CASE REPORT

Generalised lymphadenopathy in a patient with fever of unknown origin as a differential diagnostic challenge — case report

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Abstract

Fever of unknown origin (FUO) presents a major diagnostic challenge as it is a consequence of many infectious as well as malignant, rheumatologic and other diseases.

Here we present the case of a woman with mediastinal and abdominal lymphadenopathy who was initially suspected to have lymphoproliferative disease, but our histopathologic examination revealed sarcoidosis.

Sarcoidosis, especially chronic, is a rare cause of FUO, because it usually manifests as a febrile condition.

A woman presented with shoulder and ankle joint pain, mediastinal and abdominal lymphadenopathy and fever at the Infectious Diseases Clinic. Physical examination identified the presence of lupus pernio and normal respiratory noise in the lungs, and later peripheral lymphadenopathy. Peripheral blood smear indicated conspicuous eosinophilia. Biopsy examination obtained by rigid bronchoscopy suggested pulmonary sarcoidosis.

Sarcoidosis and lymphoma may have similar clinical manifestations; both present as mediastinal and abdominal lymphadenopathy with constitutional symptoms. Therefore, in the diagnosis of sarcoidosis, it is important to exclude lymphoproliferative diseases and other granulomatous diseases.

Keywords: Sarcoidosis, Lymphadenopathy, Fever of Unknown Origin.

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Introduction

Fever of unknown origin (FUO) was first defined in 1961 by Petersdorf and Beeson as a temperature lasting more than three weeks, exceeding 38.3°C several times, accompanied with undetected cause after one week of testing.[1] Durak and Street modified the definition 30 years later, and the new definition included three days of hospital testing.[2] Over 200 causes of fever of unknown origin have been described in the literature and they are divided into four groups: infectious, malignant, rheumatologic and other diseases.[3] In developing countries, the most common causes of FUOs are infectious diseases, while in developed countries they are non-infectious inflammatory diseases, although until recently in developed countries these have been lymphoproliferative diseases.[4,5]

The most common malignant diseases associated with FUO are lymphomas.[5] Cervical, axillary, inguinal, mediastinal and abdominal lymphadenopathy generally present with nonspecific symptoms, such as fever, night sweating, weight loss, and fatigue. Here we present the case of a woman with mediastinal and abdominal lymphadenopathy who was initially suspected to have lymphoproliferative disease, but histopathological examination demonstrated sarcoidosis.

Sarcoidosis, especially chronic, is a rare cause of FUO.[6] It is a multisystemic disease of unknown aetiology, characterised by non-caseating granules consisting of macrophages, epithelial and mononuclear cells, CD4+ and CD8+ T lymphocytes.[7] Intrathoracic lymphadenopathy is present in 87% of cases, while 50% of diseases have pulmonary parenchymal infiltration.7 Although it has been previously known that eosinophilia is observed in peripheral blood smears in a certain percentage of sarcoidosis patients, we encountered a patient with very high eosinophilia values.[8]

Here, we present a case report of chronic active sarcoidosis accompanied with prolonged fever and generalised lymphadenopathy.

Case Report

A 63-year-old woman was hospitalised at the Infectious Diseases Clinic, in Clinical Center Kragujevac in Serbia in April 2018 for the evaluation of fever of unknown origin. The ailments began six months earlier in the form of exhaustion, shoulder and ankle joint pain, productive cough and fever of 38 to 39°C, which occurred almost daily.

