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LOFGREN'S SYNDROME: CLINICAL CASE

Abstract

Sarcoidosis is an inflammatory disease characterized by the formation of non-necrotising granulomas in various organs and tissues. The clinical signs of sarcoidosis are determined by the number of affected organs, the degree of their structural and functional impairment, and the severity of inflammatory symptoms. The article presents a clinical observation of one of the forms of sarcoidosis — Lofgren's syndrome, which is characterized by a triad of intrathoracic lymphadenopathy, acute arthritis and erythema nodosum. The diagnosis was confirmed histologically. Under the prescribed treatment, signs of acute inflammation reversed and the patient's state improved. The authors emphasize that they do not recommend widespread use of systemic glucocorticosteroids in patients with this disease, since their use may be associated with its relapsing course.

Key words: *Lofgren's syndrome, sarcoidosis, acute arthritis*

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Sarcoidosis is an inflammatory disease characterized by the formation of non-necrotising granulomas in various organs and tissues. Inflammation is modulated by the monocyte-macrophage system cells and lymphocytes, and can have a different degree of severity [1].

The clinical signs of sarcoidosis are determined by the number of affected organs, the degree of their structural and functional impairment, and the severity of inflammatory symptoms. Most often, intrathoracic lymph nodes, lungs, skin and eyes are involved in the process. Damage to the musculoskeletal system is less common. About 10–15 % of patients with sarcoidosis have an associated arthropathy [2].

Acute sarcoid arthritis most often is manifested as part of Lofgren's syndrome characterized by the triad of intrathoracic lymphadenopathy, acute arthritis and erythema nodosum. Acute arthritis is predominantly oligoarticular (87 %), symmetrical (76 %), and most often involves ankle joints (>90 %), usually both, as well as other larger joints of the lower limbs, therefore it is often mistaken for reactive arthritis [3]. As an example, we would like to present our own clinical observation.

Clinical case

Patient L., 31 years of age, was admitted to the hospital on 20/08/2018 with complaints of intermittent, migrating, aching pain in ankle, knee, radiocarpal joints and metatarsophalangeal joints of toes 3–5 of the left foot. There was no pain in the morning after waking up but the pain increased

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during movement, its intensity progressed during the day and reached a maximum in the first half of the night, which resulted in nocturnal sleep disturbances. Pain intensity was 5–6 points on a visual analogue scale (VAS). No morning stiffness was observed. Also, he experienced a cracking sound during movement in the knee joints and right radiocarpal joint, as well as swelling and local hyperthermia of ankle joints. He suffered from pain in lumbar and cervical regions of the spine towards evening and after exertion throughout the day. He experienced a rise in body temperature up to 37.4–37.6 °C (with maximum of 38.6 °C) by 3.00 p. m., after prolonged load on joints (walking), temperature was normalized after taking naproxen and paracetamol. He lost 3 kg within the last month, without loss of appetite.

The patient considers himself sick since 01/08/2018, when he experienced hyperemia, swelling, and local hyperthermia of the ankle joints in the morning, after getting out of bed with increasing pain in these joints. He had no catarrhal signs or sore throat. On the next day, temperature rose to 37.4 °C, injection of scleral vessels occurred. He sought medical attention at his health service provider on 03/08/2018, was followed up with diagnosis of ARVI and treated with Anaferon without effect.

Due to injection of scleral vessels, he was referred to the ophthalmologist, who made a diagnosis: episcleritis of both eyes. From 06/08/2018 he was treated with amoxicillin prescribed by a general practitioner. Laboratory data dated 07/08/2018: ESR: 30 mm/hour; WBC: 8.4×10^9/L, RBC: 4.19×10^{12}/L, HB: 129 g/L, segmented neutrophils: 79.1 %, lymphocytes: 15.6 %; monocytes: 5.3 %; PLT: 263×10^9/L.

