DOI: 10.17816/KMJ2020-913

Dermatomyositis syndrome in small cell lung cancer

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Abstract

Dermatomyositis is a progressive systemic disease clinically manifested by a muscle lesion with impaired motor function as well as skin rashes, often in the form of erythema. In some cases, dermatomyositis can be the onset of cancer. In this regard, the doctor is required to be highly alert and focused on detecting the tumor process in patients with progressive muscle weakness and characteristic skin manifestations of dermatomyositis. The article presents a clinical case of paraneoplastic dermatomyositis co-existing with small cell lung cancer. The malignancy was diagnosed during cancer screening in a patient with classic manifestations of dermatomyositis. Improvement of clinical manifestations of dermatomyositis appeared with glucocorticosteroid therapy and surgical treatment, but the patient died, since small cell lung cancer has an aggressive clinical course with an unfavorable prognosis.

Keywords: dermatomyositis, paraneoplastic syndrome, autoimmune diseases, case report.

For citation: Musin S.T., Berezhnoy S.G., Khrapova I.A. et al. Dermatomyositis syndrome in small cell lung cancer. *Kazan Medical Journal.* 2020; 101 (6): 913–918. DOI: 10.17816/KMJ2020-913.

Background. Dermatomyositis (DM) is a systemic progressive autoimmune disease characterized by skin lesions and severe muscle weakness [1,2]. According to some authors, the incidence in the general population is 9.6 per 1,000,000 patients per year [3]. In population studies, the average age at diagnosis is 40 to 50 years. In addition, a particular gender trend exists among those with the disease, as women have the disease twice as often as men [4–6].

DM is a multifactorial disease. Today, two conflicting theories, the immune theory, and the infectious theory, seek to explain this pathology's origin.

According to the immune theory, humoral immune disorders occur in association with the activation of the complement system, the development of vasculopathies, the deposition of immune complexes in small vessels, and inflammatory infiltration of skeletal muscles. $CD4^+$, T-lymphocytes, macrophages, and B-lymphocytes are actively involved [7].

The infectious theory is based on epidemiological studies that indicate infectious diseases in patients with DM within three months of the disease manifestation. Coxsackie viruses, parvovirus B19, Epstein-Barr virus, human immunodeficiency virus, and human T-cell leukemia virus type I are etiologically significant [8].

According to the literature, trigger factors for disease development are exacerbations of focal infection, physical and mental trauma, hypothermia, overheating, hyperinsolation, vaccination (against typhoid, cholera, measles, rubella, epidemic parotitis), and drug allergy [6,9].

The relationship between DM and malignant tumors is noteworthy. Therefore, a thorough oncological search should be conducted in all patients [10, 11]. Tumor DM accounts for 20% to 30% of all disease cases, especially in patients over 50 years old [10,12]. The most common causes of paraneoplastic DM are tumors of the mammary gland (44.8%), lungs (34.5%), pancreas, and colon (26.1%) [13, 14]. The active use of glucocorticoids at high doses contributes to a significant improvement in patient prognosis [15–17].

In paraneoplastic DM, surgical intervention combined with glucocorticoid therapy is crucial. According to the literature, such an approach contributes to preserving the 32% survival rate and 27% after 5 and 10 years in this patient category [18]. However, DM remains a complex problem in medicine regarding both diagnostics and choice of treatment approach.

Case history. Patient G., 52 years old, was hospitalized at the Clinical Medical and Surgical Cen-

For correspondence: amans@bk.ru Received 11.09.2020; accepted 13.10.2020.

ter in Omsk from February 1, 2018, to March 16, 2018. Upon admission, she complained of constant stabbing and pressing pain in all muscle groups, which sharply intensified with movement, without a precise localization. Her movement was restricted because of a sharp increase in muscle pain. She had a rash on the skin of her thighs' internal surface, her chest, and on her face around her nose. She had dyspnea of a mixed nature at night, palpitations throughout the day, difficulty swallowing solid and liquid food, and severe general asthenia.

A month before admission to the hospital, a small papular rash appeared on the dorsum of her hands, and itching. Therefore, the patient visited a dermatovenerologist in a primary care facility, who prescribed therapy with antihistamines for 10 days. During this therapy, negative dynamics were recorded, and the rash spread to the trochanteric region of both thighs.

On day 15, after rash onset, the patient felt a sharp sore throat, accompanied by an increase in body temperature to 38°C and pain in the proximal muscles of the extremities. She visited a primary care physician. Lacunar tonsillitis was diagnosed, and therapy with amoxicillin (flemoxin) was prescribed. During antibiotic therapy, her body temperature returned to normal, and her sore throat subsided. However, severe pain appeared in all her muscle groups, making it difficult for the patient to move independently.

