports about individual predisposition for DRESS associated with the presence of certain histocompatibility (HLA) alleles.

Symptoms usually occur within 1 to 8 weeks after treatment initiation [2, 3, 8, 11] and resemble acute infection (elevated body temperature, pain, dysphagia, pruritus), followed by a fully symptomatic syndrome with cutaneous manifestations (confluent, erythematous rash, typically affecting the face, upper trunk and limbs, often including facial oedema, blisters and mucosal lesions),

blood abnormalities (eosinophilia, atypical lymphocytes) [3, 6, 11] and involvement of internal organs (liver, kidneys, lungs, muscles, gastrointestinal tract, pancreas, spleen and thyroid) [2, 6, 8, 12]. The cutaneous lesions persist for a long time, even after prompt discontinuation of the triggering drug. However, the syndrome may present without skin eruptions, although such cases are rare (up to 20%).

DRESS is increasingly often taken into consideration during differential diagnostics; however, as other diseases with similar course need to be excluded (e.g. Viral and bacterial infections, lymphoproliferative disorders, autoimmune diseases, serum sickness, Stevens-Johnson syndrome, toxic epidermal necrolysis) [2, 3, 14], the time to discontinuation of the triggering drug and initiation of proper treatment is still long. In the presented case nearly a month had passed before the right diagnosis was established.

Recommended treatment includes glucocorticoids [3, 13] or systemic immunoglobulins, and it may need to be continued for up to a few months. If the therapy is ineffective, plasma exchange (plasmapheresis) should be considered or N-acetylcysteine can be administered; as a precursor of glutathione, involved in the detoxification process, it may accelerate elimination of drugs – in particular anticonvulsants – from the organism [2, 9]. There are a few reports of patients with severe DRESS demonstrating poor response or completely refractory to glucocorticoids, but responding well to cyclosporine [15, 16]. In our patient the drug also proved highly effective.

Early diagnosis and proper treatment improve the prognosis; however, the course of the diseases is often severe, as in the presented case. Over 10% [4, 5] of cases are fatal.

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The potential of viruses as a biological weapon. Possible threat levels

Wirusy jako potencjalna broń biologiczna. Możliwe zagrożenie

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Abstract. The COVID-19 pandemic has made it clear that viruses like SARS-Cov-2, but artificially created in the laboratory, may be intentionally used to achieve political goals and that states have to be prepared for such a possibility. Moreover, future pandemics may occur also without human involvement. The risk that such a situation may occur requires states to organize and maintain appropriate reserves of personnel, institutions, materials, as well as the preparation of and training for emergency procedures. At present it is possible, from the technological point of view, to create laboratory modifications to animal viruses able to infect humans. Moreover, it is also possible to prepare an appropriate vaccine in advance in order to protect one's own population. Furthermore, an attack by such a weapon may be more effective in gaining economic dominance than through traditional weapons. All this shows that the armed forces have to be prepared to counteract such an attack.
Keywords: biodefence, epidemics, respiratory viruses

Streszczenie. Pandemia C0VID-19 uświadomiła, że wirus podobny do SARS-Cov-2, ale wytworzony laboratoryjnie, może zostać wykorzystany intencjonalnie w celach politycznych i że państwa muszą się przygotowywać na taką ewentualność. Możliwa jest zresztą również kolejna pandemia wywołana bez udziału człowieka. Groźba zaistnienia takiej sytuacji wymaga od państw utworzenia i utrzymywania odpowiednich rezerw kadrowych, instytucjonalnych i materiałowych, a także przygotowania i przećwiczenia procedur awaryjnych. Obecnie istnieją techniczne możliwości dokonania w laboratorium takiej modyfikacji wirusa zwierzęcego, by stał się zakaźny dla człowieka. Istnieją również możliwości wcześniejszego wyprodukowania szczepionki w celu ochrony własnej populacji. Co więcej, atak za pomocą takiej broni może lepiej służyć uzyskaniu dominacji ekonomicznej niż atak za pomocą broni tradycyjnych. To wszystko wskazuje również na konieczność przygotowania sił zbrojnych do przeciwdziałania takiemu atakowi.
Słowa kluczowe: obrona biologiczna, wirusy oddechowe, epidemia

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The Biological Weapons Convention (BWC), Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological [Biological] and Toxin Weapons and on their Destruction, bans the development, transfer and acquisition of biological weapons. Signed in 1972, it is still in force, although no convention can guarantee that this kind of weapon will not be produced and used. Therefore, states must be prepared for such a possibility, as well as for the fact that a similar threat to the population will occur naturally, resulting from mutations in one of existing microorganisms. The SARS-CoV-2 pandemic raised suspicions [1] that the virus was accidentally released from the laboratory where it had been developed as a potential biological weapon or a carrier of certain HIV genes for vaccination against human immunodeficiency virus, or simply studied to analyse the biological characteristics of viruses.

None of these hypotheses has been confirmed so far [1, 2]; however, the course of the pandemic and its health-

related and economic consequences for the affected countries [3] indicate that using a virus for political purposes might be a relatively inexpensive and very effective method of achieving global dominance by a country that could prepare such a tool. It would only require the selection and suitable genetic modification of one of the available viruses, development of an effective vaccine against the virus, vaccination of the country's own population, and release of the modified organism into the environment. Before other states could develop effective defence methods against the new virus, their importance and resources would decrease significantly, while the country using the weapon would achieve dominance. Although Poland is a highly unlikely primary target of such an attack, it is exposed to a secondary risk in the event the consequences of a biological attack extending to other countries. In this article I will address some of the key questions related to this issue.

Is there a technology that allows intentional modification of viruses in order to change their infectivity?

For over 30 years we have been able to carry out the intentional genetic modification of viruses. This involves the quite commonly used recombination of nucleic acids. Moreover, for over 20 years the methods have been successfully used to change the infectivity of viruses [4], although the intention behind these alterations was to reduce it. Current gene therapies (including the approved therapies for neoplastic diseases using CAR-T cells) consist in the introduction of new genes into cells with the use of vectors [5]. Vectors are modified viruses or retroviruses, or lentiviruses (e.g. HIV). In a laboratory setting, the genes coding the proteins necessary for virus replication are removed from the viruses, which eliminates their infectivity. These proteins are then introduced into modified viruses from a different source (typically a cell line), to enable one-time infection by the modified virus (used as a vector, i.e. gene carrier). Thus, it may deliver the desired gene to certain cells, but then cannot replicate and is eliminated.

To infect a cell, a specific protein of the virus recognises a molecule on the surface of a cell, and binds with that molecule, used as a receptor (Fig. 1). This attachment allows the virus to enter the cell, where it enforces replication of its genetic material, produces its own proteins, recreates itself, destroys the cell, from which is released outside, and attacks other cells. Certain molecules on the cells of different mammals are similar, but not identical. Therefore, most viruses are species-specific, i.e. they recognise given molecules only on the cells of one or a few related mammalian species. However, just as various mutations in the course of evolution made the receptor molecules slightly different in individual species, viruses can also mutate. As a result, the mutated viral protein can recognise the receptors on other species of mammals than previously. The virus gains a new host and, for the susceptible species, a new threat.

For such a mutation to become permanent, the species that could transmit the mutated virus must remain in certain proximity. In the case of humans, this could apply to farmed animals or wild animals that are, for example, to be consumed, or to an intermediary organism (e.g. mosquito or tick) that can transfer the virus. Similarly to the natural mechanisms, suitable modification can be obtained using genetic engineering, by introducing suitable sequences to the genome of the virus, as well as with the use of classical methods, by passaging the virus in properly selected cell cultures.

Do we have the technology to detect laboratory genetic modifications?

If the modification were performed using genetic engineering, the answer would be "largely yes". Sequencing of the genetic material of a new virus is presently relatively simple and inexpensive; there are gene banks that enable comparison of obtained sequences with other viruses or with the sequences of different origin, e.g. from plants. This allows us to identify promptly both the similarities and differences in the sequence, as well as in the organisation of the viral genome [1, 2]. As the mechanism of mutation are known, it is possible to detect whether a given mutation could have occurred naturally. However, if the infectivity of the virus is changed through passaging in cell cultures, where it may undergo natural mutation, followed by selection of the desired clones, such a modification would be indistinguishable from a mutation occurring spontaneously in nature.

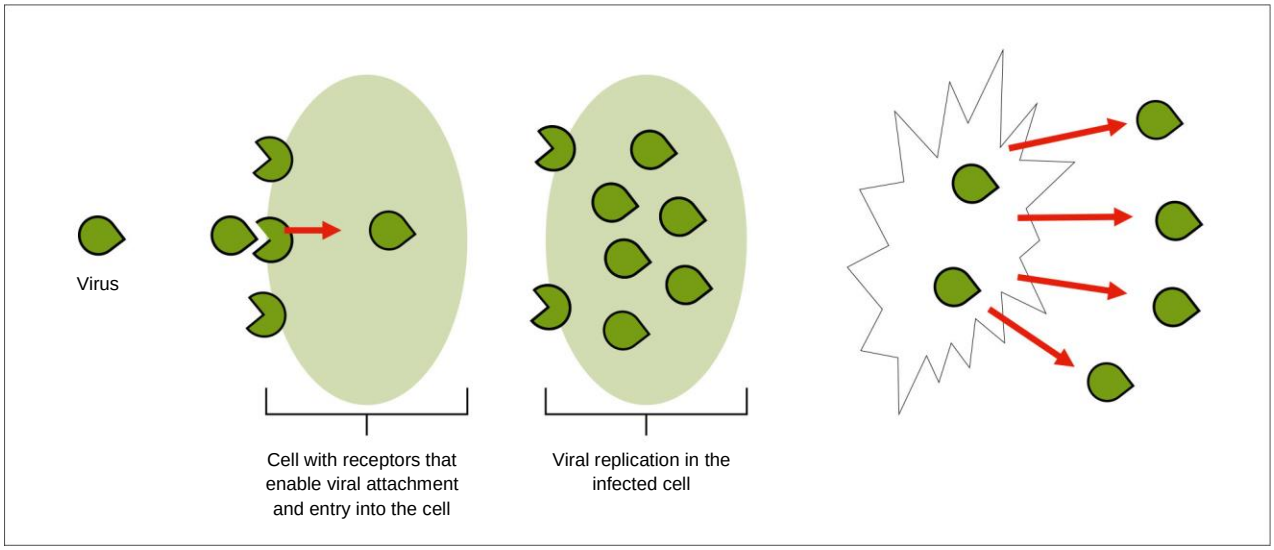

Figure 1. General scheme of infection and cell lysis by virus
Rycina 1. Ogólny schemat zakażania i lizy komórki przez wirusa

What conditions are required to use the mutated virus as a biological weapon?

Traditionally it has been established [6] that for an infectious factor to be used as a biological weapon, it should demonstrate the following characteristics:

- high morbidity, and potentially lethal,
- high infectiousness or high toxicity,
- suitability for mass production and storage until delivery without loss of pathogenic potential,
- suitability for wide-area delivery, and resilience sufficient to withstand the delivery process,
- stability in the environment after dissemination for a period long enough to infect humans.

Assuming rational planning, the potential aggressor developing the biological weapon should take steps to protect their own population. In other words, prior to using their weapon, they should create an effective vaccine, and vaccinate their own population, as this is the only way to diversify the effects of the weapon: minimise their own losses while maximising the losses of the enemy. Therefore, the aggressor must have a sufficient scientific and manufacturing potential to produce a new human virus, develop and verify an effective vaccine, produce it in adequate quantities to vaccinate a whole population, and conduct the vaccination.

However, history offers accounts of suicidal aggressors, ready to sacrifice their own population in an effort to hurt the enemy. They limited their preparation to obtaining a new virus.

From the aggressor's point of view, it is also important that the opponent only realises too late that they were attacked, so that the counteraction is delayed. Preferably, the symptoms should develop some time after the infection and resemble those of other diseases common in this population [6 – 8].

Finally, the aggressor's goal it is also important: whether they want to eliminate the attacked population physically, or achieve economic dominance. For the latter purpose, SARS-CoV-2 would be the appropriate type of virus, but in this case, the country it originated from was its first victim. Nevertheless, considering the effects of the pandemic, if China had had an effective vaccine and immunised its citizens early enough, within a year it could have become the most powerful state in the world, with relatively limited physical elimination of the hypothetical opponents. A virus of the SARS-CoV-2 type is not suitable for physical elimination of the enemy population, as it is lethal primarily to elderly people, who do not pose much threat from the military point of view, and the general morbidity and mortality caused by the virus is limited compared to other potential weapons.

One could also imagine a situation in which the potential aggressor does not create a new virus, but verifies which standard preventive vaccinations have been discontinued by the opponent and uses this virus from the storage in the research laboratories. It should be emphasised, that some of the viruses stored in laboratories are highly lethal.

