Quiz

Correct answer to the quiz. check your diagnosis

Hodgkin's lymphoma mimicking tuberculosis in cervical lymph nodes

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The authors present a case description of an 81-year-old male with general symptoms (fever, night sweats, weight loss) and cervical/supraclavicular lymphadenopathy. The revised lymph node histopathological examination revealed nodular sclerosis classical Hodgkin's lymphoma associated with abundant tuberculosis-mimicking granulomatous reaction. The diagnosis may be difficult due to similarities in clinical course, laboratory tests and imaging. The morphology of Hodgkin-Reed-Sternberg cells and the immunohistochemical profile are the most helpful in differential diagnosis. In cases where granulomas coexist with negative acid-fast staining, pathologists should always recommend evaluation of further and broader diagnostic procedures to exclude *Mycobacterium tuberculosis* infection.

Key words: Hodgkin's lymphoma, tuberculosis, granuloma, non-infectious granulomatous reaction.

Introduction

Sarcoid-like granulomas may sometimes occur in patients with malignant tumors (e.g. of uterus, breast, lung, stomach) and lymphomas. Such reaction is reported in 4.4% of cancers, 7.3% of non-Hodgkin's lymphomas and 13.8% of Hodgkin's lymphoma (HL) [1-4]. In parallel, cell-mediated immunity is broadly distorted in HL; therefore immunodeficiency may cause infections, mostly viral [Epstein-Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus] and *Mycobacterium* species including *M. tuberculosis* [5]. A close link between HL and autoimmune disorders is also reported. The increased risk of lymphoid malignancies may be associated with some autoimmune diseases; the phenomenon is initiated and stimulated by numerous factors such as genetic predispositions, viral infections, immunosuppressive agents, persistent antigen exposure, chronic inflammation, uncontrolled B-cell proliferation or apoptosis defects [6]. In exceptional cases, the overlapping image of two different diseases may be found (HL with latent tuberculosis or sarcoidosis) [7]. Differential histopathological diagnosis may prove a tough challenge and it usually requires additional immunohistochemical stainings as well as microbiological, serological or molecular tests.

The authors present a case description of an 81-year-old male with general symptoms (fever, night sweats, weight loss) and cervical/supraclavicular lymphadenopathy. The revised lymph node histopathological examination revealed HL associated with abundant tuberculosis-mimicking granuloma-

tous reaction. The differential diagnosis and the supportive role of ancillary tests are discussed.

Case description

An 81-year-old male was admitted to the Institute of Hematology and Transfusion Medicine with a 3-month history of progressive cervical and supraclavicular lymphadenopathy. The patient also reported significant weakness, impaired exercise tolerance, increased sweating and weight loss of about 10 kg. Initial diagnostic examinations were performed in the general hospital. Results of chest X-ray examination showed no specific changes; computed chest tomography (CT) revealed only minor fibrotic changes in lung parenchyma; no mediastinal lymphadenopathy was found. The cervical and axillary ultrasonographic study revealed a mass of painless lymph nodes (max. diameter of 58 mm) along both left and right sternocleidomastoid muscles. Lymphadenopathy of the right axillary region was also reported (max. diameter 45 mm). The right cervical lymph node was surgically excised and sent for histopathological evaluation with suspicion of lymphoma.

On admission to the Hematology Department the patient complained of general weakness, fatigue, and lack of appetite. Physical examination confirmed peripheral lymphadenopathy: cervical lymph nodes (up to 6 cm diameter) on the right side, in the subclavian and axillary region (2 cm and 4 cm respectively). In palpable examination the liver and spleen were not enlarged. Auscultation of the lung fields revealed correct vesicular murmur and basilar crepitant rales. Laboratory tests included: white blood count (WBC) 8.84 $\times$ 10^9 g/l [without neutropenia (neutrophil count: 7.4 $\times$ 10^9 g/l), and with lymphopenia (lymphocyte count: 0.62 $\times$ 10^9 g/l)], red blood cell count (RBC) 2.8 $\times$ 10^{12} g/l, hemoglobin concentration (HGB) 9.0 g/dl, platelet count (PLT) 370 $\times$ 10^9 g/l. Erythrocyte sedimentation rate (ESR) was elevated (110 mm/h). Biochemistry revealed normal concentrations of serum electrolytes, increased creatinine level (1.4 mg/dl), elevated serum alkaline phosphatase (241 U/l), moderately increased concentration of -glutamyltranspeptidase activity (71 U/l), and normal serum lactate dehydrogenase. Elevated concentrations of C-reactive protein (90.1 mg/l) and β_2-microglobulin (5.19 mg/l) were found and profound hypoalbuminemia (20.4 g/l) was reported. Hepatitis B and C, HIV and EBV serum tests were negative; low levels of IgG class immunoglobulins against CMV and toxoplasmosis were detected. Chest CT was consistent with the results described above. Cardiac ultrasonography showed normal myocardium and valves with effective flow 64%.