Physical examination demonstrated erythematous

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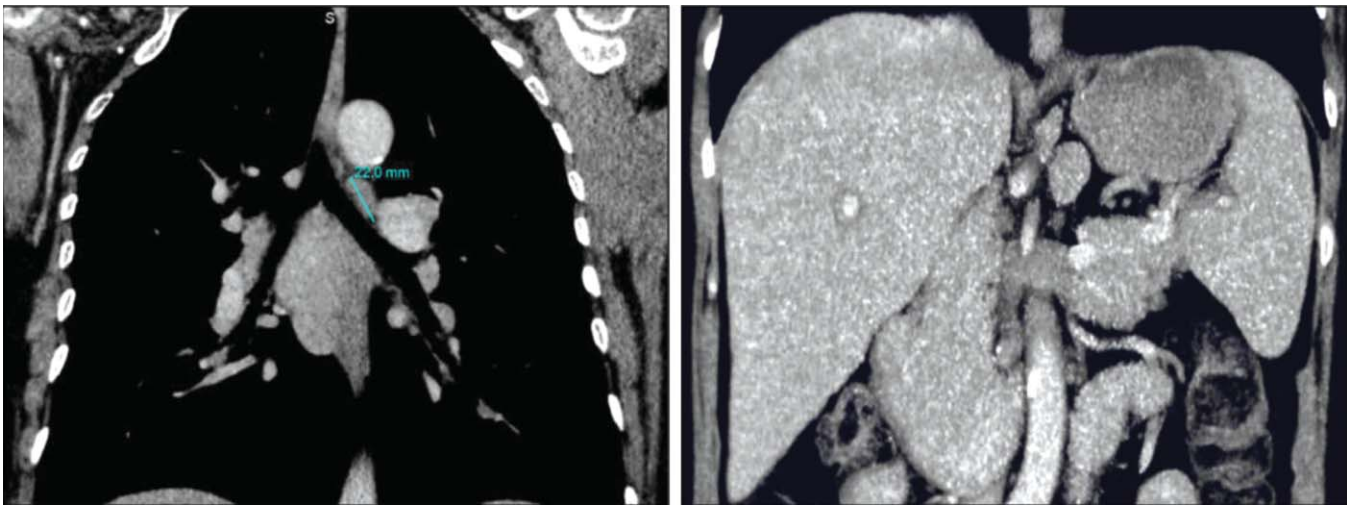

Figure-1: MSCT examination of the thorax and abdomen.

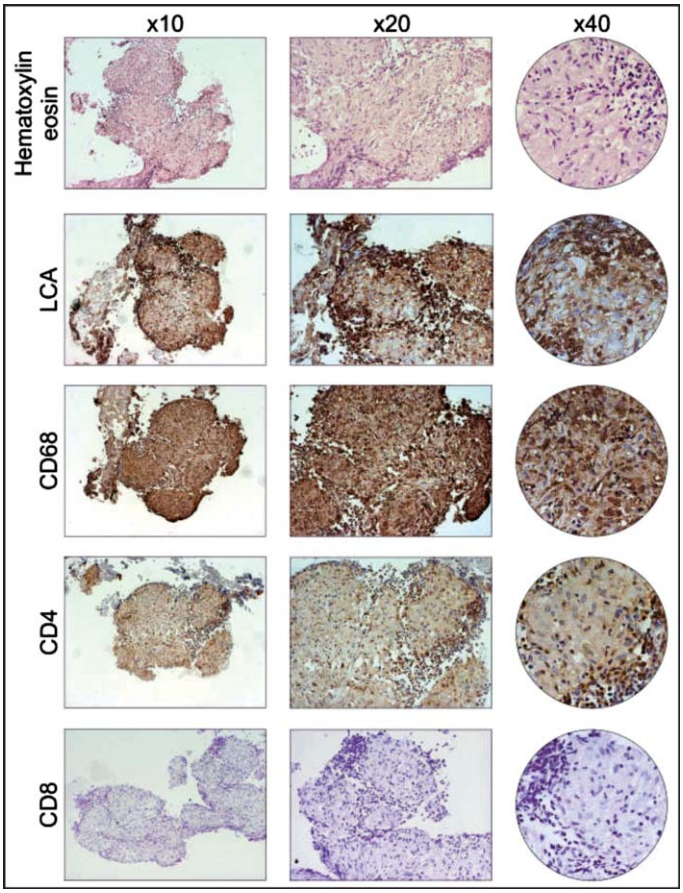

Figure-2: In the analysed material, fragments of a non-necrotizing granuloma, made up of epithelioid-altered histiocytes, with a bulbous border with chronic inflammatory infiltrate, by lymphocyte type, are observed.
Immunohistochemical analysis was performed and the following immunophenotype was obtained: expression of CD68, LCA, CD4 was present, without expression of CD8.
The histomorphological picture described in correlation with the immunoprofile corresponds to specific granulomatous inflammation by type of sarcoidosis.

plaques on the nose and cheeks. No peripheral lymphadenopathy was recorded at the time of admission.

Laboratory analysis revealed signs of positive inflammatory syndrome (erythrocyte sedimentation 100 mm / h, Le 13.9 x109 / l, C - reactive protein 123.1 mg / L). Peripheral blood smear showed conspicuous eosinophilia (28.6%), which was maintained in control analysis as well. Other laboratory analyses were within the reference range (total serum Ca 2.27 mmol / l, urine Ca 2.33 mmol / l). Serologic analysis indicated old cytomegalovirus and Epstein-Barr infection and excluded HIV infection, hepatitis B and C. Tumour markers — NSE and CYFRA, CEA, AFP, CA 125, CA 19-9 — were within reference values. Immunological analyses were negative. Activity of angiotensin converting enzyme (ACE) was at the upper limit of the reference values (52.1 U / l). Swabs of the tongue and pharynx, and urine culture test as well as six chemo cultures taken during fever remained sterile. Alcohol-resistant bacilli were not detected by direct bacilloscopy of the sputum. The QuantiFERON test for latent tuberculosis infection was also negative.

