VIA MEDICA

PRACA KAZUISTYCZNA

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Fatal clinical outcome in a patient with sarcoidosis-lymphoma syndrome

Niekorzystny przebieg kliniczny u chorej z zespołem sarkoidozy współistniejącej z chłoniakiem

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Abstract

A 62-year-old female suspected of malignant disease underwent a splenectomy that revealed noncaseating granulomas in the histological specimen. Chest X-ray (CXR) and lung CT scans suggested sarcoidosis stage II. TBLB showed noncaseating granulomas. A diagnosis of sarcoidosis was made. Initially no treatment was needed as partial remission on CXR and normal lung function were observed. During the follow up she underwent open lung biopsy and axillary lymph node biopsy because of radiological progression with presence of CXR opacities imitating metastases and recurrent lymphadenopathy. No malignant cells were found. Spontaneous partial resolution of disseminated changes on the CXR was observed. Because of progressive deterioration in lung function and the clinical course of the disease strongly suggesting the progression of systemic sarcoidosis, the patient was given steroid treatment, which initially resulted in partial remission of pulmonary disseminated changes, peripheral lymphadenopathy and improvement in lung function test. Eight months later severe deterioration in general condition, anaemia, leukocytosis, hypoxemia, massive hepatomegaly and recurrence of general lymphadenopathy along with progression of disseminated changes were found. She died before the final diagnosis was established. Post-mortem examination showed a nodal marginal zone B-cell lymphoma with monocytoid B-cells, according to WHO classification. The malignant cells were found in the jugular, mediastinal, paratracheal, paragastric, paraintestinal and retroperitoneal lymph nodes and they infiltrated the lungs, pleura, liver, thyroid gland and pancreas. No sarcoid granulomas were found in the autopsy.

Key words: sarcoidosis-lymphoma syndrome, sarcoid-like reaction, noncaseating granulomas, diagnostic procedures

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Streszczenie

U 62-letniej kobiety, z klinicznym podejrzeniem choroby rozrostowej układu krwiotwórczego, wykonano splenektomię. W badaniu histopatologicznym stwierdzono obecność licznych nieserowaciejących ziarniniaków. Badania obrazowe klatki piersiowej pozwoliły na rozpoznanie sarkoidozy płuc w stadium II, którą potwierdzono badaniem histopatologicznym materiału uzyskanego drogą przezoskrzelowej biopsji płuca. Chora początkowo nie wymagała leczenia systemowego, ponieważ w trakcie obserwacji stwierdzono samoistną częściową regresję zmian rozsianych w płucach. W toku obserwacji, z uwagi na progresję zmian rozsianych w płucach, których morfologia mogła odpowiadać zmianom o charakterze przerzutów oraz z uwagi na powiększenie węzłów

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obwodowych zweryfikowano rozpoznanie sarkoidozy pobierając wycinki z płuc podczas otwartej biopsji płuca oraz biopsję węzła chłonnego pachowego prawego. Nie znaleziono komórek nowotworowych. Ze względu na pogorszenie parametrów wentylacyjnych płuc oraz progresję sarkoidozy płucnej i układowej w toku dalszej obserwacji pacjentkę zakwalifikowano do leczenia steroidami systemowymi. Obserwowano poprawę kliniczną, radiologiczną i czynnościową. Po 8 miesiącach leczenia stwierdzono nagłe pogorszenie stanu ogólnego, niedokrwistość, leukocytozę, hipoksemię, znaczną hepatomegalię oraz nawrót uogólnionej limfadenopatii i zmian rozsianych w płucach. Chora zmarła przed ustaleniem ostatecznego rozpoznania. Na podstawie badania autopsyjnego rozpoznano uogólnionego chłoniaka strefy brzeżnej z komórek B, monocytoidalnego. Komórki chłoniaka stwierdzono w węzłach chłonnych szyjnych, śródpiersia, rozwidlenia tchawicy, krzywizny większej żołądka, krezki jelita i zaotrzewnowych oraz stwierdzono naciekanie narządów wewnętrznych: płuc, opłucnej płucnej, wątroby, tarczycy i trzustki. W badaniu autopsyjnym nie stwierdzono obecności ziarniniaków sarkoidalnych w badanych narządach.