On 08/08/2018, he was examined by a rheumatologist, on whose recommendation the following tests were performed on 10/08/2018: PCR for HLA-B27, passive hemagglutination test for detection of *Yersinia* species, *Salmonella* species, *Shigella* species, PCR for *Chlamydia* species, *Mycoplasma* and *Ureaplasma* species, EIA for HBV, HCV, HIV were negative; antistreptolysin O: 70.7 U/mL, CPK: 95 U/mL. Ultrasound scanning of visceral organs on 10/08/2018: No abnormalities were discovered. ECHO-CG dated 16/08/2018: Sizes of the cardiac chambers were normal, the valvular heart apparatus without abnormalities, the left ventricle contractility was satisfactory, ejection fraction was 75 %. The patient took naproxen when body temperature was elevated, as recommended by the rheumatologist. No significant improvement of the patient's condition was observed, low-grade fever persisted. On 20/08/2018, he was electively admitted in the rheumatology department for examination and treatment.

On physical examination at admission: Patient's gait was sparing. The symptom of lateral compression of the foot was positive at the left side. The metatarsophalangeal joints of toes 3-5 of the left foot were tender on palpation. The plantar fascia of both feet, Achilles tendons, and their points of attachment to the calcaneus bones were tender on palpation. The left Achilles tendon was swollen. Ankle joints: were swollen, circumference of the left joint was 28 cm, circumference of the right joint was 27 cm, the joints were tender on palpation, had a full range of motion. Knee joints: had no visual abnormalities, were tender on palpation in the projection of the left joint space, the range of motions in the knee joints was not restricted, the popliteal fossae were tender at maximum flexion of both knee joints. Hip joints: movements were nontender, not restricted. Small joints of the hands were looking normal and were nontender. The patient closes the hand into a fist completely, hand grip strength is sufficient. Radiocarpal joints: were painful, not swollen, symmetrical, range of motions was normal. The elbow and shoulder joints were nontender on palpation, the range of motions was complete, and the motions were painless. No tenderness on palpation of the paravertebral points and spinous processes was observed.

Investigations

On admission: WBC: 7.9×10^9/L; RBC: 4.3×10^{12}/L; HB: 130 g/L; PLT: 476×10^9/L, ESR: 69 mm/hour; AST: 15.0 U/L, ALT: 12.0 U/L, total protein: 85.0 g/L; albumin: 46.0 g/L; glucose: 5.3 mmol/L; cholesterol: 4.9 mmol/L; sodium: 143.0 mmol/L; potassium: 3.9 mmol/L; urea: 6.4 mmol/L; uric acid: 285 μmol/L; creatinine: 82.0 μmol/L; total bilirubin: 17.5 μmol/L; prothrombin time: 13.4 sec, PI: 80 %; fibrinogen: 7.0 g/L; rheumatoid factor: 3.0 U/L; antistreptolysin O: 96.0 U/mL. Immunogram: IgA:

2.7 g/L; IgM: 0.9 g/L; IgG: 11.6 g/L; C3: 135.4 mg/dL; C4: 26.4 mg/dL; CIC: 219.3 U/mL; the procalcitonin test is negative. Urinalysis: yellow, clear, specific gravity: 1,030 g/L; protein: 0 g/L; WBC: 0–1 per field of view; pH: 6.0.

Clinical signs of joint disease necessitated radiologic imaging. Frontal X-ray of the hands and feet on 21/08/2018: No bone pathology was revealed. Sacroiliac joint X-ray on 22/08/2018: there was no evidence of sacroiliitis, subchondral sclerosis was discovered on the left side. Ultrasound scanning of the knee joints on 21/08/2018: there were signs of bilateral gonarthrosis and increase in the amount of synovial fluid of the upper and lateral recesses on both sides. Ultrasound scanning of ankle joints on 22/08/2018: signs of tendonitis were discovered in the left lateral ligament. Lumbosacral spine MRI on 27/08/2018: There were no abnormalities of the spinal cord and intervertebral discs of the lumbosacral spine, there was a perineural arachnoid cyst at the S2 vertebra level, there was no evidence of sacroiliitis.

In the rheumatology department, the patient received 100 mg of nimesulide 2 times a day upon admission, with a moderate effect: there was a decrease in pain, persistent low-grade fever with a periodic increase in the body temperature to febrile levels. Due to the lack of effect of oral NSAIDs, high clinical and laboratory disease activity, two drip intravenous infusions of methylprednisolone 250 mg (23/08, 24/08/2018) were given to the patient with a good effect for the period of administration: normalization of the body temperature was observed, there were no pains in the joints, and their swelling decreased.