The patient was admitted to Medical Unit No. 11 with these symptoms, where she was treated with prednisolone (30 mg) and antihistamines. At the time of hospital discharge, a minor improvement was noted as she moved using a wheelchair due to severe pain syndrome in all muscle groups.

Seven days after discharge, the patient's condition worsened significantly. The pain syndrome became more pronounced, and the woman could not move independently. She was admitted by ambulance to the Clinical Medical Surgical Center in serious condition.

The physical examination revealed signs of her objective status, namely, forced lying position because of severe pain in her muscles; difficulty speaking due to dysarthria; petechial rash on her skin in the area of her hips, chest, and elbow joints; all muscle groups on palpation were sharply painful and diffusely dense. Her chest was emphysematous, symmetrical. Her respiration rate was 19 breaths per minute, with mixed respiration type, and nkwith soreness of the intercostal muscles on palpation. Her pulse was regular, 98 per minute. The left border of her heart was extended to the left by four cm from the midclavicular line (in the supine position). Her heart sounds were muffled and regular, and her blood pressure was 100/60 mm Hg. Swelling of her lower extremities was noted.

Her life history showed no abnormalities, without genetic and allergic history. Her smoking experience was 20 years, 10 cigarettes per day, and her smoker's index was 10. The patient had menopause for 1.5 years.

Results of physical, laboratory, and instrumental studies at the time of admission.

Complete blood count: hemoglobin 159 g/l, leukocytes 21.3 × 10^9/l, erythrocytes 5.48 × 10^{12}/l, erythrocyte sedimentation rate (ESR) 13 mm/h.

Biochemical blood test: total protein 62 g/l, total bilirubin 13.4 μmol/l, alanine aminotransferase 150 U/l, aspartate aminotransferase 690 U/l, lactate dehydrogenase 370 U/l, creatine phosphokinase (CPK) 14,000 IU, urea 9.2 mmol/l, creatinine 108 μmol/l, C-reactive protein 48 mg/l, procalcitonin 0.41 ng/ml, potassium 4.7 mmol/l, chloride 84 mmol/l, sodium 112 mmol/l, cholesterol 5.8 mmol/l, negative rheumatoid factor, and troponins 0.025 ng/ml.

Electrocardiography showed sinus tachycardia of 115 beats per minute, a deviation of the electrical axis of the heart to the left; moderate diffuse changes in the myocardium, more pronounced on the lower wall.

Based on significantly increased CPK values, skin rash, and patient complaints of muscle pain, the high activity DM was suspected with a differential diagnosis with DM syndrome as a paraneoplastic reaction in malignant neoplasm of unspecified localization.

The patient underwent a skin biopsy. The biopsy showed the epidermis with signs of atrophy. There were foci of sclerosis and disorganization of the connective tissue in the dermis, particularly collagen fibers. Also, perivascular infiltrates around small vessels, the lumens of capillaries and small arterioles were narrowed, and sweat, sebaceous glands, and hair follicles were subatrophic. This nosological presentation was unclear since it was possible with various vasculitis, systemic scleroderma, DM, and other conditions.

The immune status was assessed. The assessment of immunoglobulins (Ig) by Mancini's method revealed a total IgG of 4.7 g/l, total IgA of 0.7 g/l, and total IgM of 0.52 g/l. The investigation of the humoral component of the immune system showed circulating immune complexes of 15 units and the reaction of middle molecules of 0.49 units.

Neurodiagnostics were technically complicated because of the patient's serious condition, severe pain syndrome, and swelling of her extremities. According to the rhythmic stimulation data, there were no signs of damage at the pre- and

postsynaptic levels (the decrement test result was negative). The examination of the upper extremities revealed that conduction along the ulnar and median nerves was not impaired. No spontaneous activity was detected with needle stimulation. Motor unit action potentials were derived from the muscles of the upper extremities, with reduced duration. Also, the motor unit action potentials of increased amplitude were derived from the muscles of the lower extremities, with reduced duration.

Ultrasound examination of the thyroid gland, abdominal organs, mammary glands, and organs of the small pelvis revealed no oncological pathology. In addition, diffuse changes in organs were described. Fibrogastroduodenoscopy showed focal erythematous gastritis, biliary duodenogastric reflux, and pronounced proximal superficial duodenitis. Echocardiography revealed diffuse changes in the heart. There were signs of type I left ventricular diastolic dysfunction, signs of pulmonary hypertension, and the ejection fraction was 65%.