Słowa kluczowe: zespół sarkoidoza-chłoniak, odczyn sarkoidalny, nieserowaciejące ziarniniaki, procedury diagnostyczne

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Introduction

Sarcoidosis is a systemic disease of unknown aetiology, with a variable clinical course and multiple organ involvement. Massive splenomegaly with minimal changes in other organs is rare.

The presence of granuloma in a biopsy specimen is not specific to sarcoidosis. Sarcoid-like granulomatous reaction may be present in chronic inflammatory, infectious and malignant diseases [1].

Sarcoid reaction in the course of neoplastic disease can be found in lymph nodes draining the area of a tumour, in the tumour itself and in non-regional tissues. Overall, sarcoid reaction occurs in 4.4% of cancers, 13.8% of patients with Hodgkin's lymphoma (HL) and in 7.3% of cases with non Hodgkin's Lymphoma (NHL) [2]. On some occasions sarcoid reactions may be extensive and may cause difficulties in establishing diagnosis of an underlying malignant disease [3].

Malignant lympho-proliferative diseases develop at least 5.5 times more often than expected in middle-aged patients with chronic active sarcoidosis, possibly as a consequence of the immunologic abnormalities observed in this disease [4].

In most reported cases of sarcoidosis--lymphoma syndrome, the diagnosis of sarcoidosis preceded the diagnosis of lymphoma.

We present a history of a 62-year-old woman with sarcoidosis-lymphoma syndrome with fatal outcome.

Case report

A 62-year-old female was referred to the Haematology Department in October 2002 because of massive splenomegaly. She had no significant past medical or family history. She was asymptomatic. On physical examination she was alert with no apparent distress. Her spleen was palpable 10 cm below the left costal margin and was soft. She had no peripheral lymphadenopathy and there was no other abnormality on physical examination.

Abnormal laboratory findings included: Haemoglobin (Hb): 9.6 g/L; Haematocrite (Hct) 27.5%, low absolute number of leukocytes 2300/mm^3 (48% of Neutrophils and 29% of Lymphocytes); lactate dehydrogenase (LDH): 594 U/L, low total protein (5.6 g/dL) with normal serum protein electrophoresis. Mild hypercalcaemia was also noted (2.7 mmol/L).

Chest X-ray (CXR) showed a discrete hilar and paratracheal lymphadenopathy and bilateral disseminated changes. Computed Tomography (CT) of the abdomen revealed splenomegaly (17 cm × 12 cm), no hepatic changes and multiple enlarged parapancreatic and retroperitoneal lymph nodes (maximal diameter — 15 mm).

In order to exclude possible lymphoma, a bone marrow biopsy was performed and showed normocellular bone marrow, intact cellular distribution and maturation, 3 lymphoid aggregates, increased marrow fibrosis and increased number of eosinophils. Immunophenotyping of cells demonstrated CD5(+) — 71%, CD19(+) — 3%, CD20(+) — 12%, CD20(+)10(+) — 2%, CD10(+) — 4%, CD34(+) — 7%, CD34(+)33(+) — 5% and CD33(+) — 16%.

The conclusions were normal lymphocytes T CD5(+) count, normal lymphocyte B count; myeloid line stem cells CD34(+)/CD33(+) were present.

The patient underwent splenectomy because of progressive enlargement of the organ. The histopathological examination revealed small, sarcoid-like epithelioid granulomas with giant cells and no necrosis, with fibrosis (Fig. 1). The initial diagnosis was systemic sarcoidosis, and the patient was referred to the Pulmonary Department in June 2003. Her general condition was very good, with no complaints. CXR revealed bilateral hilar lymphadenopathy and disseminated changes with partial resolution, when compared to

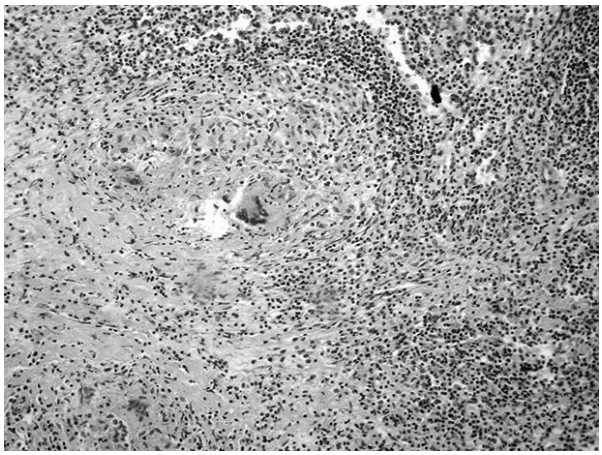

Figure 1. Granulomas of spleen. Small, sarcoid-like epithelioid granulomas with giant cells and no necrosis, with fibrosis. Microphotograph. H+E stain, low magnification

