





Sarcoidosis as a diagnostic challenge – a case report

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Sarcoidosis is considered a disease of unknown etiology which usually affects several organs and systems of the body and is manifested by the development of non-caseous granulomas. It is predominantly a multisystemic granulomatous disease that most often affects the respiratory and lymphatic systems, but varies clinically from patient to patient, making it difficult to diagnose correctly. The diagnosis is based on clinical and radiological data, the results of the sarcoidosis biomarker examinations, confirmed by the histological picture of non-caseous epithelioid cell granulomas. The use of modern instrumental methods of examination such as magnetic resonance imaging, high-resolution computed tomography, 18F-fluorodeoxyglucose-positron emission tomography has significantly improved the diagnosis of sarcoidosis.

Aim. The purpose of this paper is to present a clinical case of pulmonary sarcoidosis with atypical initial origin needed for additional differentiation and specific confirmation of the diagnosis.

Materials and methods. Diagnostic and differential diagnostic procedures were provided for a 24-year-old patient at the Therapeutic Department of the Regional Hospital of War Veterans (Chernivtsi, Ukraine). Complete examination included general clinical, laboratory and instrumental testing. Results of the clinical data were analyzed in dynamics, clinical diagnosis was confirmed by specific biomarkers, imagine tests and transbronchial lung biopsy with histology.

Results. The authors have presented the case of the 24-year-old man with atypical sarcoidosis associated with vertebrogenic thoraco-lumbalgia and persistent severe pain syndrome. He was admitted due to fever, increased temperature up to 37.2–37.4 °C, headache, muscular thoracic spine pain, unexplained general intoxication. He had a history of nephrectomy and mine-explosive injury. His specific objective findings were negative, but some nonspecific inflammatory biomarkers were imbalanced. Respiratory and inflammatory manifestations worsened in several days after admission that led to further diagnostic search and raised suspicion of sarcoidosis. Given the nonspecific clinical presentation and laboratory findings, the diagnosis needed a confirmation by chest computed tomography, sarcoidosis biomarkers and transbronchial lung biopsy with histology.

Conclusions. Thus, this case illustrates that even classic pulmonary sarcoidosis may started atypically, and diagnostic procedure requires extensive differentiation and specific confirmation by using modern diagnostic tools.

Ключові слова:

саркоїдоз, атиповий початок, діагностика, диференційний діагноз, біомаркери.

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Саркоїдоз як діагностичний виклик – клінічний випадок

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Саркоїдоз – мультисистемна патологія невідомої етіології, що характеризується наявністю неказеозних гранульом. Це системне гранулематозне захворювання, яке переважно уражає легені та лімфатичну систему пацієнта, але клінічно відрізняється від випадку до випадку, що ускладнює встановлення клінічного діагнозу. Зазвичай діагноз ґрунтується на клініко-рентгенологічних даних, визначенні біомаркерів саркоїдозу, що підтверджені гістологічною картиною неказеозної епітеліоїдно-клітинної гранульоми. Застосування комп'ютерної томографії високої роздільної здатності, магнітно-резонансної томографії та 18F-фтордезоксиглюкозно-позитронно-емісійної томографії сприяло поліпшенню діагностики саркоїдозу.

Мета роботи – описати клінічний випадок саркоїдозу легенів з атиповими початковими клінічними проявами, що потребувало додаткового диференціювання та специфічного підтвердження діагнозу.

Матеріали і методи. Хворому віком 24 роки у терапевтичному відділенні Обласного комунального некомерційного підприємства «Чернівецький обласний госпіталь ветеранів війни» (Україна) здійснили діагностичне та диференціаль-но-діагностичне обстеження для встановлення клінічного діагнозу. Повне обстеження передбачало загальноклінічні, лабораторні й інструментальні дослідження. Результати клінічних даних аналізували в динаміці; клінічний діагноз підтверджено за допомогою спеціальних біомаркерів саркоїдозу, за даними трансбронхіальної біопсії легень із гістологічним дослідженням біоптату.