Multispiral computed tomography of the chest organs showed signs of the focal formation of the upper lobe of the right lung.

Post-inflammatory changes in the lower lobe on the right were revealed. Videothoracoscopy with biopsy of the peripheral formation of the upper lobe of the right lung was required to verify the detected neoplasm. However, the surgery was not performed due to the severity of the patient's condition. Prednisolone was prescribed at a dose of 60 mg/day *per os* from February 8, 2018, to February 21, 2018, to relieve the manifestations of DM syndrome. As a result of therapy, the CPK level decreased from 14,000 to 4320 IU, the pain syndrome in the muscles stopped, and the volume of active movements in the muscles increased significantly.

On February 22, 2018, the patient underwent surgery, namely atypical thoracoscopic resection of the right lung with neoplasm and total biopsy.

The histological conclusion of the biopsy revealed small cell carcinoma with neuroendocrine differentiation. Outside the tumor, there were signs of chronic nonspecific bronchitis with epithelial metaplasia, chronic bronchoalveolitis, interstitial pneumonitis with focal infiltration, and fibrosis. In addition, there was a deformation of individual bronchioles and acini, intracapillary sclerosis, and partial hypertrophy of the vessels' muscular membrane.

Diagnosis. The secondary dermatopolymyositis with skin lesions (erythematous-papular rash, periungual erythema, palmar capillaritis) was diagnosed based on studies. There was damage to the proximal upper and lower extremities muscles, neck muscles (CPK 14,000 IU), and nephritis with proteinuria. Also, there was small cell carcinoma of the upper lobe of the right lung (T1N0M0 St. 1a. Cl. Group 2). She had ischemic heart disease; grade II angina pectoris; arterial hypertension stage III, risk 4; diastolic dysfunction of the left ventricle; grade II chronic heart failure IIA; cholelithiasis; condition after cholecystectomy; chronic gastritis, morphologically unspecified, not in exacerbation; chronic duodenitis, moderate exacerbation; biliary duodenogastric reflux; polycystic kidney disease; thyroid nodes in both lobes.

Treatment. After surgery, the patient continued to receive prednisolone with a dose reduction of up to 30 mg/day. During therapy, she began to move independently as her ability to self-service was restored. Her CPK level returned to normal and at the time of discharge was 115 IU. The patient was discharged on March 16, 2018, in satisfactory condition, with recommendations to continue treatment under an oncologist's supervision with a decrease in the prednisolone dose of 2.5 mg every five days until complete.

Outcome and follow-up results. After discharge, the patient underwent treatment at the Clinical Oncological Dispensary in Omsk. During palliative chemotherapy, severe asthenia, fever up to subfebrile levels, facial swelling, dyspnea at rest, and dry cough appeared. A general blood test revealed pancytopenia.

On May 17, 2018, due to the deterioration of the patient's condition, she called an ambulance, and was hospitalized repeatedly at the Clinical Medical and Surgical Center.

Upon admission, the patient's condition was severe. She was hospitalized in the intensive care unit.

Complete blood count. Hemoglobin 97 g/l, leukocytes 0.6×10^9/l, erythrocytes 3.4×10^{12}/l, mean cell hemoglobin 28 pg, platelets 19×10^9/l, ESR 52 mm/h, basophils 1, eosinophils 1, stab 1, segmented 13, lymphocytes 34, and monocytes 1 per 50 cells.

Biochemical blood test: total protein 63 g/L, total bilirubin 24.6 μmol/L, direct bilirubin 11.0 μmol/L, alanine aminotransferase 57 U/L, aspartate aminotransferase 358 U/L, urea 7.9 mmol/L, creatinine 124 μmol/l, potassium 2.6 mmol/l, sodium 142 mmol/l, and glucose 5.4 mmol/l.

Electrocardiography showed severe sinus tachycardia of 135 beats per minute, the horizontal position of the electrical axis of the heart, 1 supraventricular extrasystole, and moderate diffuse changes in the myocardium.

Chest X-ray. The transparency of the right pulmonary field was inhomogeneously reduced. A homogeneous parietal formation with indistinct contours, up to 4.5 × 5.5 cm in size, and small decay cavities, were determined. The root of the right lung was not differentiated, with the shadow of

tantalum sutures in the projection of the upper lobe of the right lung (surgical treatment for a history of malignant neoplasm of the lung). On the left, the pulmonary field was normal. The contours of the diaphragm were clear.