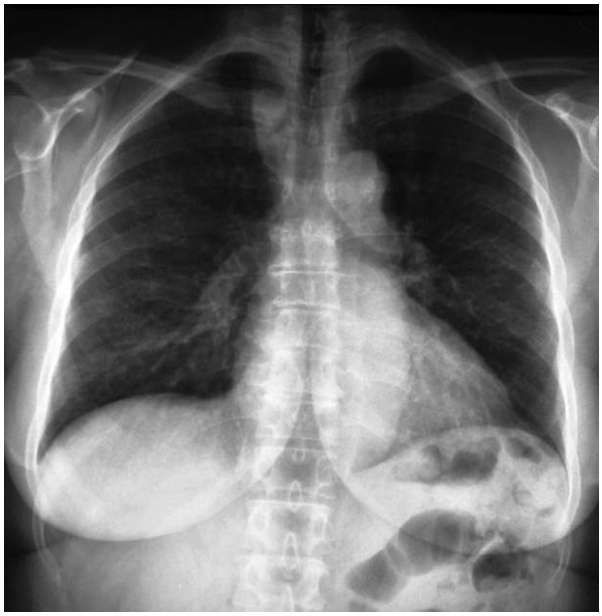

Figure 2. Chest X-ray: diffuse reticular and nodular opacities predominantly in the middle lung zones. Slightly enlarged hilar and mediastinal lymph nodes. Widening of the upper mediastinum on the right mostly due to prominent superior vena cava. No significant changes in comparison with previous radiograph from April 2003 were shown

CXR from the Haematology Department (Fig. 2). Thoracic CT revealed numerous enlarged mediastinal and pulmonary lymph nodes associated with disseminated changes typical for sarcoidosis. No anaemia or leukopenia were observed. Blood biochemical parameters were within normal limits, including liver function tests, total protein level and serum protein electrophoresis. The serum activity of angiotensin-converting enzyme (ACE) was elevated (113 U/L, normal value 8–52 U/L).

Contrast enhanced abdominal CT after splenectomy showed partial remission of the abdominal lymphadenopathy. On bronchoscopy, no macroscopic abnormalities were detected. Transbronchial lung biopsies (TBLB) contained multiple noncaseating, epithelioid cell granulomata, without signs of malignant disease. Cultures and staining for acid fast bacilli (AFB) and fungi were negative. Lung function testing (LFT) revealed a mild decrease in static lung compliance (Cst =1.59 L/kPa, 65% of predicted value), with no impairment of other parameters.

A diagnosis of systemic sarcoidosis involving the lungs, lymph nodes and spleen was confirmed. Because of her good general condition, no complaints, almost normal LFT and partial resolution of disseminated changes in chest CT scan, the patient did not receive any systemic treatment.

She was readmitted to the Pulmonary Department two months later (August 2003) because of fever, sweats and weight loss associated with non-productive cough. She appeared quite well on physical examination and no rash or lymphadenopathy were noted. Late inspiratory crackles were heard at both lung bases. The liver was not palpable. Blood analysis showed mild anaemia (Hb 11.5 g/dL, Hct 38.1%, RBC 4.57), mild leukocytosis (WBC 12 100/mm^3), normal smear and a slight impairment of liver function tests (aspartate aminotransferase AST 52 U/L; alanine aminotransferase ALT 73 U/L; alkaline phosphatase ALP 337 U/L) with normal bilirubin concentration and negative serology for hepatitis.

