Sinus histiocytosis with massive lymphadenopathy

A report of a case with severe articular involvement

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Case report
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A case is described of a 37-year-old female patient presented several times with moderate to severe swelling and arthralgies of the small and large joints, accompanied with fevers, cervical and axillary lymphadenopathy, elevated erythrocyte sedimentation rate, hyperglobulinaemia and upper respiratory tract obstruction. The biopsies were performed and the diagnosis of sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) was established, both in lymph nodes (axillary, forearm and parotid area lymph nodes) and extranodal sites (submucosa of the maxillary sinus). Serum antibody titres against Epstain-Barr virus were elevated. Remissions were achieved by administration of antirheumatics and corticosteroids.

Key Words: sinus histiocytosis with massive lymphadenopathy, articular involvement

INTRODUCTION

In 1969, Rosai and Dorfman (17) described an entity which they named sinus histiocytosis with massive lymphadenopathy (SHML). SHML is a non-neoplastic, pseudolymphomatous, usually protracted self-limited disease that characteristically manifests as painless bilateral cervical adenopathy. It is due to sinusoidal distention by a marked proliferation of morphologically benign histiocytes within whose cytoplasm large numbers of cells, predominantly lymphocytes, have been engulfed. The disease is accompanied by low-grade fevers, leucocytosis, elevated erythrocyte sedimentation rate and polyclonal hypergammaglobulinaemia (17,18). Patients who have this disease are most commonly in their first or second decades, but persons of any age may be affected (22). A few cases have shown familial incidence (14,22). Extranodal involvement is known to occur in approximately 28% of cases (4,22). The aetiology of the disease is not known. There has been no satisfactory therapy for the more severe cases.

We describe a patient with SHML who has clinically severe articular involvement. Remissions were achieved by the administration of antirheumatics and corticosteroids.

CASE REPORT

A 37-year-old female patient was admitted to our hospital with moderate swelling of the big joints accompanied with arthralgia of the two years' duration.

Past medical history was unremarkable. Family history revealed that patient's mother died of rectal cancer and one of her sisters died of endometrial carcinoma. Her husband was treated of pulmonary tuberculosis twenty years before.

Severe pains and moderate to severe swelling of the big joints had been present two years before the admission. They first occurred in the ankles. Knees and elbows were involved later. Acute purulent tonsillitis usually, but not always, preceded those painful attacks.

On physical examination, the patient was noted to have moderate to severe swellings of the first joints, elbows and of the right knee as well as of the ankle. The patient had elevated erythrocyte sedimentation rate (55/92, later 85/112), normochromic anaemia with normal different blood cell count. However, eosinophilia (9%) was noticed once, and eosinophils were found in the sternal punctate. Hyperglobulinaemia was present (IgG 26,0 g/L, IgA 3,6 g/L), with reversal of the albumin – globulin ratio. Rheumatoid factors, anti-nuclear and anti-DNA antibodies, LE cells were not tra-

ced. AST and tonsillary microorganisms cultures were not performed. Roentgenographic examination was performed due to nasal obstruction, indicating pansinusitis. Following administration of non-steroid antirheumatics and antibiotics, the patient's state gradually improved and she was discharged.

During the following month the patient was readmitted to hospital with fever, tonsillitis and left axillary lymphadenopathy. The biopsy of 12 x 4 mm axillary lymph node was performed and misdiagnosed as nonspecific lymphadenitis. Arthralgias did not react to the administration of antibiotics and sulphonamides. Tonsillectomy was performed, but PHD was not available. Mild enlargement of the cervical lymph nodes and lymphopenia were noted. High sedimentation rate and anaemia persisted. Chest roentgenograms were normal. Antirheumatics were administered again with positive result.

A few months later, the patient presented with eyelid swelling, arthralgia, loss of weight, fevers and pains in the parotid area bilaterally. Results of CT examination of the abdominal region and the liver biopsy were both normal. After the same therapy, her state gradually improved.