Microscopic examination of bone marrow smears revealed low cellularity with maintained erythropoiesis, myeloid lineage with segments domination (43%), insignificant increase in percentage of plasma cells (3%) and single megakaryocytes. Lymphoma infiltrates were not found in trephine biopsy. Histopathological evaluation showed complete lymph node architectural effacement by neoplastic nodules, a limited number of birefringent collagen bands, numerous non-caseating granulomas with scattered Langhans giant cells as well as granulomas with focal central necrosis and presence of neutrophils (Fig. 1 A-C). Characteristic Hodgkin and Reed-Sternberg cells (HRS cells) and lacunar cells were found scattered and in small cell aggregates (Fig. 1 D). Results of immunohistochemical stainings confirmed the neoplastic origin of HRS cells: CD30 (Dako, RTU, clone: Ber-H2), CD15 (Dako, RTU, clone: Carb-3), fascin (Dako, RTU, clone: 55 K-2) were strongly positive; BSAP (Dako, RTU, clone: DAK-Pax5) was dim positive (Fig. 1 E-H); CD20 (Dako, clone: L26), LCA (Dako, RTU, clone: 2B11+ PD7/26), EMA (Dako, RTU, clone: E29), OCT2 (Leica Microsystems, clone: Oct-207), BOB.1 (Leica Microsystems, clone: TG14), CD3 (Dako, RTU, clone: F7.2.38) and CD246 (RTU, clone: ALK1) were negative. The acid-fast stain (Ziehl-Neelsen) was performed to exclude *Mycobacterium tuberculosis* lymphadenopathy. Examination with an oil immersion lens (1000×) did not confirm the presence of organisms within the necrosis. The final histopathological report stressed the necessity of performing ancillary tests to eliminate coexistence of Hodgkin's lymphoma and tuberculosis.

The results confirmed the diagnosis of nodular sclerosis, classical Hodgkin's lymphoma, clinical stage III B and with 5 of 7 unfavorable International Prognostic Index factors (serum albumin, anemia, sex, age, lymphopenia). Administration of the ABVD (Adriamycin-bleomycin-vincristine-dacarbazine) regimen was not possible due to advanced age, general condition and no consent for hospitalization every two weeks so the patient was qualified for the COPP chemotherapy regimen (cyclophosphamide – vincristine – procarbazine – prednisone). Persistent fever was reported during hospitalization. Microbial cultures from blood, urine, cerebrospinal fluid as well as virological tests were negative. The QuantiFERON Gold in-Tube assay was used as a diagnostic tool for latent tuberculosis infection. The test was based on the quantification of interferon-γ released from sensitized lymphocytes in whole blood incubated overnight with purified protein derivative from Mycobacterium tuberculosis and control antigens. The result was negative. Broad-spectrum anti-infective treatment was administered and led to a significant improvement in the overall clinical status. The first course of chemotherapy according to the COPP scheme was launched after steroid pre-treatment. The second and third chemotherapy courses were com-