Chest CT scan showed extensive disseminated ground–glass opacities with mild mediastinal and hilar lymphadenopathy (Fig. 3). The abdominal CT scan showed enlarged lymph nodes in

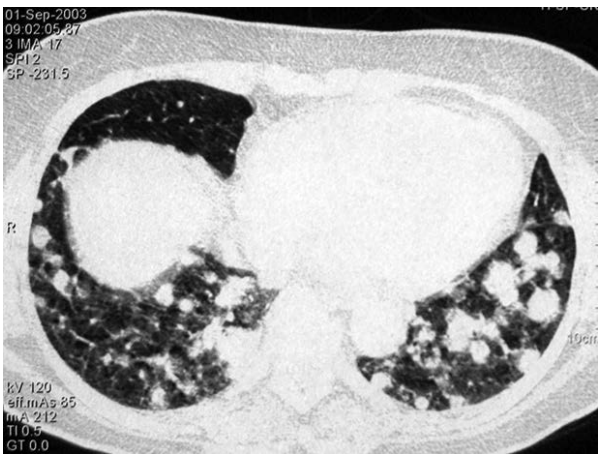

Figure 3. HRCT; multiple, various sized nodules in both lungs predominantly in the lower lung zones

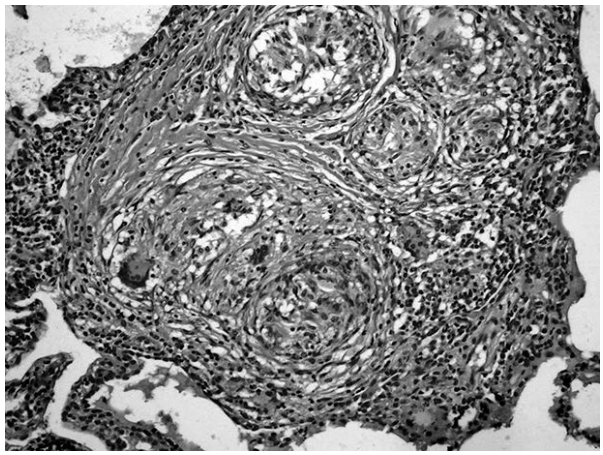

Figure 4. Open surgical wedge biopsy of lung. Multiple, well-formed granulomas consist of predominantly epithelioid cells, giant cells with peripheral rim of inflammatory cells and fibrosis. Microphotograph. H+E stain, high magnification

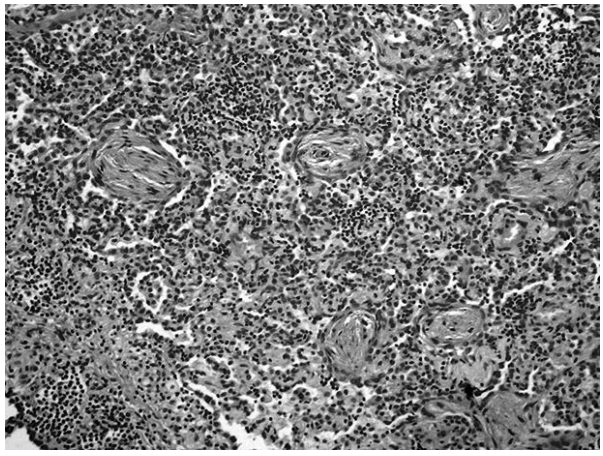

Figure 5. Open surgical wedge biopsy of lung. Organizing pneumonia pattern with polypoid plugs of loose connective tissue filling airspaces. Mildly thickened alveolar septa with mild lymphocytic infiltrate. The architecture of the lung is preserved. Microphotograph. H+E stain, low magnification

the left para-aortic region and left renal hilum (18 mm). No other abnormalities were found. Bronchoscopy did not reveal any abnormalities.

Chest CT scan findings were not consistent with sarcoidosis. She underwent an open lung biopsy in order to exclude any neoplastic disease. The histopathological examination of biopsy specimens revealed three types of abnormalities: multiple, well-formed granulomas consisting predominantly of epithelioid cells, giant cells with a peripheral rim of inflammatory cells and fibrosis, organizing pneumonia pattern with polypoid plugs of loose connective tissue filling airspaces, and intra-alveolar organizing exudates forming small granuloma-like patterns (Figs 4–6).