Two months later, she was admitted again with arthralgia and upper respiratory tract obstruction. Elevated erythrocyte sedimentation rate persisted (20). Clinical suspicion of tuberculous infection arose. Following administration of antituberculous therapy and corticosteroids, her state definitely improved, although lymphadenopathy persisted. A left forearm lymph node biopsy was performed. Marked capsular and pericapsular fibrosis was noted (figure 1). The sinuses were dilated and occupied by a mixed cell population: histiocytes with haemophagocytic activity, lipid-laden histiocytes, lymphocytes and plasma cells. Multinucleation of the histiocytes was not noted, but binucleation was present. Haemophagocytosis was characterised by the presence of apparently viable cells of haematopoietic origin within the cytoplasm of many of the sinus histiocytes. These were represented by lymphocytes in the large majority of instances, but plasma cells and red blood cells were occasionally seen. The compressed intersinusal tissue contained mature lymphocytes and a variable number of plasma cells. Lymphoid follicles and germinal centres were inconspicuous. Paucity of eosinophils and the absence of necrosis or granuloma formation were also observed.

A review of the previous lymph node biopsy was performed. This time, rare dilated sinuses with histiocytes exhibiting prominent haemophagocytosis were noted (figure 2). The intersinusoidal lymphoid tissue consisted mainly of plasma cells, some of which contained Russell's bodies, and capsular fibrosis was absent.

Serum antibody titres against Epstain-Barr virus were elevated. Leucocyte alkaline phosphatase was nor-

FIGURE 1.
Biopsy no 2 – the lymph node from the left forearm. Marked capsular and pericapsular fibrosis is clearly visible, with a few small areas of preserved lymphoid tissue.
SLIKA 1.
Biopsija br. 2 – limfni čvor s lijeve podlaktice. Uočljivo je vezivno zadebljanje čahure s nekoliko manjih područja očuvanog limfoidnog tkiva.

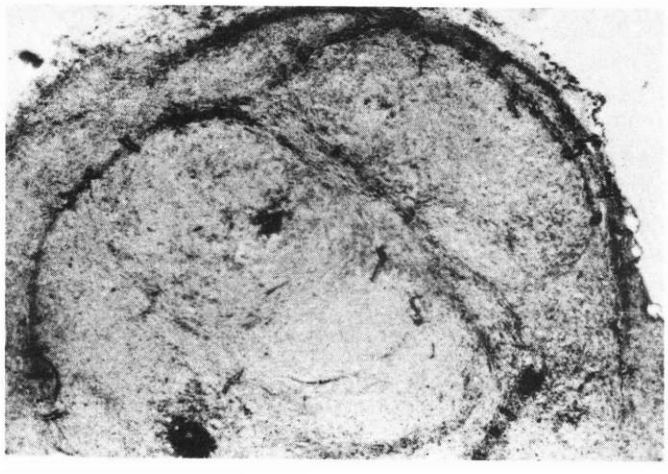
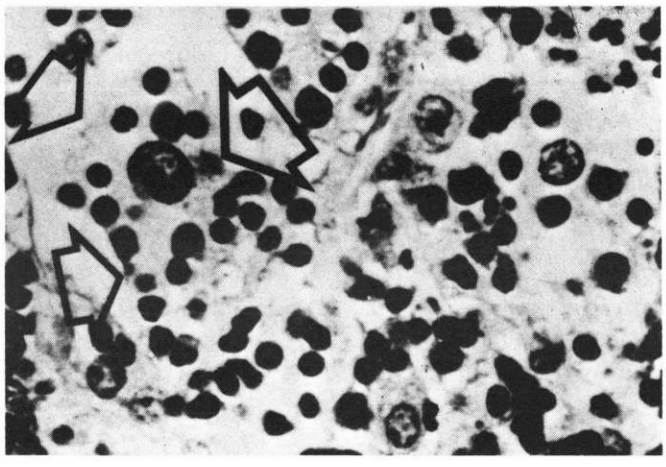