Erythema nodosum, severely tender on palpation, that appeared on the lateral surface of the right shin on 28/08/2018, allowed to suspect Lofgren's syndrome. CT scanning of the chest was performed on 29/08/2018 to reveal the third component of the characteristic triad. Conclusion: The lungs were pneumatized. Lung tissue density was 850 HU. The pulmonary pattern was slightly thickened due to peribronchial fibrosis and interstitium. Bronchi were patent, with no signs of local dilation; bronchial walls were indurated. In both lungs (predominantly in the upper parts), foci measuring 2–3 mm which were partly confluent were visualized around the lymphatic vessels. The structure of the pulmonary hila was defined perfectly, slightly dilated due to lymph nodes. The pleura and interlobar fissures were not changed. Lymph nodes: paraaortic, paratracheal, bifurcation, peribronchial, bronchopulmonary lymph nodes were enlarged to 12–13 mm on the short axis. Conclusion: CT signs of sarcoidosis, stage 2, mediastinal-pulmonary form.

From 31/08/2018, due to renewed pain in the joints, low-grade fever, regarded as extrapulmonary presentation of sarcoidosis, oral methylprednisolone was prescribed at a dose of 8 mg per day. The patient was discharged on 10/09/2018 with improvement: pain in the joints decreased significantly, ankle joint swelling subsided. Low-grade fever persisted.

The patient was referred to the Republican Clinical Tuberculosis Hospital with diagnosis of sarcoidosis, stage 2, Lofgren's syndrome, in order to rule out tuberculosis infection and confirm the diagnosis, where a video-assisted thoracoscopic biopsy of mediastinal lymph nodes was performed. Histological study: The lymph node tissue was subtotally replaced by epithelioid cell granulomas with giant Pirogov — Langhans cells, had no signs of necrosis, and had so-called "stamped appearance". A number of granulomas were surrounded by annular fibrosis peripherally. Conclusion: This histological pattern was more consistent with sarcoidosis.

The following recommendations were given to the patient at discharge: treatment with oral glucocorticoids and antioxidants under the supervision of a pulmonologist, follow-up by a general practitioner at the community-based facility, helical CT of the chest and abdominal ultrasound in 6 months.

Conclusion

In the clinical case presented, a young man went to a clinic with a primary lesion of ankle joints, which in combination with the erythema nodosum which appeared later, agrees with the data of other authors. A prospective cohort study of patients with recent arthritis showed that the persistence of symptoms for less than two months, symmetrical ankle arthritis and age younger than 40 years had high sensitivity (85 %) and specificity (99 %) in sarcoid arthritis. Therefore, the next step in the diagnostic search for the young man with acute,

bilateral arthritis of the ankle joints with or without painful, red nodules on the shins, is the use of diagnostic radiology exams to detect intrathoracic lymphadenopathy [4], which was performed in our patient.

The patient was discharged with significant improvement in well-being. However, the treatment performed should not be recommended for widespread use. When choosing a treatment method for a patient with sarcoidosis, systemic glucocorticosteroids (GCS) should be used with caution, since, according to literature data, recurrent course of the disease in patients with Lofgren's syndrome who took GCS was 33.3 % more frequent than in those who did not take these drugs [5]. Young age, acute onset of the disease, the presence of Lofgren's syndrome are favorable prognostic factors of sarcoidosis in this patient [6].

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COMMENTARY ON THE ARTICLE «LOFGREN'S SYNDROME: CLINICAL CASE»

Commentary written after reading an article may seem negative and overly strict. But this is far from the case. The purpose of the commentary is to analyze the logic of action so that in such cases the physician will be guided by modern knowledge of sarcoidosis. A series of monographs on sarcoidosis has been published in Russia, national clinical guidelines have been prepared, where the algorithms for diagnosing and treating this disease are quite clearly presented. However, in real clinical practice, the management of patients with sarcoidosis is not based on these provisions, but is a result of the intuition of the physician faced with such a patient.

The case presented is of great practical interest for a number of reasons. Firstly, in recent years, the number of cases of sarcoidosis has increased (probably due to both real growth and improved diagnostics). Secondly, the clinical signs of sarcoidosis are very diverse, and of these, the acute forms — Lofgren's syndrome and Heerfordt — Waldenstrom syndrome — are associated with the greatest diagnostic and therapeutic errors, and thirdly, the attitude to the use of systemic glucocorticosteroids in rheumatology and in the treatment of sarcoidosis is not equivalent and has various effects.