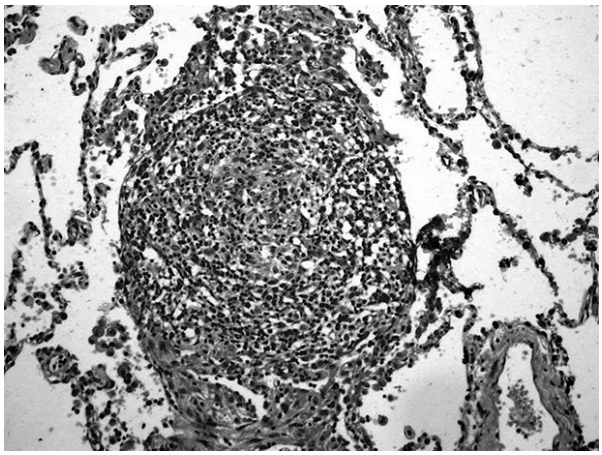

Figure 6. Open surgical wedge biopsy of lung. Intra-alveolar organizing exudates forming small granuloma-like pattern. Granuloma consists of epithelioid cells and lymphocytic infiltrate. Microphotograph. H+E stain, high magnification

One month later (September 2003), seen at the outpatient clinic, the patient reported a significant improvement in general condition. She only complained of painful hands and joints, palm X-ray revealed no abnormalities. The only abnormality found on physical examination was an enlarged (1.5 cm diameter) right supraclavicular lymph node. Because of suspicion of systemic disease, she was screened for serological markers in order to exclude connective tissue disease. No rheumatoid factor or antinuclear antibodies could be demonstrated. Neurological and dermatological examination revealed no abnormalities.

CXR and CT scans revealed partial spontaneous resolution of diffuse nodular opacities.

Regarding the multiple specimen examination (spleen, TBLB, open lung biopsy specimens) consistent with sarcoidosis, the clinical outcome and spontaneous regression of lung and abdominal pathology in the radiological examinations, the diagnosis of sarcoidosis was re-confirmed.

The patient was admitted again to the Pulmonology Department in January 2004 with fever, weight loss and sweats. The physical examination revealed generalized peripheral lymphadenopathy (supraclavicular, jugular, axillar, inguinal). Peripheral blood counts showed microcytic anaemia (Hb 11,1 g/dL, Hct 34%; Mean Corpuscular Volume MCV 78 fl, Mean Corpuscular Haemoglobin Concentration MCH 25.5 pg), normal WBC (8.6/mm^3) with 52% of Neutrophils and 25% of Lymphocytes. The erythrocyte sedimentation rate (ESR) was modestly elevated — 35/hour. Serum ACE activity level was elevated (143 U/L). Low total protein count (5.6 g/dL) was found, with normal serum protein electrophoresis. Other

parameters were within normal limits (including liver function tests and serum calcium level).

A biopsy specimen of a right axillary lymph node revealed only reactive inflammatory changes. The immunohistochemistry for CD20, CD3, CD30 and CD15 were negative.

CXR showed progression of disseminated changes. Skin test with purified protein derivative tuberculin test (PPD tuberculin test) was negative. On the third bronchoscopy no abnormalities were detected macroscopically. The biopsy specimen was reported as consistent with sarcoidosis. Examination of the bronchoalveolar fluid showed 57% macrophages, 39% lymphocytes and 3% neutrophils. The T cell helper-suppressor ratio was 3: 1. Cultures and staining techniques for fungal, mycobacterial disease or AFB were negative. Lung function testing revealed a marked decrease in the diffusion capacity for carbon monoxide (DLCO 39% pred). The diagnosis of sarcoidosis was confirmed, based on compatible clinical and radiological features and histological demonstration of non-caseating granulomas. Progressive deterioration in lung function and the clinical course of the disease strongly suggested the progression of systemic sarcoidosis. She was given steroids, starting from a dose of 30 mg/ /day of prednisone for one month, followed by 6 months of gradually tapering the dose to 10 mg/d. Corticotherapy resulted in partial resolution of pulmonary disseminated changes, total resolution of peripheral lymphadenopathy but no improvement in LFT.