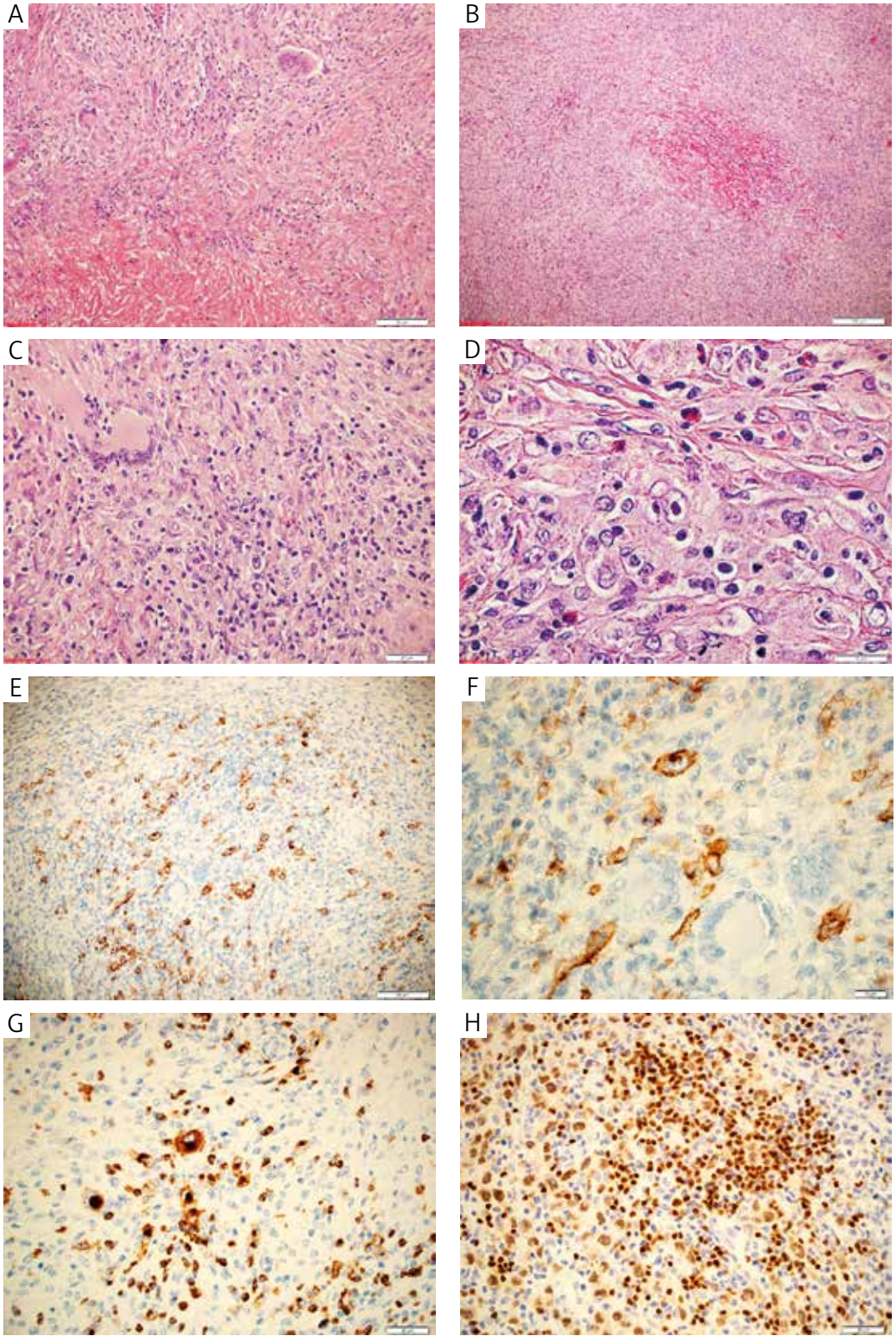

Fig. 1. A-C) complete lymph node architectural effacement by neoplastic nodules, numerous non-caseating granulomas with scattered Langhans giant cells as well as granulomas with focal central necrosis and presence of neutrophils (A – HE, 20×. **B)** HE, 10×; **C)** HE, 40×. **D)** characteristic, scattered Hodgkin and Reed-Sternberg cells (HE, 100×). **E, F)** CD30 positive immunohistochemical reaction in Hodgkin and Reed-Sternberg (HRS) cells (E – 20×; F – 100×). **G)** CD15 positive immunohistochemical reaction in HRS cells with characteristic "dot-like" staining; small, CD15 positive cells in the background are eosinophils and neutrophils (40×). **H)** dim pax-5 positive immunohistochemical reaction in HRS cells; strong staining present in reactive B lymphocytes (20×)

plicated by urinary tract infections (*Klebsiella pneumoniae etiology, ESBL positive*). The patient's condition improved after targeted antibiotic therapy and the control urine culture was sterile. During the last hospitalization the patient presented no fever or features of active infection. On physical examination, cervical and supraclavicular lymph nodes were reduced in size to max. 2 cm in diameter. Laboratory tests showed: WBC 7.82 × 10^9 g/l, HGB 10.7 g/dl, PLT 133 × 10^9 g/l, lymphopenia 0.37 × 10^9 g/l, ESR 42 mm/h, serum uric acid level 74 mg/dl; no other deviations were detected. The overall follow-up lasted 7 months with the last observation in October 2013.