The diagnostic path of the patient in this clinical observation, as well as the sequence of drug use, are quite typical.

As noted in the clinical case, before making the first diagnosis, the patient had already taken naproxen and paracetamol due to articular syndrome, and achieved relief.

The first diagnosis was ARVI, acute respiratory viral infection. At the same time, the authors noted that the patient had no catarrhal symptoms, sore throat, rhinitis, cough, so, there were no respiratory symptoms. The symptom complex included low-grade fever, articular syndrome, and injection of scleral vessels. Anaferon was prescribed to the patient, which is a drug which simulates the humoral and cellular immune response, affecting the system of endogenous interferons and associated cytokines, inducing the formation of "early" endogenous interferons. The authors noted that there was no clinical response — an improvement in the condition — to this treatment. It should be noted that the described mechanism of action of this immunomodulator partially overlaps with the stages of the sarcoidosis pathogenesis. The sarcoid reaction in patients receiving interferons has been repeatedly described in literature. It is possible that the use of an immunomodulator could play a negative role in the further progression of symptoms.

Prescription of aminopenicillin by an ophthalmologist due to the diagnosed episcleritis probably corresponded to protocols in ophthalmology practice. The drug effect is not presented in the clinical case. Amoxicillin could not have any effect on the course of sarcoidosis. At least, there are no published data on the effect of aminopenicillins on the course of sarcoidosis.

At the next stage, the rheumatologist carefully examined the patient in a number of aspects, except for respiratory and phthisiological ones. Contradictory information is provided regarding the nimesulide prescribed. It has been noted that the drug eased the pain, but did not prevent rise in body temperature. At the rheumatology department, these changes were evaluated as a lack of effect, and, without further examination (at least, fluorography, search for an infectious cause of fever), high intravenous doses of systemic glucocorticosteroids were prescribed to the patient. The question arises, what are the indications for intravenous administration to a patient who is able to take drugs per os? Why was radiological lung exam not performed on a patient who was admitted with fever before prescribing such potent immunosuppressive therapy?

The authors evaluate the effect of steroids as fast and positive: arthralgia disappeared, temperature returned to normal. But four days after two infusions of methylprednisolone, the patient developed an erythema nodosum. That is, steroids have not stopped the disease. The appearance of erythema nodosum led physicians to the idea of Lofgren's syndrome, and X-ray computed tomography was performed, intrathoracic lymphadenopathy and limited dissemination were revealed. A systemic glucocorticosteroid was prescribed to the patient again. With this immunosuppressive therapy, the patient was referred to an antituberculosis institution for video-assisted thoracoscopic biopsy. The question arises, was it possible for such a patient to be referred for a biopsy to a non-antituberculosis institution, without exposing him to an undue risk of infection? If the diagnosis of sarcoidosis was originally discussed, then referring the patient to the antituberculosis institution is not logical, the VIII group of dispensary observation of patients with sarcoidosis in anti-tuberculosis institutions was abolished in Russia in 2002. If the tuberculous nature of the lesion was suspected, then why were systemic steroids prescribed without an initial TB examination? In the clinical case, we do not find any information about conducting tuberculin skin tests or PCR diagnostics before prescribing hormones.

The following recommendation of long-term use of systemic glucocorticosteroids is consistent with the provisions of the International Statement on Sarcoidosis of 1999 and Russian clinical guidelines, since only long-term use of prednisolone or its analogs can achieve cure or lasting remission. But the same documents do not include Lofgren's syndrome to the indications for steroid therapy. The recommendation of the follow-up examination after 6 months also does not comply with these documents. Early (after 3 months) assessment of the effect of hormonal drug therapy is needed in order to switch to alternative drugs if there is lack of effect without exposure to the risk of Cushing's syndrome and other consequences of long-term use of adrenal hormones.

The case presented is of great practical importance, and gratitude should be given to the authors for reporting it. The publication suggests the need to increase knowledge of sarcoidosis among doctors of various specialties. This acquires special meaning nowadays, when clinical guidelines are becoming the main guiding document for physicians.