Eight months later she was readmitted due to severe deterioration of health status, anaemia (Hb 10.9 g/dL; E 4.65/mm^3), leukocytosis (20/ /mm^3), hypoxemia (partial arterial oxygen pressure PaO_2 47 mm Hg, partial arterial carbon dioxide pressure $PaCO_2$ 31 mm Hg, pH 7.38), massive hepatomegaly, general lymphadenopathy and progression of disseminated changes on CXR. Contrast enhanced abdominal CT was performed before the patient was readmitted to the Pulmonary Department and showed multiple enlarged parapancreatic, retroperitoneal and paravertebral lymph nodes, a focal lesion (25 mm in diameter) in the right lobe of the liver — haemangioma and perihepatic fluid collection (Fig. 7). The patient died due to respiratory distress before the final diagnosis was made. The post-mortem examination showed nodal marginal zone B-cell lymphoma with monocytoid B-cells, according to WHO classification. The malignant cells were found in the jugular, mediastinal, paratracheal, paragastric, paraintestinal and retroperitoneal lymph nodes

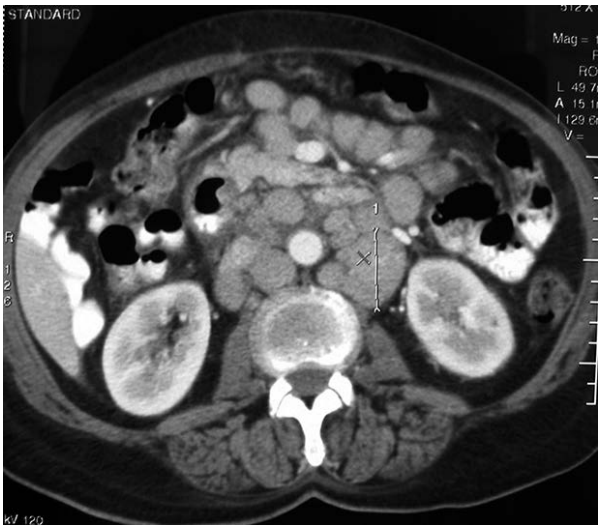

Figure 7. Contrast enhanced abdominal CT. Multiple enlarged parapancreatic, retroperitoneal and paravertebral lymph nodes. Focal lesion (25 mm in diameter) in the right lobe of the liver – haemangioma. Perihepatic fluid collection

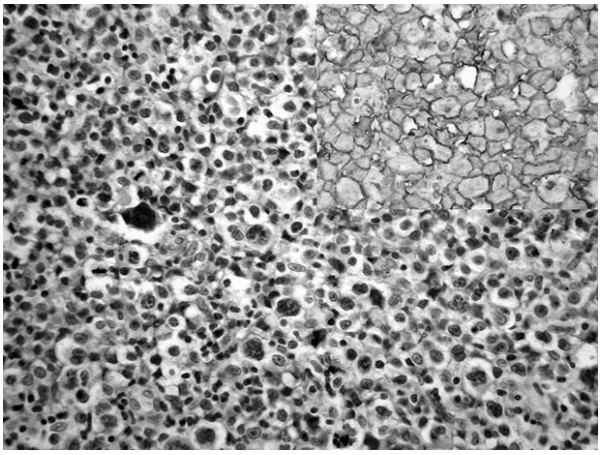

Figure 8. Lymph node involvement by diffuse infiltrate of B-cell lymphoma. Tumour cells are strong positive for CD20. Microphotograph of lymph node. H+E stain and immunostain CD20 (inset), low magnification

and they infiltrated the lungs, pleura, liver, thyroid gland and pancreas. No sarcoid granulomas were found in the autopsy (Figs 8, 9).

Discussion

The presented case should be discussed from three points of view:

— sarcoidosis-lymphoma syndrome,
— the clinical picture of sarcoidosis, that is associated with malignant disease,
— the risk and incidence of malignant disease in sarcoid patients.

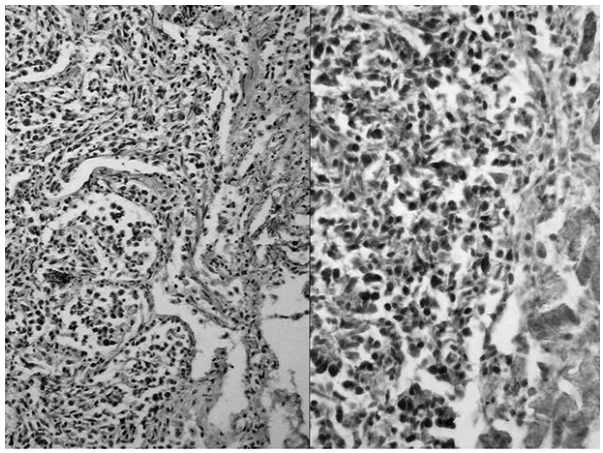

Figure 9. Lung and liver with diffuse infiltrate of large B-cell lymphoma. Microphotograph. H+E stain, low magnification

According to Papanikolaou and Sharma, the diagnostic criteria of sarcoidosis-lymphoma syndrome are biopsy-proven sarcoidosis, based on American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and Other Granulomatous Diseases (ATS/ERS/ /WASOG) criteria coexisting with biopsy-proven lymphoma according to WHO classification, with the exclusion of local sarcoid reaction [5]. Those entities may occur simultaneously, but in most described cases sarcoidosis precedes lymphoma.