Результати. Описано клінічний випадок 24-річного чоловіка, у якого саркоїдоз мав атипову початкову клінічну картину з проявами вертеброгенної торако-люмбалгії з постійним вираженням больовим синдромом. Пацієнт надійшов у клініку з приводу лихоманки, підвищення температури до 37,2–37,4 °C, головного болю, болю у м'язах грудного відділу хребта на фоні ознак загальної інтоксикації нез'ясованого ґенезу. В анамнезі хворий переніс нефректомію та міно-вибухову акубаротравму. Під час надходження до стаціонара не було виявлено специфічних об'єктивних ознак саркоїдозу, але лабораторно зафіксовано розбалансовані зміни певних неспецифічних запальних біомаркерів. Через кілька днів після госпіталізації виникли та посилювалися респіраторні та загальні запальні симптоми. Це обґрунтувало продовження діагностичного пошуку, який

завершився припущенням про саркоїдоз. Враховуючи неспецифічну клінічну картину та лабораторні дані, діагноз потребував підтвердження за даними комп'ютерної томографії грудної клітки з контрастуванням, дослідження біомаркерів саркоїдозу та трансбронхіальної біопсії легень із гістологічним дослідженням біоптату.

Висновки. Наведений випадок демонструє, що навіть класичний саркоїдоз легень може починатися атипово, а діагностичний процес потребує широкого диференціювання та специфічного підтвердження за допомогою сучасних лабораторно-інструментальних методів дослідження.

Sarcoidosis is a multisystem pathology of unknown etiology characterized by the presence of non-caseating granulomas. It is stated in modern literature that more than the respiratory, lymphatic, cardiovascular, nervous systems as well as parenchymal organs and skin can be involved in the pathological process in 10–30 % of patients [1]. Sarcoidosis was firstly described by the British clinician-scientist Jonathan Hutchinson in 1877. But even in the 21st century, the diagnosis and effective treatment of sarcoidosis remains a challenge for both clinicians and scientists [2].

The true incidence of this disease around the world has not been definitively determined due to a sufficiently large number of asymptomatic cases that do not fall into statistical data. In general, sarcoidosis occurs in patients of all age groups, people of different ethnicities or races. But most often this disease develops in young people (20–40 years old), with a significant increase in the incidence rate among women, and also more frequently among non-smokers in comparison to smokers as well as among people living rurally. Statistics show a higher prevalence of sarcoidosis among a Northern European population and a significantly decreased incidence in the countries of Southern Europe (60 and <10 per 100,000, respectively) [2,3,4].

Furthermore, the global sarcoidosis incidence is the highest in Sweden (64/100,000) and the United Kingdom (20/100,000) [2,4,5]. Sarcoidosis is also commonly diagnosed in patients with certain autoimmune diseases including Sjogren's syndrome ankylosing spondylitis, autoimmune thyroid disease, and systemic sclerosis [6].

The diagnosis is based on clinical and radiological data, sarcoidosis biomarkers, confirmed histologically by non-caseous epithelioid cell granulomas. High-resolution computed tomography, magnetic resonance imaging, and 18F-fluorodeoxyglucose positron emission tomography have improved the diagnosis of sarcoidosis. These methods are also effective in assessing a patient's response to treatment [4,7,8].

It should be noted that granulomas of known etiology and local sarcoid reactions are not sarcoidosis. Commonly observed immunological signs include suppressed cutaneous delayed-type hypersensitivity and enhanced T-helper (Th1)-mediated immune response at the disease manifestation site. High activity of B cells and an increased number of circulating immune complexes can also be seen. The course and prognosis can be correlated with different initial manifestations and the disease duration. An acute onset with erythema nodosum or asymptomatic bilateral lymphadenopathy of pulmonary hila usually indicates a high probability of spontaneous resolution, whereas a gradual onset with multiple extrapulmonary lesions may be accompanied by long-term progressive fibrosis of the lungs and other organs [4,8].

While significant progress has been made in understanding the pathogenesis, clinical and pathomorphological

signs of the disease, there are still many questions about the etiology and genetic factors contributing to the disease onset and manifestation. Therefore, the treatment of the disease has not been sufficiently developed.

Aim

The purpose of this paper is to present a clinical case of pulmonary sarcoidosis with atypical initial origin needed for additional differentiation and specific confirmation of diagnosis.