Another condition for a virus to be used a biological weapon is an effective method of distribution among the target population. Viruses are spread through various routes, typically involving a direct transmission between one animal organism (in this case human) to another [10]. The counteraction measures will differ at least partially, in

the case of human-to-human transmission, compared to the situation where the virus is carried by animals, including those close to humans, such as dogs and cats. The most infective virus is the measles virus, transmitted between humans in the aerosol formed during breathing [9, 11]. Larger viruses, including SARS-CoV-2, are spread primarily through droplet infection [12]. Nevertheless, among the human-to-human transmission routes, the most effective one is through the respiratory tract, and RNA viruses will be the most suitable ones.

It is worth pointing out the differences between droplet infection and aerosol-transmitted infection. In the case of droplet infection, the inhaled droplets are over 5 μm in diameter and can remain in the air for several minutes (although on plastic or metal surfaces they can remain for up to several hours). They are transmitted no more than 1-2 m from the exhaling person. In the case of aerosol route, the droplets are smaller than 5 μm, can remain in the air for long period of time and be transmitted over distances greater than 1 – 2 m [13].

How should the healthcare system be prepared for the possibility of using modified viruses as biological weapons?

In the USA and in other countries special agencies are established to prepare the state for the biological threat [14]. In the USA it is Public Health Emergency Medical Countermeasures Enterprise (PHEMCE). These services use a special term for biodefence against the effects of a natural or man-created infection hazard: medical countermeasure (MCM) [15]. However, despite the activity of PHEMCE, the country has not been prepared for COVID-19 better than other states, which – understandably – raises certain questions. On the one hand, it seems that the disregard of the government authorities for the agency played a major role (the information about the first victim of COVID-19 in the USA was announced in January 2020). On the other hand, the unpreparedness resulted from the inability to re-organise the healthcare system for the fight against the epidemic. Private institutions with varying internal organisation structures, different owners and procedures cannot be managed quickly and effectively.

Therefore, public institutions carry the main burden. There are two principal systems of public healthcare: first aid and insurance-based medical assistance, additionally supplemented by entirely private services. Without getting into all the complexities of the American healthcare system, it offers a relatively limited component of first aid services, and only this part, centrally administered, can be quickly re-organised to fight a new threat. In other words, systemic preparation must include the ability to re-organise the system so that it can cope with the assigned tasks. Importantly, every element of the system must have its own transformation procedures developed, and be familiar with them [16]. On the central level, procedures and resources are required for financing the centrally taken over medical institutions and their tasks.

Finally, the system must necessarily include institutions able to detect the pathogen causing the hazard, to identify and define its transmission routes, and to determine actions required to limit the transmission. As we know, viruses are transmitted via various routes, and their infectivity differs. A virus can reach a given population not only through people, but also through animals, so relevant institutions must be capable of identifying viruses also in animals.

States must always have sufficient stocks of materials, which need to be rotated based on their expiry date, following the principle that the basic materials are the most required ones, and they play the key role in the case of mass infections. The example of SARS-CoV-2 revealed that not only Poland, but also the most powerful states in the world, had problems with providing face masks for their citizens, although randomised studies confirm their protective effectiveness in immunocompromised patients [17].

States must also be able to mobilise specialised personnel to battle the biological hazard. Naturally, this applies mostly to healthcare professionals, but also to veterinarians and representatives of other services generally associated with human environment. Although most countries have procedures for calling healthy men to military service, this process is limited by a number of legal regulations, significantly obstructing conscription in a situation other than open military aggression. Moreover, in the context of biological warfare, so-called cannon fodder, i.e. untrained young men, will be of limited use, as opposed to the personnel with specific qualifications. Therefore, a separate mechanism should be established for appointing people with required qualifications to service as public officers. This should include provision of protection equipment and legal security regarding preservation of employment and protection for their family members, that is all the benefits states grant to their officers [18].

In Poland these issues (but only with regard to natural biological threats) were discussed in a recently published “National Security Strategy for the Republic of Poland” in the chapter “State resilience and general defence”, including the importance of maintaining strategic reserves of healthcare protection products and medical equipment in case of epidemic [19].

How should the armed forces be prepared for the possibility of using modified viruses as biological weapons?

First, armed forces must have specialised services, corresponding to the civilian ones, as a reserve in case the latter are paralysed. Second, during an epidemic operating in compact troops will render soldiers susceptible to infection, resulting in their inability to act. Therefore, the armed forces need to develop and practice procedures and methods of operating in a biological warfare setting, including the use of viruses, corresponding to those prepared for other weapons of mass destruction, e.g. nuclear or chemical weapons. Finally, all soldiers must be provided with personal protection equipment, which are much less expensive than the chemical protective equipment.

We can picture two main types of situations: in one the primary and principal target of the viral attack is the army, and in the second one the target is the community that created the armed forces. The two situations could also occur simultaneously. Clearly, with reference to Poland, we are considering a hypothetical situation where our county is the victim of a biological attack, not the aggressor.

If the armed forces are the primary target of a biological warfare, the virus used would rather demonstrate infectivity similar to that of measles [9], not SARS-CoV-2. With such target, the effect would have to be fast and pronounced, so that the army is paralysed immediately.

If the primary target of the biological attack is the population, a virus resembling SARS-CoV-2 type will be used, as its symptoms, especially the early ones, resemble other common infections (in this case flu), occur after some time (at least a few days) following the infection, and do not result in dramatic biological outcomes (the mortality rates are at a few percent). It is also related to the hypothetical purpose of such aggression. Traditional wars were fought for territories, in order to provide space for constantly growing population, whereas all the high-technology states (the only ones capable of using such weapons, due to technological requirements) deal with depopulation, and the territory itself is no more a source of wealth. Therefore, the aim will rather be to gain economic dominance, including taking control over raw materials, but with the local population in the role of miners.

In the first scenario, the armed forces must focus on protecting themselves, including the command centres, by division, followed by the use of personal protection equipment and re-organisation for action based on the type of (nature) of the attack. In the second case, the army needs to be prepared to conduct clean-up operations and maintain order, while the appropriate military services (sanitary, healthcare) must be ready to support the corresponding civilian services.

Based on the experience from the present pandemic, the most effective method to limit the effect of biological weapon is personal and social distancing, i.e. maintaining an appropriate (different for individual pathogens) distance from people with unknown exposure to infection, especially from those with direct or indirect contact with the infection, and certainly from the infected individuals, as well as avoiding large groups of people in poorly ventilated rooms. The distancing must involve grouping people into cohorts based on different exposure levels to the infective agent. The classification should always be taken into account, and all the services offered should be adjusted accordingly [16], including separate bathrooms.

In fact, present global experience with COVID-19 significantly helped societies in preparation for similar events, either caused by enemy states, or occurring naturally. It can only be expected that politicians and special services also learned from the experience.

Conclusions

A biological attack using virus weapon, conducted by terrorists or as part of war between states, is not unfathomable. Similar threat can occur naturally, and states must be prepared for such event in terms of proper personnel, institutions and resources, as well as develop and practice procedures for this situation. It includes preparation of the armed forces, the largest and most comprehensive state service, capable of taking on the roles of all other services, if necessary. It is important to use the experience with COVID-19 to prepare better for the next biological threat.

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The role of Social Work in Health Care for Veterans in the United States of America

Praca socjalna w lecznictwie weteranów służby wojskowej w USA

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Abstract. Clinical social work in the American system of health care and its specific features in Veterans Affairs (VA) for veterans are described in this paper. VA hospitals are the largest employers of social work worldwide. Because health care for veterans is paid from government funds, VA hospitals are subject to regulations developed on the basis of research into the system's effectiveness and efficiency. Clinical social workers cooperate with physicians and nurses to comprise an integral part of the health care team. Social workers fulfil the usual tasks related to social well-being but also act as health educators and counsellors. All social workers of the hospital are members of their own division, in which they receive support, supervision, and assistance in further education and professional development. The example of serving homeless veterans in Cleveland, Ohio, is used to describe the function of social workers in VA hospitals.
Keywords: clinical social work, COVID-19, health care team, homelessness, psychotherapy

Streszczenie. W pracy scharakteryzowano kliniczną pracę socjalną w amerykańskim systemie ochrony zdrowia oraz jej specyficzne cechy w lecznictwie weteranów (VA). Szpitalnictwo VA zatrudnia największą liczbę pracowników socjalnych na świecie. Ponieważ służba zdrowia VA jest finansowana z funduszy rządowych, podlega wielu regulacjom ustalanym na podstawie badań jej skuteczności i opłacalności. Kliniczni pracownicy socjalni współpracują z lekarzami i średnim personelem medycznym, stanowiąc integralną część zespołów medycznych. Pracownicy socjalni, poza wypełnianiem zwykłych zadań socjalno-bytowych, pełnią rolę edukatorów zdrowotnych i psychoterapeutów. W szpitalach VA są członkami własnych specjalistycznych zespołów, w których uzyskują wsparcie, superwizje, pomoc w szkoleniu i zdobywaniu kolejnych doświadczeń zawodowych. Działalność pracowników socjalnych w VA przedstawiono na przykładzie pomocy bezdomnym weteranom w Cleveland, w stanie Ohio.
Słowa kluczowe: kliniczna praca socjalna, zespół medyczny, psychoterapia, bezdomność, COVID-19

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Introduction

The main role of a doctor is to take care of the patients' physical and mental health, while the main role of a social worker is to help them function properly in their community. Depending on their environment, people demonstrate different needs. For instance, the needs of an individual who can afford good living conditions vary from those of a homeless person. Both people may deal with the same health problem, but their financial and social resources will be different. These differences can determine the effectiveness of the treatment process, as well as of the healing process. Factors such as increased level of stress in the life of a homeless person, problems with hygiene and an unhealthy diet may adversely affect the outcomes of even the best therapy. Therefore, in most hospitals the patients are taken care of not only by physicians and other medical personnel, but also by social workers. The importance of the patient's environment is emphasised in the ecological approach, which is the fundamental framework in the professional training of social workers [1, 2].

Figure 1. Louis Stokes Cleveland VA Medical Center, University Circle, Cleveland, Ohio
Rycina 1. Centrum Medyczne VA im. Louisa Stokesa w Cleveland, Ohio

Social workers in a general hospital offering services for a small area are in a privileged situation, as they are familiar with the scope of assistance that the local community may offer to the hospital patients. Based on this knowledge, they can refer patients for further outpatient or community care outside the hospital. Moreover, they can probably offer to contact personally the organisation to which the patient is referred. After a medical intervention, convalescents often require new contacts, medications and rehabilitation equipment that they never heard about before. A social worker provides contact between the hospital and the community in which the patient will live following the hospitalisation [1, 2].

Apart from the referral level, hospitals also differ in the scope of treatment offered. Speciality hospitals include psychiatric hospitals and those created by various professional associations and organisations. Their patients may arrive from distant areas. In general, the larger the catchment area of a hospital, the less likely the social worker is to be familiar with the environment to which the patient will return after treatment. In the case of industry-based hospitals, the patient's environment may be determined not only geographically, but also by the profession. This applies to military hospitals, and in the USA also to hospitals for veterans [3].

As a Google Scholar and Case Western Reserve University (CWRU) search did not provide information about social work in military hospitals in Poland, this article will present social work in the Veterans Affairs (VA) hospitals in the USA. One of the authors (JRR) has experience as a social worker administrating the VA programme for homeless veterans, and the other one (FCE) is the Chief of Social Services in the VA hospital in Cleveland, Ohio.

Social work in American hospitals differs from social work in Poland in many respects. Although various functions are similar, especially those related to the patient's environment, there is a set of clinical skills that are not required from Polish social workers. For instance, in a psychiatric hospital (or ward) a social worker can conduct a diagnostic interview with a patient, and suggest the treatment course. Following a consultation with a psychiatrist, the patient may receive pharmacological treatment and therapy conducted by the social worker, who is a qualified psychotherapist. Thus, the physician has more time for medical observation and assessment of the pharmacological therapy, and the patient has more time for individual and/or group therapy. As the social worker performed the diagnostic interview, he or she already knows the initial diagnosis, which is very useful for his/her role as the psychotherapist [3, 4].

Social workers in the USA are employed in hospitals at all referral levels. They are metaphorically compared to "the oil that keeps the wheels in motion". Without them, the system is not properly "lubricated", and could stop working. The demand for social workers results from their education and competences in five areas: I **Acting on behalf of the patient (patient's representative).** Social workers learn about the patient's needs, both those related to the hospitalisation, and those occurring in their community setting. They ensure performance of all the necessary services in the hospital, and help patients cope in their own environment. For instance, a patient who does not follow the physician's orders requires the special care of a social worker, when the physician refuses to continue treatment. This patient may also need careful attention after the hospitalisation.