FIGURE 2.
Biopsy no 1 – the lymph node from axilla. Lymphocytes and plasmacytoid cells are present within the cytoplasm of the sinus histiocytes (arrows).
SLIKA 2.
Biopsija br. 1 – limfni čvor iz pazuha. U citoplazmi sinusnih histicita nalaze se limfociti i plazmacitoidne stanice (strelice).



mal. A parotid area lymph node and maxillary sinus biopsies were also performed. The lymph node near the parotid salivary gland was of the very same appearance as the one removed from the forearm. Biopsy material of the maxillary sinus was yellow due to numbers of histiocytes with lipid content in cytoplasms, situated beneath the respiratory epithelium of the sinus, accompanied with plasma cells and few histiocytes showing haemophagocytosis. Again, antirheumatics and corticosteroids proved to be useful and another remission was achieved.

When last seen six months later, the patient was asymptomatic, on no medication, but the slight cervical lymphadenopathy persisted.

DISCUSSION

Although the cervical region is by far the commonest site of involvement, other peripheral or central lymph node groups can be affected in SHML, with or without cervical disease (19). In over one fourth of the cases, the disease involves the following extranodal sites: eyes and ocular adnexa (3,4,22), upper respiratory tract (5,22), skin and subcutaneous tissue (22,23,24), central nervous system and vertebral canal (2,6,7,10), gastrointestinal tract (15,22), thyroid (11) and bones (20,22,25).

To our knowledge, articular involvement in SHML was mentioned once, by Azoury and Reed, (1) before the SHML was recognized as a separate entity. Their patient had two bouts of arthritis of the small and large joints associated with positive agglutination tests for the rheumatoid factor. Authors believed that rheumatoid arthritis may be a result of altered immunity (autoimmune disease) and may be a result of altered immunity (autoimmune disease) and may be related to repeated infections. Recidiving tonsillitis in our patient may indeed point to an undefined immunological disturbance in patients with SHML. We believe that articular involvement may be the manifestation of the SHML itself, together with others reported above. Unfortunately, articular tissue biopsies were not performed, so the proofs are missing.

The aetiology of SHML remains unknown. Possibilities are viruses (Epstain-Barr virus) (8,13) or some other microorganism (*Klebsiella rhinoscleromatis* /12/) infection and the manifestation of an undefined immunological alteration (possibly in the process of histiocyte activation) (3,9,13). As in our case, elevated serum antibody titres against Epstain-Barr virus are frequently reported in patients with SHML (68% of the cases). (22) However, viral particles and Epstein-Barr viral nuclear antien were not demonstrated in histiocytes from these patients.

As was described earlier (17,22). we also noted that the pericapsular and capsular fibroses were absent in the initial biopsy (e. g. in the early phase of SHML). We agree with the observation that fibrosis tends to be more pronounced and lymphophagocytosis less conspicuous in extranodal involvement (22). Histiocytes containing the lipodic material in the cytoplasmas appear to be much commoner in the extranodal sites than those performing haemophagocytosis.

The presence of lymphocytes and occasionally of other haematopoietic cells within the cytoplasm of the histiocytes is certainly not unique to SHML. It has been seen, among other conditions, in lymph nodes involved by salmonellosis, rhinoscleroma, histoplasmosis and virus-associated haemophagocytic syndroma (18,21).