Voluminous hiluses were seen on radiographs of the heart and lungs. By using computed tomography (MSCT) of the chest and abdomen, infracarinal conglomerates of enlarged mediastinal lymph glands were observed, the largest one being 65 x 50 x 30 mm, as well as a nodular change in diameter of 6.5 mm. In the right hilus, there were more lymph nodes up to 26 mm, while in the left hilus they were up to 124.5 mm. Suprapancreatic lymph nodes were also detected in the abdomen, the largest one being of 20.5 x 13.5 mm (Figure-1).

Endoscopic procedures, gastroscopy and colonoscopy did not indicate the pathological findings.

Due to suspected haematological disease, a bone marrow biopsy was performed, which excluded the existence of bone marrow infiltration. In the further course of the disease, the patient developed peripheral lymphadenopathy and, for the purpose of supplementary diagnosis, a biopsy of the supraclavicular lymph node, as well as rigid bronchoscopy with transbronchial biopsy, were performed.

Through biopsy of the supraclavicular lymph node, nonspecific findings (reactive hyperplasia) were obtained. However, the pathohistological examination of the bioptic material obtained by rigid bronchoscopy was much more specific: Lymphadenitis granulomatosa specifica vs sarcoidosis (Figure-2).

Informed consent of the patient has been obtained for publication of the report.

Discussion

Numerous etiological agents meet the criteria for fever of unknown origin in which, in addition to temperature, lymphadenopathy dominates as well. Some of the diseases manifested by mediastinal and abdominal lymphadenopathy may have benign aetiologies (tuberculosis, viral, fungal, bacterial diseases, connective tissue diseases, Castleman disease, Wegener's granulomatosis, sarcoidosis) or malignant aetiologies (Hodgkin's and non-Hodgkin's lymphoma as well as secondary cancers of glands, oesophagus, lungs, biliary tract, and pancreas).[9,10]

Sarcoidosis is a chronic, inflammatory, multisystem disease characterised by specific non-caseating granulomas.7 The disease may be acute and chronic.[11] LÖfgren is an acute form of sarcoidosis and is characterised by erythema nodosum, bilateral hilar lymphadenopathy, polyarthritis, or polyarthralgia. Chronic disease may be asymptomatic despite progressive radiographic findings.[10]

Sarcoidosis is primarily an afebrile disease, while main clinical manifestation in our patient was fever itself, which is a rare manifestation of chronic sarcoidosis. The exceptions to this rule are LÖfgren's syndrome, Heerfordt's syndrome, which includes uveoparotid fever, and neurosarcoidosis, which manifests itself with signs of basilar meningitis.[6]

Our patient also had peripheral neck lymphadenopathy as clinical picture, which is a less common manifestation of sarcoidosis. Also, the patient had a cutaneous manifestation in the form of lupus pernio, as part of the clinical picture of chronic sarcoidosis, which, in addition to the pathohistological findings, complemented the diagnosis of chronic sarcoidosis.

Typically elevated serum ACE, hypercalcaemia, and hypercalciuria were not detected by biochemical analysis in our patient. It is well known that ACE may not be elevated at a late stage of the disease or when using an ACE inhibitor.[12] In the smear of the peripheral blood, a striking eosinophilia was detected on several occasions, which completely withdrew after the introduction of corticosteroid therapy. Eosinophilia can occur in patients with sarcoidosis. Takahashi et al published a study where 35,4% of sarcoidosis patients in a group of 178 patients had an increased number of peripheral blood eosinophils (> 4%).[8] The immune response in sarcoidosis is characterised by the dominance of the Th1 response, which is mediated by the accumulation of CD4 + T lymphocytes in non-caseating granulomas. An increased CD4 + / CD8 + ratio in granulomas is a characteristic diagnostic parameter for sarcoidosis, which has been registered in the histopathologic findings in our patient.[7]

The presence of non-caseating granulomas may indicate sarcoidosis as well as lymphoma. In patients with sarcoidosis and lymphoma cough, dyspnoea, weight loss, peripheral as well as mediastinal lymphadenopathy, hypercalcaemia may be present. In rare cases, both diseases may coexist, hence it is called sarcoidosis lymphoma syndrome.[13]

Tuberculosis, which can be clinically manifested by long-term fever, cough and lymphadenopathy, should also be considered. However, its existence was excluded in this case by supplementary microbiological and immunological tests.