- **Mental health problems.** At any medical department there may be a patient with additional treatment needs due to mental health problems. It may be an oncological patient who has received a diagnosis, or a patient of the gastroenterological patient who learns that alcohol abuse destroyed his organism. Social workers can offer therapeutic support to such patients, or refer them to a specialist.
- **Patient education.** Explaining patient's health status, course of treatment and possible choices, i.e. what medicine can offer and what resources are available to the patient in his community. If necessary, preparing patients to deal with stress and emotions on their own. Assistance with solving co-existing problems (e.g. alcohol or medication abuse).
- **Social organisations.** After the diagnosis (cancer, liver cirrhosis, progressing diseases), many patients require a support system when they leave the hospital. A social worker can help find or create support groups in the patient's community. Patient-oriented approach helps social workers find out about the resources

available in the patients' community, and allows activation of the patients' own abilities, of which they might not have been aware previously (empowerment).

- **Organisation of society.** On the macro level, social workers helps shape social policy focused on the improvement of healthcare and the well-being of patients. This may concern air pollution or availability of healthy diet programmes. It may also involve a change of priorities in screening tests or prevention programmes.

The American veteran healthcare system is the largest in the world. It comprises 152 hospitals and 971 outpatient centres [5]. The VA system employs 14 thousand social workers, and offers professional education to approximately 1,500 students specialising in this field per year [4]. Organisation of such a large system must meet two requirements:

- uniform provisions and regulations to ensure compatibility of all the healthcare facilities;
- each unit (hospital, clinic) is an integral part of local structures created to help veterans.

Understanding the way one hospital works does not translate to understanding VA hospitals in other cities or states. The organisation of each hospital is determined by the needs and resources of the local community, its history, relationships with other military institutions in the region, and the needs of veterans. In this article we are using the example of the VA hospital in Cleveland, Ohio [6].

The VA healthcare system in Northeast Ohio comprises 18 entities, including one main hospital in the University Circle in Cleveland. In 2019, the system provided employment to 5,389 workers, and offered services to 112,395 veterans. The most numerous group of patients were veterans of the war in Vietnam (45%), Persian Gulf (23%), Korea (7%) and the Second World War (3%). Nine thousand veterans are women. The system offers 674 hospital beds. In 2019, two million outpatient admissions, 35 thousand telemedicine consultations, and 58 thousand house calls were recorded.

The organisation of social work in every VA health centre is determined by the local needs and conditions. As this is a government (federal) system created to offer services for army veterans, the work of VA social workers is highly regulated, and their tasks are strictly defined [4]. The best source of knowledge about this profession is "Handbook of military social work" from 2013, by Allen Rubin, Eugenia L. Weiss and Jose E. Coll [7]. The chapter structure of the book is specific. It starts with the introduction of social work to military service – initially through co-operation with the Red Cross organisation, followed by employing social workers within the framework of military service. The next chapter discusses the nature of social work, explaining the culture and complexity of military service. In working with patients, it is necessary to understand the specificity of the type of military service they performed, their personal achievements and military ranks. One must be aware if the principles governing the specific type of service, of the military professional ethics, understand collaboration between the soldiers having equal ranks, and appreciate the professional relationships. The next chapter presents women in the army: a constantly increasing group of soldiers [7]. It should be emphasised that although in this study we use male forms when referring to workers and patient, the female form would be equally appropriate.

Subsequent parts and chapters of the handbook explore issues specific for military service, such as mental health problems due to post-traumatic stress disorder or brain injuries, dependency and homelessness. The last part discusses work with the families of soldiers. VA websites present the specificity of social work in hospitals for veterans, from tasks associated with financial assistance and improving the living situation to mental health therapy. The typical tasks of a VA social worker include:

- providing information regarding financial and residential assistance; how patient can pay for his flat using help from the community;
- explaining how to apply for benefits, obtain financial support based on the military service history;
- presenting the benefits of service, e.g. how to participate in the study programme and look for professional counselling;
- providing opinions about short-term and long-term treatments;
- documenting in the patient register the dispositions regarding medical management in the case the patient cannot take informed decisions;
- providing psychotherapy to enable coping with mental health problems;
- assistance with solving problems in the patient's family.

The tasks of a social worker are integrated with the work of the medical team, including professionals of various specialities who help the veteran in the recovery process or rehabilitation of life functions. It may be a trauma centre (polytrauma department), post-traumatic stress disorder treatment team, dependency treatment department, or assistance for the homeless or professional counselling. Military social workers are highly qualified. VA requires them to have higher education (MA) and at least two years of supervised internship to achieve the optimal level of professional preparation, confirmed by the licence of independent social worker [4, 7].

As the nature of warfare changes, so does the scope and type of medical needs of veterans. Social workers must constantly improve their professional qualifications. Using advanced diagnostic methods and therapeutic programmes is required. The diagnostic approach considers the biological, psychological and social background for the mental problems [5, 8]. Therapy uses empirically verified methods, applied by teams of specialists [5, 9]. It is patient-oriented, and patients actively participate in setting the goals. Due to the nature of military service, the most commonly used therapies are focused on trauma [10]. Intensive work with veterans in the healthcare system can be both satisfying and challenging. Studies demonstrate that many social workers like working with veterans, and they consider it an honour to be able to help. Other sources of satisfaction for the VA social workers include engagement in improving the healthcare system, and the visible impact their work has on the lives of veterans. Negative feelings are reported in relation with the inability to provide patients with the required services (20%), bureaucracy in VA (15%) and lack of appreciation for the profession (5%). Social workers value the most their role as a patient's representative (23%), therapist (29%) and guide in the rehabilitation process (25%) [5].

The VA system is very complex and is subject to many regulations and limitations resulting from its dependence on the USA government. It is associated with certain procedures and detained financial decisions, frequently translating into delayed treatment processes. Therefore, in the VA system patients' representatives can demand fast action to serve their interests. As previously mentioned, bureaucracy adversely affects satisfaction with work. The VA system and the role of social workers in it is monitored, and the obtained study results are conducive to improvements and changes within the system [11]. Enhanced working conditions increase the satisfaction with one's competence [12]. The presented rules of procedure in the VA create a bureaucracy that is cumbersome, but it is meant to warrant justice and fairness, and its principal goal is to ensure well-being of patients.

Social workers require professional support from their colleagues, who understand the nature of work and can offer advice and assistance. Therefore, in the system created in the past few years social workers not only form an integral part of the medical teams of specialists, dealing with particular health problems (e.g. neurological or gastroenterological), but also members of the team gathering representatives of their own speciality – social work, with its own structure within the hospital's framework. The chief of social services is in the group of leaders of all medical teams, who report directly to the hospital authorities. In this way he can speak on behalf of his charges in all cases where the patient's interests in the VA system depend on the social worker and relevant decisions remain in the control of the hospital management [6, 11].

The social work team has its own administration, which records the specialisations of each team member, helps to suggest training that could be of interest for them, and lists their supervisors and seniors who evaluate their work. Internal meetings and discussions allow team members to suggest changes in the structure of patient service from admission to discharge from the hospital. Many such solutions significantly enhanced the organisation and effectiveness of treatment [11]. Contribution to the improvement of functioning of hospitals increase the prestige of social work in VA healthcare. Many VA centres collaborate with universities conducting research that provides evidence that the methods used in social work have an empirical basis [11].

In their preface to the special edition of *Clinical Social Work Journal* (2018, vol. 46), focusing on social work in VA, Bloeser and Ray [13] present some statistics regarding this profession. They report that 63% of social workers had worked for VA for less than 5 years, 73% were women, and 70% were veterans or members of veteran families. One third of employees of VA played the basic roles of social workers: 35% worked at psychiatric departments, 12% at medical or surgical departments, 8% in PTSD clinics, 3% in cerebral injury clinics, and 7% in administration. The competences of social workers must include the ability to communicate with medical professionals specialising in various areas [14]. Clinical social workers in the USA are not only prepared to co-operate with other medical disciplines, but can perform certain activities, e.g. psychotherapy, independently [5, 11]. As part of the patient-oriented approach, every social worker should understand the way military service has affected the veteran. Regardless of the previously mentioned specific culture and system of values, understanding of the nature of active military service is also very important. It includes the ways armed conflicts and their social determinants could have affected the physical and mental health of different groups of veterans, as well as their lives after the service. It is related to the ecological approach to patient, which assesses a person's functioning taking into account the conditions in which he lived [8].

Bloeser and Ray provide examples from the history of armed conflicts that are essential in the work with different generations of veterans [13]. For instance, one must realise that after the Second World War, African Americans experienced racist bias when distinctions for service were granted. The preparations for the Korean War were poor, and many veterans suffered frostbite, because the commanders did not take Korean winter into

account. After the war in Vietnam, the number of veterans who required treatment for dependency on psychoactive substances increased significantly. Diagnosis of post-traumatic stress disorder was still uncommon at that time, and many veterans had to cope with mental problems on their own. Military operations at every period affected veterans in a specific way. In the case of recent wars against terrorism, PTSD and brain injuries were common diagnoses. Moreover, the number of suicides among veterans increased, exceeding that of soldiers who died directly in armed conflicts.

Mental health problems of the youngest generation of American veterans were described in another study [15]. The problems of the older generation are presented in the study by Clark et al. [16]. In the years 2004 – 2014, the number of people over 65 years of age increased in the USA by 10 million (from 36.2 to 46.2 million). Every second man in this group is a veteran. The most common mental problem in this population is post-traumatic stress disorder (PTSD). Veterans with previously undiagnosed PTSD had to cope with its symptoms: some used psychoactive substances, others learnt how to control their reactions in the situations that trigger panic. Today, they participate in therapeutic programmes for substance use problems, or seek psychiatric assistance when they cannot control their symptoms. This is associated with the ageing process, resulting in reduced control of the frontal cortex over emotions [16].

As the methods of warfare change, so does their effect on military life. New types of weapons and tactics necessitate modifications in training, as well as personal resources in the army. At present, approximately 10% of all veterans in the USA are women. Following the repeal of the “Don’t ask, don’t tell” (DADT) law, transsexual and non-heterosexual (LGBT) people also serve in the army. It requires modification in the professional training of social workers, as their ethical principles include providing assistance to socially excluded groups. It should be mentioned, for instance, that transsexual soldiers experience problems leading to suicide 20 times more often than the remaining army population [13].

Considering the differences between generations of war veterans, we need to bear in mind the stages of identity development proposed by Erik Erikson. Social workers are aware that veterans of the recent military operations have different life goals than the generation of the Vietnam War. Young veterans think about education and starting a family, older ones think about the history of their relationships with children and parents, and about their legacy [13].

The specificity of health problems of each generation of veterans affects organisation of departments in military hospitals. For instance, the increased number of women in military service resulted in a higher number of departments addressing their health needs. LGBT veterans also require a special approach, due to the specificity of their problems. The VA hospital in Cleveland, for example, opened a Veteran Identity Clinic, intended primarily for this group of veterans [6, 17]. The lack of an adequate response from the healthcare system to PTSD after the war in Vietnam prompted development of psychiatric healthcare and therapeutic programmes for dependency from psychoactive substances. Unfortunately, some veterans do not get the necessary help when they need it. This may be due to various complications in their life, and overlapping health problems.

The role of social workers in the operation of VA hospitals is well illustrated by the system of assistance for homeless veterans. Analysing the history of contacts of a homeless person with VA, it is usually possible to find the precise moment when insufficient support from the healthcare system resulted in homelessness. Such findings demonstrate the weaknesses of the system, and indicate the directions for necessary organisational changes [11, 18]. For years, the problem of homelessness was on the margin of other activities of the VA. It was not until veterans of recent conflicts became homeless that the public opinion changed. Many programmes were established with the goal of eliminating homelessness among veterans [19]. According to the VA Office for Research and Development, in January 2017 40 thousand out of 18.5 million of American veterans were homeless; 91% of these were men and 9% were women. It demonstrates a reduction by 45% compared to the number of homeless veterans in 2009.

The VA hospital in Cleveland offers a shelter (dormitory) for homeless veterans. A diagnostic interview in conducted with each patient admitted to the shelter, and the plan of transition from homelessness is devised in co-operation with the patient. It may involve referral for further medical tests, usually psychiatric, but also for specialist treatment due to a range of neglected health issues. Depending on the history of homelessness, competences and the environment of the veteran, he will be directed to various programmes that may help him find and sustain permanent housing. At every stage the veteran meets with a social worker, who can determine the scope of assistance that the VA hospital may provide, and assess the community resources outside the hospital. Veterans who can quickly transition from homelessness may benefit from programmes entirely outside the VA system. In such cases, VA social workers support the activities of these organisations [6, 19].

In the case of chronic homelessness, usually associated with serious mental disorders, the veteran receives accommodation in the “Housing First” model [9], and a plan of integration with the new community. Due to

their limited ability to use the VA system and environmental assistance, each veteran from the chronic homelessness group collaborates with a social worker within the HUD-VASH programme. This programme is a result of co-operation between the Housing and Urban Development (HUD) and VA Supportive Housing, i.e. two agencies of the American government.