Discussion

HL is a relatively rare neoplasm in the Polish population and accounts for approximately 0.5% of all malignancies and 30% of all lymphomas. About 700 new cases are diagnosed annually in persons aged 15-40, mainly in females (50% of males and 65% of females) [8].The second peak of HL incidence is observed in the sixth decade of life. In population-based studies, the proportion of HL patients above 60 years of age falls within the 20% and 44% range but a more recent retrospective re-evaluation indicated that a substantial proportion of elderly patients with B-cell lymphomas were initially misdiagnosed as having HL [9]. Thus, a reference pathology expert diagnosis should be applied in particular to cases of elderly patients with HL suspicion. The most significant differences in disease-related characteristics between younger and older HL patients include: more frequent presentation with B symptoms, elevated sedimentation rate, mixed cellularity (MC) histologic subtype, and poorer Karnofsky performance score. Even though MC subtype is more often reported in elderly patients (35% vs.19%), NS histology is still most frequent in both age groups (41% and 66%). Tumor biology, older age as well as factors related to comorbidity most likely contribute to the worse outcome for elderly patients [10].

The most frequent causes of lymph node granulomas may be classified according to their coexistence with an infective agent. Infectious granulomas include two groups of diseases with suppurative and non-suppurative reactions [11]. The second non-infectious granulomatous lymphadenitis may accompany several diseases with different etiopathogenesis, e.g. sarcoidosis, Hodgkin's and non-Hodgkin's lymphomas, sarcoid-like reactions in regional lymph nodes draining neoplasm or Crohn's disease, drug (phenytoin, procainamide, phenylbutazone, chlorpropamide, sulphasalazine, ibuprofen, indomethacin, allopurinol, carbamazepine, amiodarone) or foreign body (berylliosis, talc, anthracosis and silicosis) (Table I).

Table I. The most frequent causes of lymph node granulomas

Infectious		Non-infectious
Suppurative	*Non-suppurative*	
Almost all have central abscesses and necrosis in granulomas induced by Gram-negative bacteria and chlamydia.	Hypersensitivity-type granulomas induced by microorganisms; predominant histiocytes with smaller numbers of T-cells, dendritic cells and peripheral B-cells are recruited for granuloma formation.	Rarely abscesses and necrosis in the centre of granuloma
	Examples	
Tularemia lymphadenitis	Tuberculous lymphadenitis	Sarcoidosis
Cat scratch lymphadenitis	Atypical mycobacterial infection	Hodgkin lymphoma
Yersinia lymphadenitis	BCG lymphadenitis	Non-Hodgkin lymphoma
Lymphogranuloma venereum	Toxoplasma lymphadenitis	Lymph node draining neoplasm
Fungal infection	(Piringer-Kuchinka lymphadenopathy)	(sarcoid-like reaction)
	Leprosy	Lymph node draining Crohn's disease
	Syphilis	Berylliosis
	Brucellosis	
	Fungal infection	
	Cryptococcus	
	Histoplasma	
	Coccidioidomycosis	
	Pneumocystis	

In developed countries suppurative lymphadenitis is uncommon because of broad antibiotic availability. Regional lymph nodes draining pyogenic inflammation have preserved architecture and typically dilated sinuses, congested blood vessels and necrotizing granulomas with central neutrophil infiltrates, sometimes forming microabscesses. In a smaller number of cases fungal hyphae or viral inclusions may be observed. In both cat scratch and lymphogranuloma venereum lymphadenitis, peripheral, palisaded epithelioid cells and scattered multinucleated giant cells are reported. Crucial for differential diagnosis is past medical history (contact with cats, unilateral lymphadenopathy, genital or inguinal, perianal lesions involving regional lymph nodes), positive results in Warthin-Starry silver stain reaction or immunohistochemistry with anti-B. henselae antibody for cat scratch disease; lymphogranuloma venereum requires confirmation of C. trachomatis in polymerase chain reaction (PCR) test or serologic assays [12].