Sarcoidosis and lymphoma may share clinical, laboratory and histological findings, as was seen in the presented female.

The abnormality that led our patient to seek medical advice was massive splenomegaly, with mild leukocytopenia and anaemia. She was screened for lymphoproliferative disease with different biopsy specimen verification; none confirmed the malignancy.

Splenomegaly may be found in both clinical situations: sarcoidosis and sarcoidosis-lymphoma syndrome. Spleen enlargement is observed in 1–40% of sarcoid patients, depending on the method of diagnosis (physical examination, radiography) and some patients with massive splenomegaly are managed with splenectomy [6, 7], as was done in our case.

Splenomegaly is associated with clinical evidence of more extensive extrathoracic sarcoidosis and a poor prognosis [8].

In our patient anaemia and leukopenia were observed at the initial evaluation at the Haematological Department. These abnormalities were probably due to splenomegaly with related hypersplenism because the morphology parameters normalized after splenectomy. Hypercalcaemia was also observed in the initial course of disease. Hypercalcaemia in sarcoidosis is a result of the large burden of macrophages in splenic granulomas that contain hydroxylase, which converts vitamin D to its active form [9].

Hypercalcaemia and increased serum activity of angiotensin converting enzyme are common findings in active and often progressive forms of sarcoidosis but have been also described in patients with isolated lymphoma [10]. The elevated ACE levels were indicated by Papanikolaou and Sharma as a significantly differentiating feature in sarcoidosis-lymphoma syndrome with lymphoma as a second disease to sarcoidosis [5].

The diagnosis of sarcoidosis in our patient, a 62-year-old female, was consistent with cases of splenic sarcoidosis reported in the literature [6, 11–13]. In the described cases, sarcoidosis was diagnosed in middle-aged women, with splenomegaly, small mediastinal lymph nodes and some non-specific parenchymatous pulmonary nodules. The diagnosis of sarcoidosis was made on the basis of splenectomy after eliminating other causes of granulomatosis. Only in one of the described cases the diagnosis of sarcoidosis preceded that of Hodgkin's disease (HD) by 29 years [13]. Massive splenomegaly had been present for 13 years before HD was diagnosed following splenectomy. In other cited cases no malignant diseases following splenectomy in sarcoid patients were reported [6, 8, 9]. In the Papanikolaou and Sharma review of cases of patients in which sarcoidosis and lymphoma were diagnosed in the same patient, one of the cardinal feature of lymphoma, when presented as a second disease, was splenomegaly [5].

The authors underlined the necessity of an extensive investigation of the cause of splenic granulomatosis as the diagnosis of sarcoidosis remains one of elimination. Massive splenomegaly is rare in sarcoidosis and warrants exclusion of the malignancy [14].

According to Papanikolaou and Sharma, the development of new lymph node disease and splenic involvement in the course of chronic sarcoidosis should be investigated promptly in order to rule out concomitant lymphoma. These findings correlated with the predominance of non-Hodgkin lymphoma (NHL) in selected cases [5, 15]. Our patient underwent multiple invasive diagnostic procedures (splenectomy, open lung biopsy, lymph nodes biopsy, transbronchial lung biopsy) to exclude any possible malignant concomitant condition, but all of the obtained specimens revealed sarcoid-like granulomas.

Sarcoidosis preceding lymphoma manifests with bilateral hilar lymphadenopathy and parenchymal disease [5, 16–18]. Such radiological pathology was found when the patient presented for the initial evaluation at the Haematological Department.