The tasks of the HUD-VASH social worker include visiting the veteran at his place of residence, transporting him to medical appointments, assistance with shopping, and contacting special assistance centres on his behalf to improve the veteran's functioning. HUD-VASH workers react to crisis situations and provide psychotherapy. It is a patient-oriented work, involving different stages of involvement: from intensive assistance in everyday life, to gradual withdrawal of the social worker in order to enable the veteran independent living. Due to the complexity of functions, only social workers with the highest professional competences are selected for the programme. This position is known in the VA as offering the greatest scope of professional freedom, and the best payment. Along with this freedom increases the responsibility for the veteran's successful functioning, and the need to raise one's professional competences and usefulness [19].

The COVID-19 epidemic is the latest example of a situation in which the challenges faced by the entire nation necessitate changes in the work of the VA. The state of threat, affecting the mental status of both patients and the clinical teams, changes the priorities of the previous hospital organisation system. New procedures for contacts with patients, contacts between professionals, a system of virus testing, and a system of infectious and clean wards must be developed. Social workers solve these problems, as they best know the system and its co-operation with the community. One of the solutions that in many cases quickly substituted the previous system is telehealth, i.e. provision of medical services via telephone and the Internet. The greatest challenge in this type of contact was ensuring the privacy of patients and personal data security [20]. The crisis cause by the pandemic revealed another function of social workers, important in emergencies and situations of increased stress: they can cope with their emotions, and are prepared to teach others how to recognise and control theirs. When such a small element as a virus, invisible to the naked eye, changes the existing procedures and poses a universal life threat, people experience new emotions. Even those whose work consists in helping others can give in to panic and despair. In these situations, social workers are qualified to support those in need, both colleagues, and patients [20].

The presented functions of social workers as providers and coordinators of care for veterans illustrate the importance of their work in the American healthcare system.

This article does not represent the official stance of the U.S. Department of Veterans Affairs. F. Christopher Esmurdoc is the Chief of Social Services, Northeast Ohio VA.

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Serological diagnosis of systemic connective tissue diseases - detection of ANA and ANCA antibodies according to international consensuses and guidelines

Diagnostyka serologiczna układowych chorób tkanki łącznej - wykrywanie przeciwciał ANA i ANCA według międzynarodowych konsensusów i wytycznych

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Abstract. Antinuclear antibodies (ANA) and antineutrophil cytoplasmic antibodies (ANCA) are an essential element in the diagnosis of systemic connective tissue diseases. In recent years, due to the introduction of innovative technologies for their determination, the usefulness of available methods has been reassessed. In 2014, the international EULAR (European League Against Rheumatism) expert group created recommendations for interpreting ANA using different methods. These recommendations highlighted the role of direct immunofluorescence as a reference method and the importance of determining whether we are dealing with a nuclear or cytoplasmic type of glow. In 2016 the guidelines were presented by the International Consensus on ANA Lighting Patterns (ICAP), and in 2017 the guidelines were revised by the international consensus on ANCA in granulomatosis with vasculitis (GPA) and microscopic vasculitis (MPA), according to which the high sensitivity and specificity of antigen-specific PR3-ANCA and MPO-ANCA detection tests allow the abandonment of indirect immunofluorescence tests. The article below discusses the principles for the determination and clinical interpretation of ANA and ANCA antibodies according to international consensuses and guidelines.
Key words: ANA antibodies, ANCA antibodies, ANCA-associated vasculitis, serological diagnostics

Streszczenie. Przeciwciała przeciwjądrowe (ANA) i przeciwciała przeciw cytoplazmie granulocytów obojętnochłonnych (ANCA) są podstawowym elementem diagnostyki układowych chorób tkanki łącznej. W ostatnich latach ze względu na wprowadzenie nowatorskich technologii ich oznaczania ponownie oceniono przydatność dostępnych metod. W 2014 r. międzynarodowa grupa ekspertów EULAR stworzyła rekomendacje dla interpretacji ANA oznaczanych różnymi metodami.
W rekomendacjach tych podkreślono rolę immunofluorescencji bezpośredniej jako metody referencyjnej i istotność określenia, czy mamy do czynienia z jądrowym, czy cytoplazmatycznym typem świecenia. W 2016 r. swoje wytyczne przedstawił Międzynarodowy konsensus w sprawie wzorów świecenia ANA, a w 2017 r. wytyczne zrewidował Międzynarodowy konsensus dotyczący badania ANCA w ziarniniakowatości z zapaleniem naczyń i mikroskopowym zapaleniu naczyń, według których duża czułość i swoistość testów antygenowoswoistych wykrywających PR3-ANCA i MPO ANCA pozwalają na odstąpienie od wykonywania testów immunofluorescencji pośredniej. W poniższym artykule omówiono zasady oznaczania i interpretacji klinicznej ANA i ANCA według międzynarodowych konsensusów i wytycznych.
Słowa kluczowe: przeciwciała ANA, przeciwciała ANCA, diagnostyka serologiczna, ANCA-zależne zapalenia naczyń

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Introduction

Systemic connective tissue diseases (SCTDs) result from impaired immune response, both the cellular and the humoral type. These abnormalities are manifested by the presence of antibodies in the blood serum. In clinical practice, the most frequently used tests include those for antinuclear antibodies (ANA) and antineutrophil cytoplasmic antibodies (ANCA).

The past few years brought many new methods and discoveries in the detection of ANA and ANCA. Apart from the indirect immunofluorescence assay on HEp-2 cells (IIFA-HEp-2) and ELISA tests, advanced solid phase technologies are available, including ALBIA (addressable laser bead immunoassay), chemiluminescence, FEIA (fluorescent-enzyme immunoassay) and LIA (line immunoassays). These methods demonstrate different sensitivity, specificity and antigen profiles, which results in numerous doubts regarding standardisation and the interpretation of their results. Therefore, international groups of experts have developed recommendations for those ordering and interpreting these tests.

Antinuclear antibodies (ANA)

Antinuclear antibodies (ANA) are the basic parameters in the diagnostics of systemic connective tissue diseases. Traditionally, since 1950, they have been determined using indirect immunofluorescence on Hep-2 cells (IIFA-HEp-2) [1, 2]. IIFA became the gold standard in diagnostics due to its high sensitivity to systemic connective tissue disorders (mainly lupus erythematosus and systemic sclerosis), ample body of scientific evidence confirming its practical use, and its historical importance, as results of this test were originally used to determine the criteria for diagnosing diseases.

In recent years, considering the growing need for ANA assays and the time-consuming character of the reference method, alternative methods and techniques for determination of ANA have been developed. Thus, in 2014, the European League Against Rheumatism (EULAR), an international group of experts, published guidelines for interpretation of ANA determined with different methods. These recommendations highlighted the role of direct immunofluorescence as a reference method and the importance of determining whether the observed glow is of nuclear or cytoplasmic type. Also in 2014, International Consensus on ANA Patterns (ICAP) was initiated in order to discuss and develop a consensus regarding uniform reporting of ANA test results and the morphology of luminescence patterns observed in the indirect immunofluorescence assay on Hep-2 cells and to assess whether the cytoplasmic and mitotic patterns should be reported as positive or negative.

2014 EULAR recommendations

Table 1 presents the 2014 EULAR recommendations [3].

In point 10 of the recommendations, the cut-off point for the normal values was established at a titre of 1:160. In 2018, a systematic literature review and retrospective metaanalysis of 13,000 patients with systemic lupus erythematosus, whose ANA antibodies were determined using IIF Hep-2 were conducted. The results confirm the high sensitivity and specificity of the test for ANA in the diagnostics of lupus, and which allowed the titre cut-off to be set at 1:80 [4]. Based on the above metaanalysis, the new 2019 EULAR-ACR classification criteria for systemic lupus erythematosus establish the presence of ANA titre at 1:80 as an entry criterion in the diagnostics of SLE. The reference method is indirect immunofluorescence on Hep-2 cells; due to the ongoing work on the standardisation of serological methods and potential progress in this field, a result of another equivalent solid-phase immunological test can also be considered positive [5].

If the test for ANA is positive, the type of luminescence and titre should be provided, and apart from the nuclear pattern, cytoplasmic and mitotic apparatus luminescence patterns should be described. Information about the titre, and especially about the luminescence pattern, will considerably increase our ability to differentiate between ANA-positive patients who are healthy, and those with systemic connective tissue disorders. ANA titre is higher in patients with SCTDs than in healthy individuals. Nuclear homogeneous, nuclear coarse speckled and nuclear centromere luminescence patterns are observed nearly exclusively in SCTD patients. Dense fine speckled antibodies are typically found in healthy individuals. The most frequent luminescence patterns – nuclear fine speckled – are observed in both healthy individuals and SCTD patients, although in the former the titres are lower [6]. The presented EULAR recommendations and American College of Rheumatology (ACR) guidelines propose that if the screening test is negative and there are no clinical premises suggesting SCTD, there is no need to test for specific antibodies, such as anti-dsDNA or anti-Sm. Exceptions include anti-Jo1 and anti-SSA, as antigen expression on the Hep-2 cells is often insufficient, which may cause false-negative results [7].

Table 1. EULAR 2014 recommendations for detection of autoantibodies to cellular components commonly referred to as ANA [3] **Tabela 1. Rekomendacje EULAR 2014 dotyczące wykrywania przeciwciał do składników komórkowych zwyczajowo określanych jako ANA [3]**
Diagnosis of a systemic connective tissue disease requires a set of specialist laboratory tests (including ANA, anti-dsDNA and ENA).
Tests for ANA, anti-dsDNA and ENA should be considered to detect antibodies in the diagnostics of systemic connective tissue diseases, and in certain other autoimmune disorders.
The first-line study in the diagnostics of SCTDs is a test for ANA.
They are primarily intended as diagnostic tests, and not to monitor the disease progression.
The indirect immunofluorescence (IIFA)* is the reference method for ANA screening. Alternative assays can be used while keeping in mind that false negative and false positive ratio of these methods may be different. Thus, if the clinical suspicion is strong and the alternative method is negative, it is mandatory to perform IIFA.
Diagnostic laboratories should specify the methods used for detecting ANA when reporting their results.
Tests based on a restricted mixture of defined nuclear antigens should not be referred to as ANA test or ANA screen.
Laboratories using in-house assays for detecting ANA, as well as anti-dsDNA and specific anti-ENA antibodies, should standardise each assay according to international standards (e.g., WHO, CDC/IUIS).
For ANA screening by IIFA the conjugate (solution of fluorescein-labelled anti-human antibodies) should consist of fluorochrome-labelled anti-human IgG-specific secondary antibodies.
A proper ANA–IIFA is dependent on reagents, equipment and other local factors, thus the screening dilution should be defined locally; an abnormal ANA result should be the titre above the 95th percentile of a healthy control population. In general, a screening dilution of 1 : 160 on conventional HEp-2(000) substrates is considered suitable for the detection of ANA in adult populations being evaluated for systemic connective tissue diseases.
In the case of a positive ANA test, it is recommended that the luminescence pattern and the highest dilution to demonstrate reactivity be reported.
Luminescence patterns should be reported according to standardised terminology.
Besides nuclear patterns, also cytoplasmic and mitotic apparatus patterns should be reported and specified when possible.
If ANA result is positive, testing for anti-dsDNA antibodies is advised when there is clinical suspicion of SLE.
For anti-dsDNA antibody determination, the CLIFT – indirect immunofluorescence using *Crithidium luciliae* – or Farr assay – radioimmunoassay using the liquid phase method, in which antibodies react with a labelled antigen – offer high clinical specificity; alternative methods, mainly ELISA, may yield lower specificity; therefore, it is recommended that positive results obtained by these methods be confirmed by CLIFT or Farr assay.
The method used for anti-dsDNA antibody analysis should be included in the test result.
Results of anti-dsDNA antibody detection should be reported quantitatively (or semi quantitatively for CLIFT).
For monitoring of SLE, disease activity by quantitative determination of anti-dsDNA antibodies the same method should be used.
In case of a positive ANA screen test, it is recommended to perform specific tests for anti-ENA antibodies.
For anti-ENA antibodies detection the method used should be reported; in the case of discrepancy with IIFA or with clinical suspicion, the use of an additional method should be considered.
Results of assays for antibodies to specific ENA should be reported separately; if the result of an ENA assay is reported as negative, it is necessary to communicate which ENA are present in that assay.
Quantitative determination of positive anti-RNP antibodies is recommended in case of a clinical suspicion of mixed connective tissue disease.
In case of high clinical suspicion, irrespective of the result of the ANA test, tests for antibodies to specific ENA can be ordered, for instance, anti-Sm for suspected SLE, anti-Jo-1 antibodies for clinically suspected IM, or anti-SS-A antibodies for congenital heart block, neonatal lupus, Sjögren's syndrome or subacute cutaneous lupus.
Each laboratory should verify the recommended cut-off for kits used to determine ANA; it is recommended to use age and gender matched sera from healthy subjects from the general local population; cut-off values should be defined as the 95th percentile.
Each laboratory should verify the recommended cut-off for kits used to determine anti-dsDNA and anti-ENA antibodies; it is recommended to use an adequate number of samples from patients with the appropriate autoimmune diseases, disease controls and healthy controls; cut-off points should be defined using ROC curve analysis.
ANA, anti-nuclear antibodies; anti-ENA, extractable nuclear antigen antibodies, anti-dsDNA, anti-double-stranded DNA antibodies; IFA, indirect immunofluorescence assay; WHO, World Health Organisation; CDC, Centres for Disease Control and Prevention; IUIS, International Union of Immunologic Societies; CLIFT, *Crithidia luciliae* immunofluorescence test; ELISA, enzyme-linked immunosorbent assay; SLE, systemic lupus erythematosus; anti-RNP, antibodies against ribonucleoproteins;