Ultrasound examination of the abdominal cavity showed diffuse liver changes, focal formations of the liver, condition after cholecystectomy, diffuse changes in the pancreas, and cystic formations of both kidneys.

Despite the ongoing intensive therapy, the patient's condition worsened progressively. On May 17, 2018, at 20:15, cardiac arrest was registered, resuscitation measures were performed for 30 minutes in full without effect. On May 17, 2018, at 20:45, biological death was recorded.

Discussion. The diagnostic assessment of dermato- and polymyositis is a difficult task. Therefore, if the patient has a predominance of skin symptoms, "dermatological" diagnoses are often made, and in the case of muscle-related symptoms, "neurological" diagnoses are established. The most typical are dermatitis, allergic edema, erysipelas, neurodermatitis, infectious myositis, polyneuritis, poliomyelitis, and pseudobulbar syndrome. There are often diagnoses, such as systemic lupus erythematosus and systemic vasculitis [19].

DM onset is often registered with general asthenia, myalgias, transient symmetric joint lesions, and skin lesions. Then, over several weeks (months), asthenia of the proximal muscle groups gradually increases. The disease's primary clinical sign is muscle damage, expressed by symmetrical asthenia of the proximal muscle groups of the upper and lower extremities. Damage to the muscles of the pharynx, larynx, and the upper third of the esophagus (dysphonia, dysphagia) is also typical [20].

Skin lesions in DM often precede the development of muscle weakness. Its characteristic sign is an erythematous rash localized on the upper eyelids, cheekbones, over the elbow, knee, metacarpophalangeal and proximal interphalangeal joints (erythema/Gottron papules, erythema of the scalp). There is also desquamation and cracks on the skin of the palms ("mechanic's hand"), periungual erythema, photodermatitis, and itching [18, 19].

In the complete blood count, the abnormalities are nonspecific, as in some cases, an increase in ESR is noted (mainly with the development of systemic manifestations). In DM, CPK is a biochemical marker of skeletal muscle damage with high sensitivity and specificity. CPK's level increases significantly at disease onset. If DM is suspected, an electromyographic study using needle electrodes is advised to confirm primary muscle lesions and determine the degree of activity of the inflammatory process and muscle fiber necrosis [18, 19].

It is essential not only to establish the diagnosis of DM but also to determine its clinical form, make a differential diagnosis of primary (idiopathic) and secondary (tumor) dermato- or polymyositis, and differentiate and rule out other conditions accompanied by widespread damage to skeletal muscles.

Paraneoplastic DM is characterized by the following [18, 19]:

– age over 50;

– severe skin syndrome that can be represented by necrotizing ulcerative vasculitis, which is entirely or partially resistant to therapy;

– high level of ESR;

– increased values of CPK and lactate dehydrogenase, absence of Jo-1 class antibodies.

According to various studies, including population studies, malignant tumors are often detected in DM and often cause death [20, 21]. In one of the largest studies, malignant tumors were detected in 198 (32%) of 618 DM patients. In 115 patients, cancer developed after the diagnosis of inflammatory myopathy was established [10]. It cannot be ruled out that the latter fact reflected the late diagnosis of malignant tumors. In a British population-based study, 286 patients with DM had a high incidence of lung, cervical, and ovarian cancer [18, 22].

In the clinical case presented, the patient showed a typical clinical presentation of DM with skin and muscle lesions, characteristic changes in the aspects studied using laboratory and instrumental research methods. The doctors correctly identified the diagnostic approach, which enabled them to establish the root cause of DM. In this case, it was small cell cancer of the upper lobe of the right lung. This type of cancer is characterized by high aggressiveness, rapid course, and poor prognosis. In 85% of cases, patients die during active therapy [23]. In this regard, despite the successful correction with glucocorticoids and the positive dynamics of the clinical manifestations of DM, the patient died.

Conclusion. Thus, after verifying DM syndrome, it is essential to conduct a diagnostic search for a tumor process in the body. According to the literature, the paraneoplastic DM variant occurs in 32% of cases. Timely diagnosis, proper therapy, patient referral to an oncologist for treatment of the underlying disease will improve the patient's quality of life and increase the probability of a favorable prognosis.

Patient consent. The patient's legal representatives signed voluntarily an informed consent for the publication of personal medical information in anonymized form in the Kazan Medical Journal.

Author contributions. S.T.M., S.G.B., and I.A.Kh. treated the patient; E.V.R. was responsible for collecting and analyzing the results; N.V.O and O.V.D. wrote and formalized the article.

Funding. The study had no external funding.

Conflict of interest. The authors declare no conflict of interest.

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