Non-caseating epithelioid granulomas may be found as sarcoid-like reactions in different organs. These reactions, secondary to malignancies, are thought to occur either adjacent to the primary malignant site or to local drainage nodes. Our patient was diagnosed with sarcoidosis based on ATS/ERS/WASOG criteria [19] with no evidence of coexisting malignant disease, so local sarcoid-like reaction was excluded.

In Brincker's review of 46 cases of coexistent sarcoidosis and malignant lymphoproliferative disease [4] three characteristic features appeared: the lymphoma was preceded by sarcoidosis, patients were elderly when developing sarcoidosis and sarcoidosis-associated lymphoma was more frequently Hodgkin's disease than was expected.

Our patient fulfilled the criteria of sarcoidosis-lymphoma syndrome. The presented case was consistent with two out of three Brincker's characteristics.

The time interval from onset of sarcoidosis to the development of lymphoma in our case was 23 months. In the literature the time interval from the onset of sarcoidosis to the development of lymphoma varies from months to years [12, 20]. It is estimated that the mean interval between the diagnosis of sarcoidosis and lymphoma is 24 months [21].

Our patient was 62 years old when she developed sarcoidosis, and 2 years later B cell lymphoma was diagnosed. According to the literature, lymphoproliferative disease is 5 times more frequent in middle-aged persons who have chronic active sarcoidosis than in the remaining patients. In half of them low-grade lymphomas develop [21].

In Brincker's series the most common lymphoma associated with sarcoidosis was HD [4]. Karakantza et al. confirmed the association between sarcoidosis and lymphoma, but they concluded that all types of lymphoma may develop [20]. In their study 2 out of 5 patients were diagnosed with B cell lymphoma, as was the case in our patient.

Impairment of the immune system in the form of an altered cell reaction leads to increased T-helper cell accumulation in the sarcoid tissues and secondary reduction of the circulating population of these cells. This may implicate the greater susceptibility to oncogenic viruses [22] and may partially explain the higher incidence of malignant disease in sarcoid patients.

According to Brincker's suggestions, the chronic form of sarcoidosis and treatment with steroids are predisposing factors for lymphoma development [4].

In our patient the histopathological examination of biopsy specimen of the spleen, open lung biopsy and TBLB were consistent with sarcoidosis, and the clinical course, with partial spontaneous resolution of pulmonary infiltrates, initial improvement in general condition of the patient and lack of malignant cells in lymph nodes and trepan biopsy, strongly supported the initial diagnosis of chronic sarcoidosis. Subsequently our patient developed multi-organ sarcoidosis with progressive pulmonary involvement on CTX and deterioration of LFT that needed systemic steroid treatment.

The time interval between the diagnosis of lymphoma and the last biopsy specimen verification of sarcoidosis, in our patient, was 8 months. Reich hypothesizes that clinical sarcoidosis is a generalized cell-mediated immune response to tumour antigens [23]. This may explain why malignant disease is diagnosed in most cases shortly after the onset of sarcoidosis.

Although in most described cases the diagnosis of sarcoidosis preceded the appearance of lymphoma, the time relationship between sarcoidosis and lymphoma is variable [16–18]. A case of a middle-aged women with massive splenomegaly, bone marrow involvement by lymphoma and granulomas which responded to chemotherapy was described [24]. Recently it has been confirmed that in the majority of sarcoidosis-lymphoma cases, sarcoidosis precedes the lymphoma, and the NHL types of lymphoma are most commonly found [5].

Our case is consistent with this observation.

The increased risk of malignancy in patients with sarcoidosis has been examined in several studies. Swedish authors found that among hospitalized patients in Sweden the risk of NHL was significantly increased, and this was related to deregulated immune function [25]. The same authors observed that old age at hospitalization was associated with a high risk of developing cancer in sarcoid patients, which was confirmed in our patient. This indicates the need for special clinical attention in elderly patients with diagnosis of sarcoidosis.

Because of the similarities in the clinical course, radiological picture and laboratory findings between sarcoidosis and lymphoma, it is possible

that at the initial diagnosis of sarcoidosis clinicians may not recognize the coexistence of lymphoma. Thus, without multiple biopsy specimens the distinction between benign and malignant disorders, even on the basis of sophisticated modern techniques, is not possible. In rare cases (like the one presented) extensive diagnostic procedures are not helpful in establishing final diagnosis.

In such clinical situations careful follow up of the patient is advised.

Conflict of interest

The authors declare no conflict of interest.

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