Table 2. ANA antibodies: the most commonly observed glow types [3]
Tabela 2. Przeciwciała ANA: najczęstsze stwierdzane typy świecenia [3]

Nuclear patterns	Related antigens	Related diagnosis
Homogeneous	dsDNA, histones, chromatin/nucleosomes	SLE, drug induced SLE or vasculitis, JIA
Coarse speckled	U1-SnRNP, U2–6 snRNP (Sm) – against splicesomal small nuclear RNP	MCTD, SLE, Raynaud's, SSc, SS, UCTD
Fine speckled	SS-A, SS-B, Topoisoimerase-1, (Scl-70)	SLE, SS, SSc, IM, MCTD
Centromere	Kinetochore: CENP-A, B, (C, F)	SSc, Raynaud's
Nucleolar	PM/Scl, URNP, RNA-polymerase, To/Th	SSc, Raynaud's, IM, overlap
Cytoplasmic patterns		
Diffuse	RibP (ribosomal protein P), Jo-1	SLE, IM
Fine speckled	Jo-1 (histidyl-tRNA synthetase), SRP, PDH (pyruvate dehydrogenase – **mitochondria**)	Inflammatory myopathies, DM, PBC, interstitial lung disease
Less commonly recognised patterns – nuclear		
Peripheral	LAP1/2 gp210, nucleoporin p62	SLE, RA, autoimmune liver diseases, IM
Dense fine speckled	DFS70/LEDGF-P75	Healthy subjects
Nucleolar	U3-SnRNP (fibrillarin)	SSc
multiple nuclear dots	Sp100, PML, p80-coilin	PBC, SS
Centrosome	Enolase, pericentrin	SSc, inflammatory diseases
Rare cytoplasmic patterns		Associated with neurological diseases, cerebellar ataxia, PBC and other inflammations

DM, dermatomyositis; IM, inflammatory myopathies; MCTD, mixed connective tissue disease; JIA, juvenile idiopathic arthritis; PBC, primary biliary cirrhosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome; SSc, systemic sclerosis

Importantly, antibody tests should be ordered only based on clinical indications, with a high suspicion and a systemic connective tissue disease, as in low titres they are found in up to 25% of the population, especially in pregnancy, infection, neoplastic diseases or organ-specific autoimmune disorders (e.g. autoimmune thyroiditis) [8].

Table 2 presents the most commonly found antinuclear antibodies [3].

International Consensus on ANA Patterns

The conclusions of the 2016 International Consensus on ANA Patterns (ICAP) are largely consistent with EULAR recommendations. ICAP suggested reporting ANA tests as follows: I Administration of the immunoassay (e.g. IIF on HEp-2, HEP-2000, ALBIA, ELISA etc.)

- Information on the positive or negative test result; reporting the luminescence patters (in the case of IIF) and the level of antibodies (expressed by the titre, intensity of fluorescence, or in the case of alternative methods, by units). In the case of mixed patterns, described as first should be the nuclear patterns, followed by cytoplasmic and mitotic patterns; a titre should be provided after each type of luminescence.
- Interpretation – guidance regarding the need for further testing or possible clinical context for the observed antibodies.

ACR and EASI (European Autoimmunity Standardisation Initiative) recommendations allow to use ANA tests alternative to IIF. Reporting cytoplasmic or mitotic nuclear patterns as ANA-positive or ANA-negative remains controversial: international ACR and EASI recommendations do not take a stance on this issue, suggesting only that cytoplasmic and mitotic patterns should be reported in the test results. ECGSG (European Consensus Finding Study Group on Laboratory Investigation in Rheumatology, EULAR group) suggests classification of cytoplasmic patterns as ANA-negative [9]. According to the authors of this article, Brazilian solution is worth considering, i.e. reporting of cytoplasmic luminescence patterns as ANA-positive, but with a note that ANA test detects autoantigens in all cellular structures, not only in the nucleus. This would also enable a consistent interpretation of ANA testing methods alternative to IIF, which detect as positive both the cytoplasmic and mitotic patterns, and do not allow to distinguish between or describe them. ANA-IIF detection provides the greatest number of clinically valuable information: IIF luminescence pattern and antibody titre

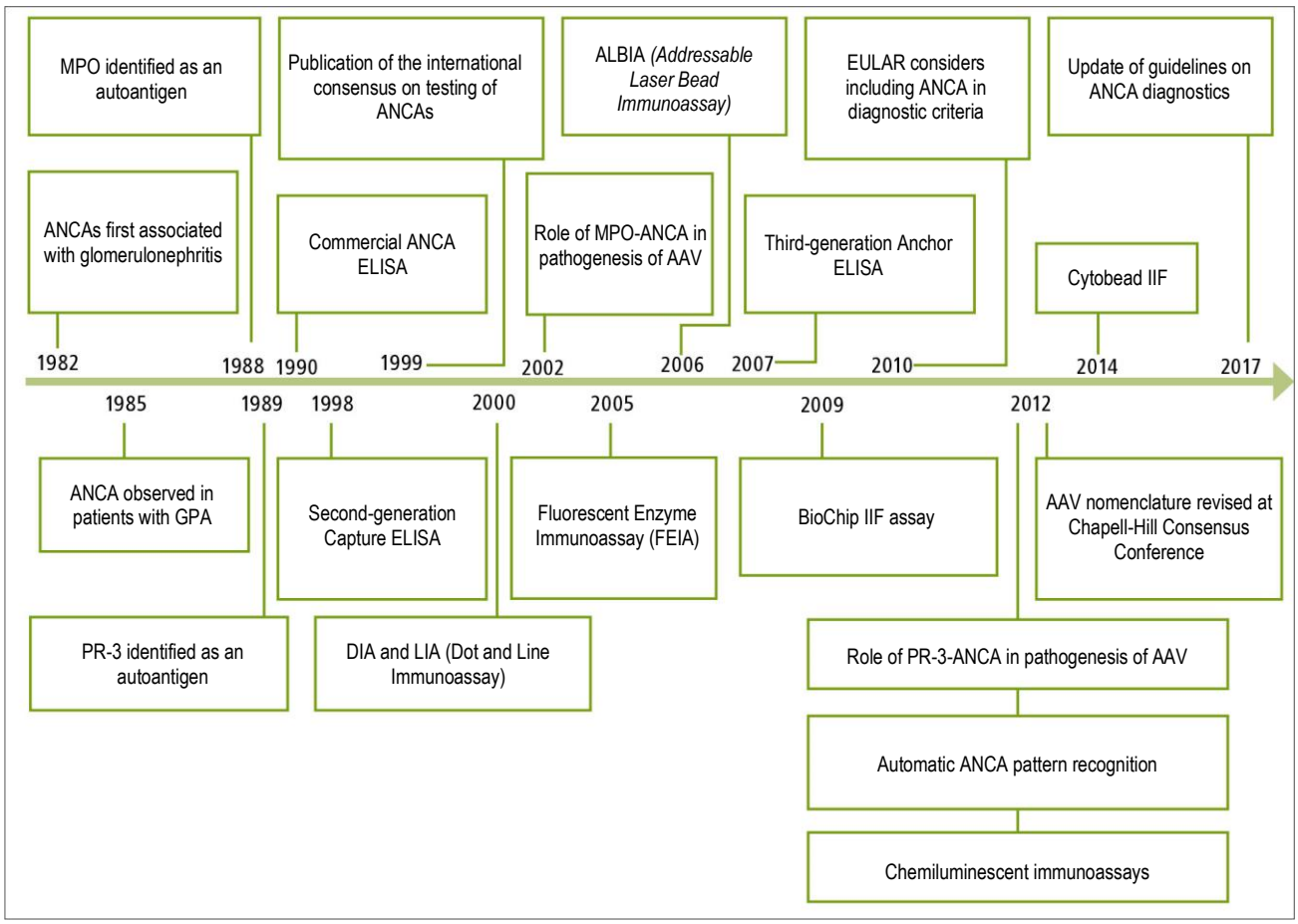

Figure 1. History of ANCA antibodies in vasculitis [18]
Rycina 1. Historia przeciwciał ANCA w zapaleniach naczyń [18]

(which is important from the clinical point of view, as higher titre is associated with a higher likelihood of a systemic connective tissue disease; moreover, higher titre is associated with a greater chance of identifying antigens recognised by antigen-specific tests, and different types of luminescence are related to different diseases). In our opinion, consistent with that of EULAR and ICAP experts, the reference method for ANA detection is IIF on Hep-2 cells.

Anti-neutrophil cytoplasmic antibodies (ANCAs)

Historical perspective

For several decades now, anti-neutrophil cytoplasmic antibodies (ANCAs) have been considered a valuable laboratory parameter in the diagnostics of small-vessel vasculitis, i.e. granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA). Two types of these antibodies are distinguished: c-ANCA (demonstrating cytoplasmic luminescence pattern in indirect immunofluorescence using neutrophils as the source of antigen; in solid-phase immunoassays they react with proteinase 3, and are referred to as PR3-ANCA) and p-ANCA – demonstrating perinuclear pattern; in solid-phase immunoassays they react with myeloperoxidase, and are referred to as MPO-ANCA [10]. First guidelines from 1999 regarding determination of

ANCA in the diagnostics of vasculitis postulated screening tests by indirect immunofluorescence (IIF) on ethanol-fixed neutrophils, and confirmation of positive results by ELISA specific for proteinase 3 (PR3) and myeloperoxidase (MPO) [11]. Metaanalysis from 2001 confirmed a high diagnostic precision of the combination of cytoplasmic IIF pattern (c-ANCA) with PR3-ANCA, or perinuclear IIF pattern (p-ANCA) with MPO-ANCA test [12]. However, numerous new methods and developments in detection of PR3-ANCA and MPO-ANCE occurred since the publication of this consensus. Apart of the original ELISA test, novel solid-phase technologies have been developed, such as addressable laser-beam immunoassays, tests based on chemiluminescence (CLIA), fluorescent-enzyme immunoassays (FEIA), LIA and others. In addition, the method of binding antigens with the solid phase has evolved, from direct binding (1st generation tests), through binding with the use of monoclonal antibody (2nd generation tests) to binding with peptide connector (3rd generation tests) [13 – 15]. The history of ANCA in vasculitis is presented in Figure 1.

New diagnostic trends – multi-centre studies

With progress in technology, the position of IIF as the optimal method in ANCA diagnostics began to be questioned. The first study, from 2008, undermined the value of IIF in ANCA testing be observing that antigen-specific tests are equally effective in detecting ANCA as the algorithm adopted by the international consensus in 1999 [16]. In 2016, a multi-centre study assessed the precision of a broad spectrum of available advanced technologies in detecting MPO-ANCA and PR3-ANCA. In the study serum samples were collected from 251 patients with ANCA-associated vasculitis (GPA and MPA), and from 924 patients in whom the diseases were suspected, but not confirmed; they formed a control group. The sera were tested for cytoplasmic / perinuclear luminescence patterns and atypical ANCA (a-ANCA) using indirect immunofluorescence (IIF) in two independent laboratories, as well as for the presence of PR3-ANCA and MPO-ANCA using seven different immunoassays, including Capture ELISA and Anchor ELISA, CLIA and FEIA. A comparison of various methods for ANCA detection demonstrated a significant variability between the two analysed IIF methods, and a high effectiveness of PR3-ANCA and MPO-ANCA tests using solid-phase immunoassays in differentiation between patients with ANCA-associated vasculitis and healthy individuals. In all the tests specificity for PR3-ANCA was slightly higher than for MPO-ANCA (98-99% vs 96-99%); in the case of the IIF method, the specificity for p-ANCA was much higher than for p-ANCA: 97% and 81%, respectively. The sensitivity of c-ANCA in detection of GPA was 63% vs 75-80% for PR3-ANCA. The sensitivity of p-ANCA in detection of MPA was 89% vs 68-86% for detection of MPO-ANCA [17]. These data provided the basis for revision of the 2017 international consensus on the methods of testing sera for ANCA.