Materials and methods

Diagnostic and differential diagnostic procedures were provided to a 24-year-old patient in the Therapeutic Department of the Regional Hospital of War Veterans (Chernivtsi, Ukraine).

Complete examination included general clinical, laboratory and instrumental testing. Results of the clinical data were analyzed in dynamics; clinical diagnosis was confirmed by specific biomarkers.

The study was performed in accordance with the Good Clinical Practice standards and the Helsinki Declaration principles, with the patient signing an informed consent. This research was approved by the Biomedical Ethics Committee of Bucovinian State Medical University (protocol No. 7 of 20.03.2025).

Case report

The 24-year-old patient A. was admitted to the hospital on the 8th day of the disease exacerbation. The gradual disease onset was over 2–3 months with complaints of fever, increased temperature up to 37.2–37.4 °C, headache, muscular thoracic spine pain. This condition was considered to be associated with a recent nephrectomy (June 2022).

Due to deterioration in the condition, he consulted a family physician and was hospitalized. At the hospitalization, he complained of severe muscular cervical and thoracic spine pain aggravated by physical exertion, that made walking difficult, constant noise and ringing in the ears, general weakness. The patient reported having been got a mine-explosive injury (MEI) in 2022.

Initial vital signs on admission were not significant. Physical examination revealed increased body temperature up to 37.4 °C and pain to palpation of the cervical and thoracic spine muscles, unexplained general intoxication. There were no other markable findings of physical examination.

Taken into account the presence of long-term hyperthermia and myalgia, a number of laboratory studies were conducted to identify the possible cause of this condition (Table 1).

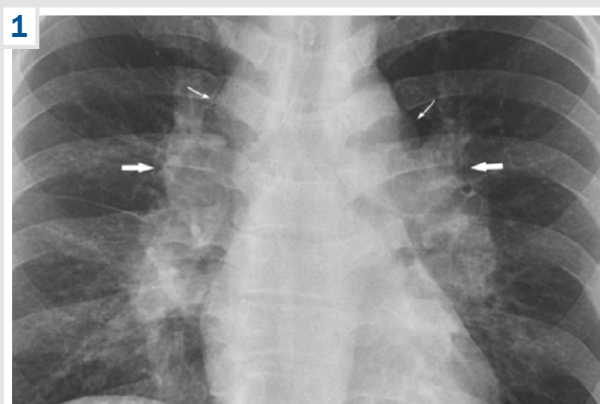


Fig. 1. Chest X-ray of the patient.

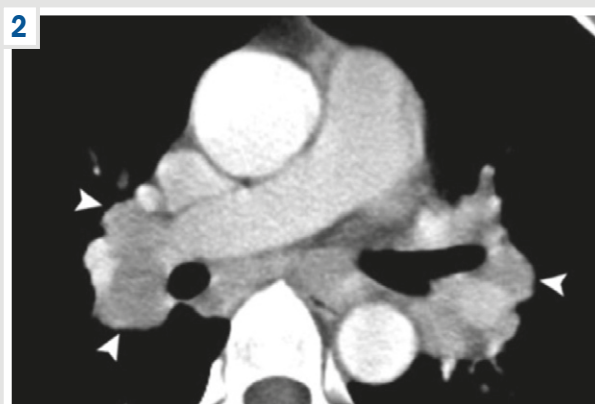


Fig. 2. CT of the patient.