Lymphadenitis is the most common form of extrapulmonary tuberculosis (TB) (5-10%) and in the developing countries its overall incidence is estimated at approximately 40%. Distinctively, in about 90% of cases superficial lymph nodes in the head and neck region are involved; rarely generalized lymphadenopathy and hepatosplenomegaly are described [13, 14]. Major histological features are: chronic granulomas, predominantly with caseation necrosis, concentric layers of epithelioid cells, Langhans giant cells. Extended fibrosis and hyalinization may be present in later phases. Acid-fast bacilli can be visualized by Ziehl-Neelsen staining. TB diagnosis must however be confirmed also by positive laboratory test: interferon-γ released assays, microbial culture or molecular tests (mostly PCR assays). Other important forms of non-suppurative granulomatous lymphadenitis are found in the outcome of atypical mycobacterial infections, BCG lymphadenitis, Toxoplasma lymphadenitis, leprosy, syphilis, brucellosis and fungal infections [15].

Sarcoidosis and HL are the two major diseases and most frequent representatives of non-infectious granulomatous reaction. Pathogenesis of sarcoidosis is based on decreased systemic cellular immunity as well as systemic and focal chronic inflammation. Diminished function of dendritic cells may play the key role in sustaining anergy to antigenic stimuli [16]. Altered dendritic cell maturation has also been reported in malignancies (e.g. breast cancer, myeloma) and infectious diseases (i.e. tuberculosis) [17]. Microscopic findings in sarcoid lymphadenopathy depend on the phase of the disease. Follicular hyperplasia and sinus histiocytosis appear in the early phase; subsequently, small epithelioid cell nodules are seen in the cortex and the decrease of histiocytes is marked. Well-demarcated granulomas composed of epithelioid cells with scattered Langhans cells can then develop. Classical sarcoid granulomas lack necrosis or only small central foci of fibrinoid necrosis can be observed. In the late phase, increased collagen fiber deposition results in fibrosis and hyalinization. The T-lymphocyte CD4/CD8 ratio is typically over 3.5 and usually CD4 positive cells are located within granulomas; thus CD8 positive T-lymphocytes surround granulomas. Other important components for granuloma formation are dendritic cells, macrophages and histiocytes. Moreover, various inclusion bodies such as asteroids or Schaumann bodies and Hamazaki-Wesenberg inclusions can be identified. Histopathological diagnosis of sarcoid lymphadenopathy requires confirmation of the disease by flow cytometric immunophenotyping for T-cell subsets in bronchoalveolar lavage fluid [12, 15].

Classical nodular sclerosis HL may be associated with granulomatous reaction; the syncytial variant mostly presents with aggregates of lacunar cells admixed with histiocytes. Areas of coagulative or suppurative necrosis may be found therefore and such lesions are sometimes misdiagnosed as infectious granulomas [18]. The key point in differential diagnostics of HL with abundant granulomas is the recognition of lacunar and/or HRS cells. The second pitfall concerns epithelioid histiocytes, which need careful examination; inspection of cytologic features does not show a prominent nucleolus. Immunohistochemistry allows one to confirm HL; HRS and/or lacunar cells express CD15, CD30, fascin, and pax-5 (dim positive) and are negative to CD45/LCA. To exclude concomitant tuberculosis, an acid-fast stain must be performed on histological specimens and further microbiological, serological and PCR tests are needed [12].

In summary, the coexistence of HL and granulomas can be tricky and may lead to inappropriate diagnosis. Cases of HL and tuberculosis are very rare and require additional tests to confirm the presence of microorganisms. Treatment of *M. tuberculosis* infection usually improves the outcome and effect of chemotherapy. Each elderly patient with HL suspicion is recommended for revised, histopathological examination. The morphology of HRS/lacunar cell as well as immunohistochemical profile are most helpful in differential diagnosis. In cases where granulomas coexist with negative acid-fast staining, pathologists should always recommend further and broader diagnostic procedures to be performed.

Authors declare no conflict of interests.

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