Table 3. International consensus on testing of ANCAs in granulomatosis with polyangiitis (GPA) and microscopic polyangiitis(MPA)2017[18]
Tabela 3. Międzynarodowy konsensus dotyczący badania ANCA w ziarniniakowatości z zapaleniem naczyń (GPA) i mikroskopowym zapaleniu naczyń (MPA) 2017 [18]

PR3-ANCA or MPO-ANCA tests are required only in case of clinical suspicion of AAV; symptoms indicative of AAV: - glomerulonephritis, especially if rapidly progressive; - pulmonary haemorrhage, especially pulmonary renal syndrome; - cutaneous vasculitis with systemic features; - multiple lung nodules; - chronic destructive disease of the upper airways; - prolonged sinusitis or otitis; - subglottic laryngitis; - *mononeuritis multiplex* or other peripheral neuropathy; - retro-orbital mass; - scleritis.
High-quality antigen-specific assays should be used, not IIF.
If results are negative, and there is still a strong suspicion of disease, then use of other immunoassays should be considered to increase the sensitivity; to improve the specificity of tests, another immunoassay may be conducted in cases of low-positive test results.
A diagnosis of AAV cannot be excluded only on the basis of negative ANCA results; in seronegative patients a biopsy of involved organs should be conducted.
ANCAs are highly valuable in the diagnostics of AAC; however, the diagnosis should be based on clinical and pathological symptoms.
Taking into account antibody titre and evaluation of the probability ratio improves the interpretation of the results.
AAV, ANCA-associated vasculitis.

Revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)

The guidelines are presented in Table 3 [18].

Detailed analysis of data confirmed that the probability ratio of AAV increases with increased levels of PR3-ANCA and MPO-ANCA in all immunoassays conducted in the study. ANCA antibodies are very helpful in diagnosing ANCA-associated vasculitis, but diagnosis should be based primarily on clinical symptoms. In up to 15% of patients with AAV ANCAs are not diagnosed, and this situation applies most often to patient with limited granulomatosis with polyangiitis [19]. Therefore, the absence of ANCA antibodies in the serum does not exclude the possibility of GPA [17]. According to the authors of this article, the high sensitivity and specificity of antigen-specific tests for PR3-ANCA and MPO-ANCA, combined with reduced effort required to conduct them, justify forgoing the use of indirect immunofluorescence tests.

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2019 – the first year in the second century of the 5th Military Clinical Hospital with a Polyclinic at the Independent Public Healthcare Centre in Kraków

2019 - pierwszy rok z drugiego stulecia działalności 5. Wojskowego Szpitala Klinicznego z Poliklinika SPZOZ w Krakowie

Artur Rydzyk

Commander of the 5th Military Clinical Hospital with a Polyclinic at the Independent Public Healthcare Centre in Kraków

Abstract. This article is a summary of achievements of one of the oldest, if not the oldest, Polish Military Hospital in 2019. The hospital obtained an accreditation certificate from the Ministry of Health, achieving compliance at the 82% level with the Healthcare Quality Assessment Centre accreditation standards. The Skin Cancer and Melanoma Treatment Center and the General, Plastic and Reconstructive Surgery Department were established. The Hospital Emergency Department was expanded and provided with additional equipment, and, looking further ahead, a major investment was initiated - the construction of an integrated operating theatre. The hospital has been awarded prizes and awards: "Outstanding Medical Facility 2019" and "Manager of 2019 in Health Care-public health-care institution". The article also acknowledges that there is very little you can do without the commitment and hard work of the entire hospital staff.
Key words: 5th Military Clinical Hospital with a Polyclinic

Streszczenie. Artykuł stanowi podsumowanie osiągnięć jednego z najstarszych - jeżeli nie najstarszego - Szpitala Wojska Polskiego w roku 2019. Szpital otrzymał certyfikat akredytacyjny Ministra Zdrowia, uzyskując 82% poziomu spełnienia standardów akredytacyjnych Centrum Monitorowania Jakości w Ochronie Zdrowia, utworzono Centrum Leczenia Nowotworów Skóry i Czerniaka oraz Oddział Chirurgii Ogólnej, Plastycznej i Rekonstrukcyjnej, rozbudowano i doposażono Szpitalny Oddział Ratunkowy, a celując w przyszłość, rozpoczęto wielką inwestycję - budowę zintegrowanego bloku operacyjnego. Szpitalowi przyznano również nagrody i wyróżnienia: „Wybitna Placówka Medyczna 2019" oraz „Menedżer Roku 2019 w Ochronie Zdrowia - placówki publiczne". Artykuł jest także formą podziękowania, gdyż niewiele można osiągnąć bez zaangażowania i ciężkiej pracy całej załogi szpitala.
Słowa kluczowe: 5. Wojskowy Szpital Kliniczny z Poliklinika

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The past year has been a busy time for us as we faced and responded to a number of challenges as well as implementing several important projects and investments. We improved the quality and safety of the health services we provide. We also expanded the Hospital Emergency Department and equipped it with some new apparatus. We reached 82% compliance with the Healthcare Quality Assessment Centre accreditation standards, where the required minimum level is 75%. We also received prestigious awards and distinctions, i.e. "Outstanding Medical Facility 2019" and "Manager of 2019 in Health Care-public health-care institution". These are just the major achievements of the first year of the second century of operation of the 5th Military Clinical Hospital with Polyclinic in Krakow.

Figure 1. Hospital Emergency Department opening ceremony. Left to right: Aurelia Ostrowska, MD, PhD – Director of the Military Medical Service Department, Piotr Ćwik – Governor of the Małopolska Region, Wojciech Skurkiewicz – Deputy Minister - Secretary of State in the Ministry of National Defence, Agnieszka Pietraszewska-Macheta – Assistant Director MOW NFZ for uniformed services, Col. Artur Rydzyk, MD – Commander of the Hospital.
Rycina 1. Otwarcie Szpitalnego Oddziału Ratunkowego. Od lewej: dr Aurelia Ostrowska-dyrektor Departamentu Wojskowej Służby Zdrowia, Piotr Ćwik - wojewoda małopolski, Wojciech Skurkiewicz - sekretarz stanu w Ministerstwie Obrony Narodowej, Agnieszka Pietraszewska-Macheta - zastępca dyrektora ds. służb mundurowych Małopolskiego Oddziału Wojewódzkiego Narodowego Funduszu Zdrowia, płk lek. Artur Rydzyk - komendant szpitala.

The Krakow Military Hospital is one of the oldest and longest operating institutions in the Polish Army that has remained in one place throughout its entire existence. The history of the hospital is closely connected with the first days after Poland regained its independence, as early as October 1918. By the decision of the Polish Liquidation Committee, the Polish administration was to expropriate the former Austrian Military Hospital. This was substantiated by the Polish Army by establishing the Regional Military Hospital.

Here we are now, one hundred years later. We might know little about the achievements of the hospital staff in 1919, except perhaps for the daily struggle for the health and lives of its patients and the shortage of supplies. The year 2019, on the other hand, was rich in important events that will certainly affect the future of our facility.

On 30 September 2019, the Hospital Emergency Department of the 5th Military Teaching Hospital with a Polyclinic in Krakow was officially opened after all the works connected with the expansion and retrofitting were completed. The event was held in the presence of the Secretary of State at the Ministry of National Defence, Mr Wojciech Skurkiewicz (Fig. 1). The investment project was co-financed with European Funds at PLN 5,950,000.00 and subsidised by the Ministry of National Defence at PLN 12,674,600.00. The hospital also allocated nearly PLN 1 million of its own funds for the undertaking. The construction works were finished within a mere 12 months. As the next step in the hospital

modernisation process, this investment provided the Polish Army, the city of Krakow and the entire region with a modern, functional Hospital Emergency Department, highly accessible to patients. The moment of project completion coincided with the relocation of the University Hospital in Krakow to a new site on the outskirts of the city. The Hospital Emergency Department of the 5th The Military Clinical Hospital with a Polyclinic has thus become the most strategically important, the largest, but also the busiest emergency room in the city centre. The event was accompanied by the scientific symposium "Clinical, rescue and battlefield medicine".

Last year our facility inaugurated the Skin and Melanoma Treatment Centre and the Department of General, Plastic and Reconstructive Surgery. We also took advantage of the clinical grants from the Ministry of National Defence, the Ministry of Health and our own funds. The centre is a response to the increasing number of skin cancers, including melanoma, in the light of the insufficient number of specialist medical facilities which provide plastic surgery services. Our team of qualified dermatologists and oncological surgeons provide specialist help to patients. We offer a wide range of surgical and conservative therapies, including the treatment of congenital defects of the face, hands and other parts of the body as well as post-traumatic deformities (scars, tissue and skin defects).

On 29 June 2019, the citizens of Kraków could participate in a "White Saturday" at the hospital and undergo free diagnostic and laboratory tests, consult specialists and listen to lectures, talks and recommendations. Held in cooperation with the Krakow authorities, the event attracted great interest from the residents, as reported by the local radio and television.

On 16-18 December 2019, the inspectors of the Healthcare Quality Monitoring Centre conducted an accreditation review of the hospital. This covered all the organisational units connected with hospital operation. At the beginning of 2020, we were informed that we had fulfilled the accreditation standards of the Healthcare Quality Assessment Centre at the level of 82%, while the minimum required level was 75%. Therefore, we received accreditation from the Minister of Health in the form of an accreditation certificate.

Last year also saw the completion of several clinical grants financed by the Ministry of National Defence, the Ministry of Health and own funds. These included the following projects:

- "Development of endoscopic surgery of the skull base in the 5th Military Clinical Hospital with a Polyclinic in Krakow" (clinical grant implemented by the Clinical Department of Otolaryngology);
- "Creation of a multidisciplinary military centre for the diagnosis of early-stage cancers of the upper gastrointestinal tract, pancreas and liver in the 5th Military Clinical Hospital with a Polyclinic" (clinical grant implemented by the Department of Internal Diseases and the Department of Gastroenterology);
- "Establishment of an innovative interdisciplinary centre for comprehensive diagnostics and reconstructive treatment after injuries of the musculoskeletal system. Preparing a team of surgeons to provide replantation services at the 5th Military Clinical Hospital with a Polyclinic in Krakow" (clinical grant implemented by the Department of Trauma Surgery and Orthopaedics);
- "Modern comprehensive treatment in the field of general and oncological surgery with the simultaneous establishment of the Training Centre for Combat Surgery and Multi-organ Injury at the 5th Military Clinical Hospital with a Polyclinic in Krakow" (clinical grant implemented by the General, Oncological and Vascular Surgery Clinic);
- "National programme to reduce chronic lung disease mortality by creating rooms for non-invasive mechanical ventilation" (clinical grant implemented by the Clinical Department of Tuberculosis and Lung Diseases).

Since the number of facilities accredited for specialisation training increased by 10 last year, the hospital currently has 119 accredited places for specialist training in 17 fields of medicine. As of 31 December 2019, 93 doctors and dentists, including 22 professional soldiers, were undergoing specialist training at the Hospital.

The past year also proved intense in terms of organisational and training work, as we introduced accreditation standards to be applied in the hospital, developed and implemented of a number of projects and procedures, and accommodated organisational changes. Virtually the entire hospital staff was involved in these projects.

Their efforts and commitment as well as their dedication to saving life and health were acknowledged and appreciated in the form of several distinctions.

- These included the "Outstanding Medical Facility 2019" award granted by the Polish Federation of Entrepreneurs and Employers – PRZEDSIEBIORCY.PL and presented on 14 June 2019 in Warsaw at the "30 Years of Freedom of the Republic of Poland" Grand Gala.
- The Minister of Health honoured and decorated 10 employees of our hospital who actively participated in saving the life and health of the people injured in the lightning strike at the Giewont dome on 22 August 2019. The award ceremony was held on 16 December 2019 in Warsaw at the Ministry of Health. We are proud that our employees were applauded for their

commitment and effort and received such an honourable distinction.

- In the "Success of the Year 2019 in Healthcare – Medicine Leaders" competition, the hospital commander won the "Manager of the Year 2019 in Healthcare – public institutions" title. The award was presented at an event held by "Menedżer Zdrowia", "Kurier Medyczny" and "Termedia" at the Royal Castle in Warsaw on 16 January 2020.