Table 1. List of conducted diagnostic tests

Parameter	Result	Normal range
Creatinine	0.88 mg/dL	0.8–1.3 mg/dL
Urea	5.4 mmol/L	2.5–8.3 mmol/L
Albumin	37 g/L	35–50 g/L
ALT (GPT)	37 U/L	5–30 U/L
AST (GOT)	24 U/L	5–30 U/L
Total bilirubin	20 mmol/l	8–20 mmol/l
Total protein	78 g/L	60–80 g/L
Glucose	5.8 mmol/L	3.3–6.0 mmol/L
Potassium	6.1 mmol/L	3.5–5.0 mmol/L
Sodium	129 mmol/L	135–145 mmol/L
Total serum iron	176 µg/dL	65–180 (men); 30–170 (women) µg/dL
CRP	7 mg/L	<6 mg/L
ASLO	200 mU/L	7.0–200.0 mU/L
RF	8 U/ml	<20 U/ml
Hemoglobin	156 g/L	130–160 (men); 120–140 (women) g/L
Hematocrit	37.7 %	40–52 (men); 36–47 (women) %
Leukocytes	$6.3 \times 10^9/l$	$4.0–11.3 \times 10^9/l$
MCV	85.6 fL	80–100 fL
Erythrocytes	$5.28 \times 10^{12} /l$	$4.1–5.1 \times 10^{12} /l$
MCH	30.1 pg	28–32 pg
Neutrophils	87 %	50–70 %
Platelets	$202 \times 10^9/l$	$150–350 \times 10^9/l$
Lymphocytes	11 %	25–40 %
Monocytes	2 %	<8 %
PTT	18 sec	25–42 sec
HBsAg	–	<0.05
antiHCV	–	<10 IU/ml

Urine test was without abnormalities.

ECG: regular sinus rhythm, heart rate – 91 bpm, sinus tachycardia, right bundle branch block, right atrial hypertrophy.

Abdominal ultrasound: ultrasound signs of urolithiasis.

Echoencephalography: no signs of the third ventricle dilatation or intracranial hypertension.

RheoEG: symmetrical pulsatile blood filling of intracranial vessels, moderately reduced in the internal carotid artery basin. Normal elasticity of large- and medium-sized arteries. Labile cerebral vascular tone, tendency to angiospasm. Slight venous dyscirculation in the vertebral artery basin. Vertebrogenic pathology.

The preliminary diagnosis was made: Chronic vertebrogenic thoracolumbalgia with persistent severe pain syndrome, exacerbation stage. Consequences of MEI (2022), acoubarotrauma with severe cephalgia, asthenoneurotic syndrome.

After a week of treatment, the patient developed non-productive cough with hemoptysis in the evening, increased body temperature up to 38.2 °C.

Additional examinations revealed changes in the laboratory tests (Table 2).

Chest roentgenography (Fig. 1): increased pulmonary vascularity. Prominent shadows of the hila with fine nodular pattern. Bilateral enlargement of hilar lymph nodes. No pleural effusions.

Chest CT was performed for further examination: CT signs of multiple nodules in both lungs and interstitial lymphadenopathy (Sarcoidosis?). No additional masses were found (Fig. 2).

Due to suspected sarcoidosis, plasma concentrations of specific sarcoidosis biomarkers were also examined to confirm or rule out the preliminary diagnosis (Table 3). Plasma levels of serum angiotensin-converting enzyme (sACE), interleukin-2 receptor (IL-2R), ionized calcium were measured, and these values were elevated with normal concentration of parathyroid hormone. For differential diagnoses, a negative result on the QuantiFERON test was obtained.

The Statement on sarcoidosis, adopted in 1999, provides for the verification of respiratory sarcoidosis by transbronchial or surgical lung biopsy [9].

The patient was referred to the National Institute of Tuberculosis and Pulmonology to verify the preliminary diagnosis of sarcoidosis. Final confirmation of the preliminary diagnosis was provided by a transbronchial lung biopsy, and histological examination results of biopsy specimens consisted in the presence of non-caseous epithelioid cell granulomas. Clinical diagnosis was formulated based on the findings of complex examinations: Pulmonary sarcoidosis, radiographic type II, acute phase.

Appropriate first-line treatment was prescribed containing of Medrol 16 mg daily, long-term follow-up. General condition of the patient improved within 2 weeks; he was discharged home on an outpatient treatment.

Discussion

Sarcoidosis is a heterogeneous disease characterized by multisystem lesions of non-caseous epithelioid cell granulomas and the development of corresponding clinical manifestations. Clinical diagnosis should be provided by differential diagnosis between other multisystem granulomatous diseases [10,11].

The multisystemic character of sarcoidosis leads to organ specific manifestations with or without general symptoms. Clinical presentation may differ from patient to patient and depend on the process localization and comorbidity types. According to ACCESS, more than 90 % of patients had pulmonary involvement, 50 % – extrapulmonary symptoms, and 2 % – pure extra-thoracic sarcoidosis [2].