In the present case, a diagnosis of pulmonary sarcoidosis was made on the basis of clinical picture, radiographic and pathohistological findings, and after exclusion of infectious and malignant diseases.

Prednisone therapy improves the patient's general condition and initiates the regression of mediastinal and abdominal lymphadenopathy and normalisation of eosinophil counts, as well as other laboratory parameters. We first started treatment with 60 mg of Prednisone for four weeks, and then successively continued to reduce the dose to 40 mg for the next two months, then 30 mg for two months, 20 mg for the next two months, considering that the patient responded well to the therapy. For another year, we treated the patient with 10 mg of Prednisone, and gradually switched off corticosteroid therapy, in the applied dose of 10 mg on every second day. To confirm a good response to the applied therapy a control scan of the abdomen and chest

was performed, on which complete regression of lymphadenopathy was verified.

Conclusion

It should be emphasised that in case of prolonged temperature in patients with generalised lymphadenopathy, one should consider sarcoidosis in terms of differential diagnosis; therefore, it is of great importance to exclude primarily lymphoproliferative and other granulomatous diseases.

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References

1. Petersdorf RG, Beeson PB. Fever of unexplained origin: report on 100 cases. Medicine (Baltimore) 1961;40:1-30. doi: 10.1097/00005792-196102000-00001.
2. Durack DT, Street AC. Fever of unknown origin--reexamined and redefined. Curr Clin Top Infect Dis 1991;11:35-51.
3. Popovska-Jovicić B, Canović P, Gajović O, Raković I, Mijailović Z. Fever of unknown origin: Most frequent causes in adults patients. Vojnosanit Pregl 2016;73:21-5. doi: 10.2298/vsp140820128p.
4. Bosilkovski M, Dimzova M, Stevanović M, Cvetkovska VS, Duganovska MV. Fever of unknown origin--diagnostic methods in a European developing country. Vojnosanit Pregl 2016;73:553-8. doi: 10.2298/vsp140827050b.
5. Brown I, Finnigan NA. Fever of Unknown Origin. Treasure Island, FL: StatPearls Publishing; 2021.
6. Cunha BA, Sivarajah T, Jimada I. Sarcoidosis with fever and a splenic infarct due to CMV or lymphoma? Heart Lung 2017;46:394-6. doi: 10.1016/j.hrtlng.2017.05.009.
7. Ungprasert P, Crowson CS, Matteson EL. Epidemiology and clinical characteristics of sarcoidosis: an update from a population-based cohort study from Olmsted County, Minnesota. Reumatismo 2017;69:16-22. doi: 10.4081/reumatismo.2017.965.
8. Takahashi A, Konno S, Hatanaka K, Matsuno Y, Yamaguchi E, Nishimura M. A case of sarcoidosis with eosinophilia in peripheral blood and bronchoalveolar lavage fluid. Respir Med Case Rep 2013;8:43-6. doi: 10.1016/j.rmcr.2013.01.004.
9. Pavlović-Popović Z, Zarić B, Kosjerina Z, Petrović D. Splenomegaly in Sarcoidosis: Frequency, Treatment, Prognosis and Long-term Follow-up. Srp Arh Celok Lek 2015;143:279-83. doi: 10.2298/sarh1506279p.
10. Kim TH. How to Improve the Diagnostic Accuracy of EUS-FNA in Abdominal and Mediastinal Lymphadenopathy? Clin Endosc 2019;52:93-4. doi: 10.5946/ce.2019.048.
11. Costabel U, Wessendorf TE, Bonella F. Epidemiology and Clinical Presentation of Sarcoidosis. Klin Monbl Augenheilkd 2017;234:790-5. doi: 10.1055/s-0042-105569.
12. Carmona EM, Kalra S, Ryu JH. Pulmonary Sarcoidosis: Diagnosis and Treatment. Mayo Clin Proc 2016;91:946-54. doi: 10.1016/j.mayocp.2016.03.004.
13. Oskuei A, Hicks L, Ghaffar H, Hoffstein V. Sarcoidosis-lymphoma syndrome: a diagnostic dilemma. BMJ Case Rep 2017;2017:bcr2017220065. doi: 10.1136/bcr-2017-220065.