We are pleased to announce that the undeniable successes of the hospital over the past year, as follows:

- we maintained a high position as a medical centre in Krakow and the region, especially in the fields of otorhinolaryngology, neurosurgery, nuclear medicine, gastroenterology, orthopaedics and traumatology of the musculoskeletal system;
- we acquired modern medical equipment and apparatus, including magnetic resonance imaging scanner and a computed tomography machine;
- we launched the largest investment in the history of the hospital, i.e. the construction of an integrated operating theatre (a design office was selected and the design intent developed);
- we implemented the projects and undertakings directly related to the continuous improvement of access to health services, the quality of services provided, maintaining high trust and recognition among patients, high level of services as assessed by other medical entities as well as very high recognition by state and local authorities;
- we remained one of the key medical entities to ensure health security in special situations and emergencies, e.g. we provided specialised medical care for injured soldiers evacuated home from the deployment area, medical support during important international events organised in Krakow or in the region, and were prepared to use crisis management strategies.

Looking back on the past year's accomplishments, we are mindful of the many challenges which lie ahead in our second century of operations.

The fact that we achieved such a high result in the accreditation review, and were awarded prizes and distinctions, results directly from the commitment and hard work of the entire hospital staff, for which I am deeply grateful.

Małgorzata Kalicińska-Buraczewska's reminiscences about her family, friends and Ujazdowski Hospital

Wspomnienia Pani Małgorzaty Kalicińskiej-Buraczewskiej o rodzinie, przyjaciołach i Szpitalu Ujazdowskim

Stanisław Ilnicki

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Abstract The subject of this article is reminiscences of Kalicińska-Buraczewska, a daughter of a military physician, Maj. Wiktor Kaliciński, MD, PhD (1896-1940), concerning her family, friends and the Ujazdowski Hospital, where she lived until September 1939. In her reminiscences, she describes her father's lineage, his military service during the fight for an independent Poland, his work at the Anatomic Pathology and X-Ray Unit of the Ujazdowski Hospital, classes with cadet-students of the Medicine Faculty at the Warsaw University and the job of secretary for the "Cancers" magazine Editorial Office. She mentioned her father's service in the Polish Legions of the First World War and his role in the embalming of the Marshal Józef Piłsudski's corpse. She describes the neighbours of her family, co-residents of Ujazdów, and the friendship with the family of Col. Jan Nelken, MD, PhD (1878-1940), the head of the Ujazdowski Hospital Psychiatric Ward. Moreover, she presents the tragic fate of both families during the Second World War and the German occupation of Poland: the death of both her father and doctor Jan Nelken in Katyn, and the death of doctor Nelken's wife Irena Borkowska-Nelken, PhD (1899-1944) and their daughter Anna (1926-1944) in the Warsaw Uprising. Her reminiscences also cover the post-war history of her family and of Jan Nelken Jr., and her activity in the Ujazdowski Hospital Association.
Key words: Ujazdowski Hospital, 1918-1939, Katyn Massacre, military physicians.

Streszczenie Tematem artykułu są wspomnienia Pani Małgorzaty Kalicińskiej-Buraczewskiej, córki lekarza wojskowego, mjr. dr. med. Wiktora Kalicińskiego (1896-1940), o rodzinie, przyjaciołach i Szpitalu Ujazdowskim, na terenie którego mieszkała do września 1939 r. Opisała w nich rodowód swego ojca, przebieg jego służby wojskowej w okresie walk o niepodległość, pracę w Pracowni Anatomopatologiczej i Radiologicznej Szpitala Ujazdowskiego, zajęcia z podchorążymi-studentami Wydziału Lekarskiego Uniwersytetu Warszawskiego, pracę na stanowisku sekretarza Redakcji czasopisma „Nowotwory". Wspomniała o służbie ojca w Legionach oraz o jego roli w balsamacji zwłok marszałka Józefa Piłsudskiego.. Opisała krąg sąsiadów swojej rodziny, współmieszkańców Ujazdowa, oraz przyjaźń z rodziną płk. dr. med. Jana Nelkena (1878-1940), kierownika naukowego Oddziału Psychiatrycznego Szpitala Ujazdowskiego. Przedstawiła tragiczne losy wojenne i okupacyjne obu rodzin: śmierć ojca i dr Nelkena w Katyniu oraz jego żony, dr Ireny Borkowskiej-Nelkenowej (1899-1944), i córki Anny (1926-1944) w Powstaniu Warszawskim. Opisała powojenne losy swojej rodziny i Jana Nelkena juniora oraz udział w działalności Stowarzyszenia Szpital Ujazdowski.
Słowa kluczowe: lekarze wojskowi, 1918-1939, Zbrodnia Katyńska Szpital Ujazdowski

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During the Easter meeting of employees and friends of the Hospital on Szaserów on 22 March 2018, General Professor Grzegorz Gielerak, director of the Military Institute of Medicine, presented Małgorzata Kalicińska-Buraczewska with the statuette of the "Animus Fortis" (Mighty Spirit) award [1, 2]. He did this in tribute to her father, Maj. dr. med. Wiktor Kaliciński, secretary general of the Committee for the Construction of the Paramedic Monument, murdered in Katyn, the prototype of the statuette [3, 4]. He did it also in recognition of the laureate's personal merits in preserving the memory of the Ujazdowski Hospital – the predecessor of the Hospital on Szaserów Street (Fig. 1).

Figure 1. Ceremony of awarding Małgorzata Kalicińska-Buraczewska with the *Animus Fortis 2017* Award [1]

Rycina 1. Akt wręczenia Pani Małgorzacie Kalicińskiej-Buraczewskiej nagrody *Animus Fortis 2017* [1]

As we were revisiting that event, we asked Małgorzata Kalicińska-Buraczewska to tell the readers of the "Military Physician" the story of her father and other people closely associated with the Ujazdowski Hospital, where she lived until 6 September 1939.

My father, Wiktor Franciszek Kaliciński (Fig. 2), was born on 18 September 1896, in Kraków. He was the third of ten children of Tadeusz Roman, a carpenter, and Maria née Buratowska. My grandfather joined the Polish Legions during World War I along with my father and his two elder brothers, Eugeniusz and Julian. The fourth brother, Wacław, volunteered to serve in the Polish-Soviet War in 1920. At the age of only 18, his entire company died in Dytiatyn, which was later dubbed the 'Polish Thermopylae' due to a similar imbalance in battle. Wacław was posthumously honoured with the Class V of the Virtuti Militari military medal [6]. The fifth brother died at an army firing range while he was performing military service.

During World War II, my father's nephew Wacław, the son of Julian, was arrested in a round-up. A student of the High School of Stanislaw Staszic in Warsaw, Wacław was deported to the Stutthof concentration camp and

Figure 2. Portrait of Lt. Wiktor Kaliciński, MD, PhD, drawn 18/10/1924 by Lt. Jan Kochanowski, MD, PhD [5]

Rycina 2. Portret por. dr. med. Wiktora Kalicińskiego wykonany przez por. dr. med. Jana Kochanowskiego 18.10.1924 r. [5]

eventually died during the 1945 evacuation. My father's youngest sister, Janina, was a coder for the Poznań Army. Halina and Maria, daughters of my father's other sister, Kazimiera, were teleprinter operators at the Main Post Office in Warsaw. All three were arrested for conspiracy, but they survived both the Pawiak prison and Auschwitz. Aunt Janina was also in Ravensbruck when it was liberated by the Allied forces in 1945. My cousins only survived because they were brave enough to escape from the death march after the evacuation in January 1945.

This is what I can say about my father's ancestry. Without going into too much detail, already available in other publications [7-10], I can describe some essential items from his biography.

He spent his first years of education in Lviv and then attended an 8-class classical gymnasium in Nowy Targ, where he obtained his matura diploma. On 6 August 1914, he joined the 6th Battalion of the First Brigade of the Polish Legions. In November 1914, he was wounded in the Battle of Krzywopłoty. He enrolled in a university course at the Faculty of Medicine of the Jagiellonian University for the 1915/1916 academic year. He joined the Polish Armed Forces in 1918, and in June 1919 he was wounded again. A few months later, in November of that year, he was appointed a second lieutenant and assigned to the Headquarters of the Mountain Rifle Division of the Podhale region. Between June 1920 and April 1921, he was an assistant doctor on medical trains at the front, and

Figure 3. General Andrzej Galica and Medical Train No. 53, Bielsko, 25 January 1921. Left to right: Capt. Nowicki, Maj. Miodoński, Mrs Rozwadowska, Gen. A. Galica, Capt. F. Bataszeskul, Lt. W. Kaliciński [5].

Rycina 3. Generał Andrzej Galica w pociągu sanitarnym nr 53, Bielsko dnia 25.01.1921. Od lewej: kpt. Nowicki, mjr Miodoński, pani Rozwadowska, gen. A. Galica, kpt. F. Bataszeskul, ppor. W. Kaliciński [5].

Figure 4. Team of Sanitary Training Center Radiology Ward (1934). First row, left to right: Col. Witold Zawadowski, Capt. Mieczysław Ossowski, Capt. Jan Kochanowski, Capt. Stanisław Wszelaki and Maj. Wiktor Kaliciński; second row: Maria Werkenthin, MD, PhD (second from left); at the top Srg. Franciszek Smurawski [5].

Rycina 4. Zespół Oddziału Radiologicznego Centrum Wyszkolenia Sanitarnego (1934). I rząd od lewej: płk Witold Zawadowski, kpt Mieczysław Ossowski, kpt Jan Kochanowski, kpt Stanisław Wszelaki i mjr Wiktor Kaliciński; II rząd, druga od lewej dr Maria W. Werkenthin; u góry st. sierż. Franciszek Smurawski [5].

then during the Third Silesian Uprising (Fig. 3). In October 1921, he was sent off back to Jagiellonian University so that he could continue his studies.

In 1924, my father was transferred to Warsaw and assigned to the Military Sanitary School. He continued his studies at the Faculty of Medicine of the University of Warsaw. Finally, in 1925, he obtained a Doctor of General Medicine degree. He was appointed junior head in the Anatomopathology Laboratory of the Officer's Medical School. This was the field in which he specialised under the supervision of Col. MD, PhD Kazimierz Kuligowski [11]. He was successively promoted to the higher officer ranks and in 1934, as a major, he became the head of the Department of Anatomopathology of the Medical Training Center (CWSan). He remained in that position until the war. In addition to his everyday hospital duties, my father gave histology and histopathology classes for second and fifth year military students at the Faculty of Medicine of the University of Warsaw. Over the years 1929-1939, he was also the secretary of the editorial board of the magazine of the Radium Institute [12]. In addition, he specialised in the field of radiology under the guidance of Col. Prof. Witold Zawadoswki (Fig. 4). In 1935 as a radiology specialist, he took the chair of Anti-tuberculosis Practice at 23 Miodowa Street, where he would spend his afternoons [13, 14].

Figure 5. Funeral of the Marshal of Poland Józef Piłsudski at the Wawel Royal Castle, 18 May 1935. Aleksandra Piłsudska stands by the casket, in the first row, left to right - Gen. Stanisław Rouppert, Maj. Wiktor Kaliciński, Assistant Professor Józef Laskowski, Gen. Bolesław Wieniawa-Długoszowski and Capt. Mieczysław Lepecki [21].

Rycina 5. Pogrzeb marszałka Polski Józefa Piłsudskiego na Wawelu, 18.05.1935 r. Przy trumnie Pani Aleksandra Piłsudska, w I rzędzie od lewej stoją: gen. Stanisław Rouppert, mjr Wiktor Kaliciński, doc. Józef Laskowski, gen. Bolesław Wieniawa-Długoszowski i kpt. Mieczysław Lepecki [21].

It would be rather difficult to list all the spheres of activity in which my father was involved [10, 15]. What, however, might prove interesting for the readers of "Military Physician", where he published two scientific papers [16, 17], is the well-known situation regarding the embalming of the body of Marshal Józef Piłsudski [18]. Together with Assistant Professor Józef Laskowski from

Figure 6. With her parents and brother on Gubałówka Peak, 1937 [5]
Rycina 6. Z rodzicami i bratem na Gubałówce, 1937 r. [5]

the Radium Institute [19], my father conducted this procedure on 12 May 1935 at the Belweder Palace. As regards the stories which suggest that "the coffin had to be soldered because the embalming attempt had failed", I would like to say that none of this has been confirmed by regular inspections carried out by a specialist commission. My parents and I visited the Wawel crypt in the summer of 1937 on our return home from a holiday and there were no signs on the Marshal's face that would indicate it was putrefying. From what I remember, the biggest problem was to effectively protect the sarcophagus against moisture in the Wawel crypt, and the Marshal's uniform had to be changed several times when it became mouldy (Fig. 5) [21].

During his transfer to study in Kraków in 1921, my father met his future wife, my mother – Anna née Drezińska. She was, as one would say, a good girl from a good home. After attending a finishing school run by nuns in Bielsko (now Bielsko-Biała), she worked in a military office.

They were married in Warsaw in 1926. A year later I was born, and my brother Kajetan 3 years later (Fig. 6) [5].