Although diagnosis of sarcoidosis presents some difficulties, a clinical classification of systemic sarcoidosis was proposed and published in the European Respiratory Journal in 2018 based on the results of a multicenter study with a stratification into five main classes taking into account predominant organ and system involvement:

- abdominal;
- ocular-cardiac-cutaneous – CNS;
- musculoskeletal-cutaneous;
- pulmonary / lymph nodes;
- extrapulmonary sarcoidosis [12].

According to authors of the publication, this classification was to improve the diagnostic process by carefully stratifying sarcoidosis patients across classes in order to optimize the choice of indications for confirmatory diagnostic methods and individualize the treatment process [12,13].

More commonly used sarcoidosis biomarkers, such as sACE, are moderately sensitive [7,13]. Recently, it has been noted in the literature that among specific sarcoidosis biomarkers, the study on the interleukin 2 (IL-2) receptor level has becoming sufficiently valuable in diagnosis. The role of IL-2 as one of the leading cytokines of the immune system is to balance the immune response and maintain a certain level of tolerance with the involvement of CD4+ regulatory T-lymphocytes. It should be taken into account that quite a large number of diseases besides sarcoidosis, including autoimmune, inflammatory infectious diseases, solid cancers and hemoblastosis, can be characterized by increased levels of serum soluble IL-2 receptor. However, scientific research has proven a clear correlation between increased serum concentrations of soluble IL-2 receptor and the incidence of sarcoidosis, demonstrating a high sensitivity in specific diagnosis. In addition, the level of this indicator and the dynamics of its concentration increase at diagnosis can be used as a predictor of chronic sarcoidosis progression [14,15].

Given the absence of sarcoidosis clinical manifestations in the patient at the time of hospitalization, specific diagnosis was delayed. The case presented has helped to additionally evaluate the patient with an analysis of relevant published clinical cases in the medical literature. Based on the clinical and laboratory data, sarcoidosis was suspected, and this clinical diagnosis was confirmed by histological verification conducting differentiation between other inflammatory, autoimmune and systemic rheumatic diseases due to underlying neurological vertebrogenic thoracolumbalgia following MEI. We have also suggested that previous injury of the patient as a combatant might become a stressful provoked factor for the clinical progression of sarcoidosis.

Table 2. List of additional diagnostic tests

Parameter	Result	Normal range
CRP	22 mg/L	<6 mg/L
ASLO	218.9 mU/L	7.0–200.0 mU/L
RF	10 U/ml	<20 U/ml
Hemoglobin	148 g/L	130–160 (men); 120–140 (women) g/L
Hematocrit	43.7 %	40–52 (men); 36–47 (women) %
Leukocytes	$6.12 \times 10^9/l$	$4.0–11.3 \times 10^9/l$
MCV	81.6 fL	80–100 fL
Erythrocytes	$4.83 \times 10^{12} /l$	$4.1–5.1 \times 10^{12} /l$
MCH	30.1 pg	28–32 pg
Band neutrophils	10 %	1–4 %
Segmented neutrophils	62 %	50–70 %
Platelets	$202 \times 10^9/l$	$150–350 \times 10^9/l$
Lymphocytes	20 %	25–40 %
Monocytes	6 %	<8 %

Table 3. List of sarcoidosis biomarkers (diagnosis and differential diagnosis)

Parameter	Result	Normal range
sACE	208 U/l	20–70 U/l
IL-2 receptor	820 kU/L	158–623 kU/L
Ionized calcium	2.27 mmol/l	1.13–1.32 mmol/l
Parathormone	24 pg/ml	16–42 pg/ml

Conclusions

The presented clinical case demonstrates that the diagnosis of sarcoidosis needs to be considered when differentiating in cases of pain syndrome, pulmonary manifestation development in relation to unclear general intoxication and fever. Although it was initial misdiagnosis in this case, timely suspected sarcoidosis followed by thorough diagnostic and differential diagnostic search have helped to start pathogenetic treatment and get positive results.

Prospects for further research are to study the diagnostic value of specific biomarkers using to confirm sarcoidosis in cases of atypical clinical presentation.

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