We moved to Ujazdów, where we initially lived in a studio apartment at the castle, and in a two-room "general" apartment a year later. It did not survive the war. General Dr. Kołłątaj-Srzednicki [11, 22] and General Wacław Karaszewicz-Tokarzewski [23] lived on the first floor with their families. There were also two studios, where tenants moved in and out. On the second floor, there were two four-room apartments. One was occupied by us, and the other by Dr Włodzimierz Dobrowolski [10, 11] and his family. There were also two other two-room apartments, where, at different times, Sgt. Grzeszczuk, secretary at the Main Headquarters, and Capt. Pauker of the quartermaster's department lived. The people on the ground floor included the caretaker, Mr Królak, Dr Wacław Kafliński [11,24], Dr Adam Kaczurba [11,24], the fencer – sergeant Radtke [11] and Plut. Nalepka, subordinate of the school doctor, Maj. Józef Wiloch [11].

The kitchen window of our apartment overlooked the closed courtyard of the Department of Mental Diseases, known as "Two", or the "Madhouse" as the kids would say, for which their parents would then scold them. My mother threatened to forbid from me from entering the kitchen if I kept sitting by the window and watching what was happening in the garden. 'Those are sick people', she would add. The scientific director of this department was Col. Jan Nelken, MD. He and his young wife had two children – Ania, who was 9 months older than me, and Janek, who was 5 years younger than me. Mrs Nelken, Irena née Borkowski, had a PhD in Philosophy and was my mother's peer. I am so particular about this because the lives of our families became tragically intertwined during the war, after our "idyllic angelic childhood" ended.

Doctor Nelken and his wife were looking for a playmate for their daughter. Mrs Nelken was then working as a Polish teacher at the Department of Adult Education of the Ministry of Religious Denominations and Public Education at 25 Szucha Avenue. We lived quite close – my parents and I in the hospital area while the Nelkens at 6 Matejki Street. I met Ania where we would later go to play, i.e. in the garden part of the Psychiatric Ward. That is where Ania used to come with her sitter. This continued until Dr Nelken retired in 1934. Then, together with our younger brothers, Kajetan and Janek, we played alternately at Matejki and at our place, when the doctor was seeing patients there. Mrs Nelken's mother lived with them. She was the niece of the composer Zygmunt Noskowski and she would read us books, play the piano and teach songs.

The thing that impressed me the most in their place was the study – a large, beautiful room with a proper library, bookcases covered with a curtain. The study was used as a living room on a daily basis. There was a leather sofa, which may also have been used as a psychoanalyst's couch since Dr Nelken did treat his patients using that method [25].

Ania Nelken and I attended the Military Family Kindergarten. It was located alternately either in a wing of

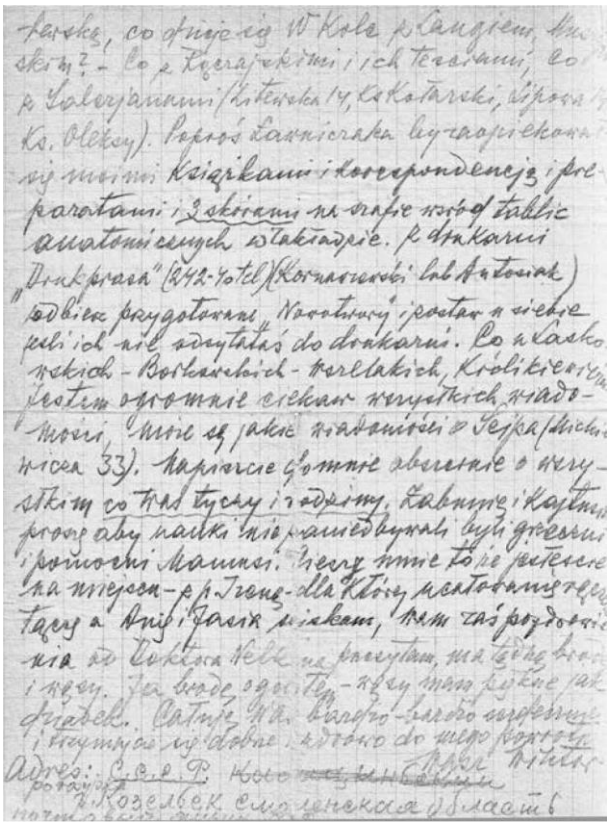

Figure 7. Excerpt from a letter sent by Maj. Wiktor Kaliciński, MD, PhD to his family from the Kozielsk POW camp [5]

Rycina 7. Fragment listu mjr. dr. med. Wiktora Kalicińskiego z obozu jenieckiego w Kozielsku do rodziny [5]

the Belweder Palace or the GISZ (the Main Inspectorate of the Armed Forces) building [26]. Then we went to different schools. I went to the Military Family School at 49 Szucha Avenue, in the wing of the now-defunct building of the Ministry of Military Affairs. Ania attended the private school of Mrs Helena Szalaj (Maria Curie-Skłodowska's elder sister) in Smolna Street. But we kept in touch anyway. During the holidays, my brothers and I would travel to Królewska Góra in Konstancin, where the Nelkens had a summer house designed by a couple of famous architects, Mr and Mrs Syrkus [27].

When the war began, my father had no mobilization assignment at first. According to documents from March 1939 was assigned to take command of a military hospital in Łódź, but this was soon cancelled. When he reported to Gen. [Stanisław] Rouppert at the beginning of June to request a new assignment, all he was told was, "Take it easy, you'll find out in time." On the night of 5 September, Assistant Professor Laskowski visited us to say goodbye. He had received a mobilisation assignment for a medical train. When my father told him that he had not been assigned, he replied, "Then go with me." Yet the next day my father joined the eastbound evacuation of the 104th Military Hospital, which was founded on the basis of the Ujazdowski Hospital. Dr Nelken, 61, diabetic and deemed "unfit for military service in the field," also went to war without a mobilisation assignment. He did so, just like my father, out of a sense of duty, I believe.

On 6 September our Ujazdów apartment was destroyed by artillery fire. All the residents were ordered to leave the hospital grounds. Mrs Nelken took us in and we lived in their flat in Matejki Street until the end of October 1939. At the beginning of November, we moved to 47 Kazimierzowska Street. Before Christmas, we received the only letter from my father, sent on 28 November 1939, from Kozielsk (fig. 7) [5].

Mrs Małgorzata Kalicińska-Buraczewska consented to publish a fragment of that letter, which illustrates her father's concerns while he was being held captive. "(...) Ask Ławniczak to take care of my books, correspondence as well as the preparations and three skins on the cupboard – they are among the anatomical boards in the facility. Collect the batch of "Nowotwory" from the Drukpress printing house (tel. 242-70) (Kornaszewski or Antosiak) and take them with you, unless you have sent them back to the printing house. How are the Laskowskis [19] – Borkowskis [10, 28, 29] – Wszelakis [11, 30], and Królikiewicz? [10, 11, 29] I want to catch up on all the news. Are there, perhaps, any messages from Seip (Mickiewicza 33) [31]? Please write to me extensively about everything that concerns you and your families. I hope Żabusia and Kajtuś are not neglecting their education – please be polite and helpful to mum. I am glad that you are together with Mrs. Nelken. Please give her my regards and hug Ania and Jaś from me. Dr Nelken sends his best wishes (...) Address: С.С.С.Р. Козельск, Смоленская область."

We found out about my father's death on 28 May 1943, from a short passage in the "Nowy Kurier Warszawski", a so-called reptile newspaper. It stated that the Germans had discovered the mass graves of Polish officers in Katyn [32, 33]. My father's body was identified by Dr Wodziński, a member of the international technical commission of the Red Cross, who conducted the exhumation. He had known my father personally.

In 1940, we moved from Kazimierzowska to the apartment of Uncle Julian at 4 Nalewki Street. He was held in captivity at the time. My mother lived there with my brother until the uprising, working as a medical secretary in the radiological clinic at 23 Miodowa Street, which my father had managed before the war. After my aunts and cousins had been arrested in 1942, as I mentioned earlier, my mother sent me to our family in Tenczynek. There, after taking secret classes, I graduated from gymnasium in 1944. The matura exam was disguised as a social event but, still, mayhem broke out. All the participants

were arrested. The five professors who examined us were sent to the prison in Montelupich Street. They only managed to escape death because Soviet troops had entered Kraków. I was released along with my friends, but they kept me under supervision. After the war, my school-leaving examination certificate was authenticated.

My 14-year-old brother Kajetan, nom de guerre "Kajtek", was injured during the uprising. Buried under the rubble after the prison in Daniłowiczowska Street was destroyed, he was rescued by his commander, Lt. Olędzki [34]. After the uprising, my mother joined the civilians marching from Warsaw to Pruszków. She survived in a village near Opoczno thanks to the help of Mrs Kaflińska, the wife of Maj. Wacław Kafliński MD, who was our neighbour in Ujazdów [24]. Evacuated from the hospital, my brother jumped out of a train and reached Milanówek. At the end of October 1944, he arrived in Tenczynek on the same day as my mother. We moved to Krakow in 1945. I applied to study medicine, but there was a *numerus clausus* limit for women. So I enrolled in a biology course. During the second year, I asked Dean Supniewski for a transfer to medicine, but he refused, claiming he was "against forming medical clans". My mother took a job in the Social Insurance Company as a medical secretary, and I worked as a governess in the family of Juliusz Leo (1861-1918), the President of Krakow. Later, I worked for a radio agency. In 1946, the three of us returned to Warsaw. We moved to Bernerowo on Telefoniczna Street. When the Military University of Technology was established in 1950, we were evicted and moved to Dzielna Street. My mother lived there until her death. Following the advice of an attorney, my mother applied for a war widow's pension in 1956. The military authorities rejected her motion, claiming "there are no documents related to [my father's] military service." Until her retirement, she was a secretary at the Art Institute of the Polish Academy of Sciences in Długa Street. She died in 1982 and was buried in Stare Powązki. My brother obtained a medical degree. For several years, he was a WHO expert on family matters as a paediatrician. He worked in Laos and the Philippines. He died in 2007.

In 1947, I ran into Prof. Laskowski in Warsaw. He offered me a job as a laboratory technician at the radiotherapy department of the Radium Institute in Wawelska Street. I worked there until 1956. Then I moved to the Institute of Nuclear Research at the Radiological Protection Laboratory, and subsequently to the Central Laboratory of Sera and Vaccines at the Radioimmunology Laboratory on Chełmska Street. I retired in 1982.

Colonel Jan Nelken MD was murdered in Katyn in March 1940. A month before my father. They both rest at the Katyn War Cemetery [29]. They were posthumously promoted in 2008 – Dr. Nelken to the rank of general [35], whereas my father to the rank of lieutenant colonel [36]. During the siege of Warsaw, Mrs Nelken worked as a nurse in the PRC clinic. She was an active underground member throughout the occupation. She died on 20 August 1944, under the rubble of the bombed insurgent hospital at 24 Miodowa Street. Her body was exhumed after the war, but not identified. She was buried in a mass grave at the Warsaw Insurgents Cemetery in Wola [25, 37]. Ania Nelkenówna passed her matura exam in May 1944, after taking secret classes at the Secondary School of Jadwiga Kowalczykówna and Jadwiga Jawurkówna. During the uprising, she was a liaison officer in the "Zośka" Home Army Battalion. On 23 September 1944, she was murdered by the Germans in the basement of a building in Solec, together with the four wounded insurgents she was minding. Awarded the Cross of Valour posthumously, she is buried in the mass grave of the "Zośka" Battalion soldiers at the Powązki Military Cemetery [25, 37].

The apartment at 23 Śniadeckich Street, where Mrs Nelken and the children lived after being evicted from Matejki Street, burnt down completely during the uprising with everything inside. Not a single family photograph of the Nelken family has survived [38]. The only item left was a photo of Mrs Nelken in her student record book. It was kept in the archives of the University of Warsaw [39]. Apart from our childhood photo, the only picture of Ania Nelkenówna was an anonymous image captured in the frame of the uprising chronicle film. I identified her in 1989 in response to the appeal by the "Stolica" weekly [40].

After the uprising, the 13-year-old Janek Nelken remained in an orphanage in Zakopane. Despite all the obstacles a son of a "Sanation officer" could have faced, he graduated from the University of Warsaw and obtained a Doctor of Law degree. He pursued a very promising academic career, continuing research, among others, on issues started by his father. Unfortunately, it was interrupted by a disease. After his death in 2019, he was buried in the grave of his grandparents at the Evangelical-Augsburg Cemetery on Młynarska Street.

As for me, after my husband's death in 1992 [41, 42], I became involved in the activities of the Association of the Creators of the Castle Museum and Military Hospital in Ujazdów, now transformed into the Ujazdowski Castle Association. Throughout the entire occupation and after the war as well, we experienced the cordial support of my father's friends. Now, within the modest bounds of my possibilities, I wish to contribute to saving from oblivion the memory of those people close to me and the matters to which they devoted their lives.

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