The differential diagnosis includes a variety of diseases. Several lymphoreticular malignant neoplasms, including histiocytic lymphoma, Hodgkin's disease, malignant histiocytosis, and monocytic leukaemia, bear a superficial resemblance to SHML, but their cytological atypia generally makes a diagnosis of malignant neoplasm obvious, as does their clinical course. Lymph nodes affected by Hodgkin's disease can have large numbers of foamy macrophages, but classical Reed-Sternberg cells have not been identified in SHML. In malignant histiocytosis (including the variant known as histiocytic medullary reticulosis), in familial haemophagocytic reticulosis and related syndromes, as in the virus-associated haemophagocytic syndrome, most of the cells present within the cytoplasm of the sinus histiocytes are erythrocytes rather than lymphocytes – there is significant hepatosplenomegaly with marked anaemia and leucopenia. »Chronic lymphadenopathy simulating malignant lymphoma« is characterized clinically by hepatosplenomegaly, high incidence of autoimmune manifestations, lack of fever, and pathologically, by a diffuse effacement of the nodal architecture by a proliferation of mature lymphocytes. Storage diseases can be excluded in view of the absence of any significant amount of abnormal lipid, carbohydrate, or mucopolysaccharide in the cytoplasm of the histiocytes in SHML. SHML clinical and pathological features differ markedly from those of the three well-recognized members of histiocytosis X group (eosinphilic granuloma, Hand-Schüller- Christian disease and Letterer-Siwe disease). From a clinical standpoint, SHML shows a lack of significant hepatosplenomegaly and skin eruption, and ultrastructurally, Langerhans' granules have not been identified in the cases so far examined. In the reactive sinus hyperplasia the histiocytes are relatively small, and lymphophagocytosis is absent. The histiocytes or rhinoscleroma (Mikulicz's cells) have fewer vesicular nuclei, with a lesser degree of nucleolar prominence, while their cytoplasm is vaculated and foamy, containing encapsulated diplobacilli, which are invariably absent in SHML. The massive cervical adenopathy of SHML has led to serious consideratin of tuberculous

lymphadenitis. However, true granulomas, necrosis and acid-fast organisms have never been identified or cultured in SHML (18).

The disease is relatively unaffected by therapy. The remissions with chemotherapy have been reported (7,16). Although combinations of corticosteroids and antirheumatics proved to be useful in treatment of articular symptomatology in the reported case, the lymphadenopathy – and the disease itself – persisted.

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Sažetak

SINUSNA HISTIOCITOZA S MASIVNOM LIMFADENOPATIJOM

Prikaz bolesnika s teško zahvaćenim zglobovima

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Rosai i Dorfman opisali su 1969. godine bolest koju su nazvali sinusna histiocitoza s masivnom limfadenopatijom (SHML). SHML je benigna i dugotrajna, ali najčešće spontano zalječujuća pseudolimfomska bolest koja se obično očituje kao bezbolna obostrana vratna limfadenopatija. Popraćena je povišenom tjelesnom temperaturom, leukocitozom, ubrzanom sedimentacijom i poliklonskom hipergamaglobulinemijom. Histološki, SHML karakterizirana je proširenim sinusima zahvaćenih limfnih čvorova ispunjenim histiocitima morfološki benignog izgleda, u čijim se citoplazmama nalazi veći broj fagocitiranih stanica, pretežno limfocita. Najčešće su zahvaćeni bolesnici u prva dva desetljeća života.

U oko 28% slučajeva zahvaćene su i ostale periferne ili centralne nakupine limfnih čvorova, kao i tkiva izvan limfnih čvorova: oči s očnim adneksima, gornji respiratorni trakt, koža s potkožnim tkivom, središnji živčani sustav, probavni trakt, genitourinarni trakt, štitna žlijezda i kosti. Uzročnik bolesti još je neprepoznat, a osumnjičeni su virusi (68% oboljelih ima povišen titar antitijela na Epstain-Barrov virus) ili neki drugi mikroorganizmi, kao i za sada nepoznati imunološki poremećaj.

Prikazujemo 37-godišnju bolesnicu koja se u nekoliko navrata liječila zbog opsežnih otoka malih i velikih zglobova popraćenih bolima, povišenom tjelesnom temperaturom, ubrzanom sedimentacijom, hiperglobulinemijom, vratnom i pazušnom limfadenopatijom, kao i opstrukcijama gornjeg respiratornog trakta. Nakon biopsija tkiva pazušnih, podlaktičnih i parotidnih limfnih čvorova, te sluznice maksilarnog sinusa, postavljena je patohistološka dijagnoza SHML ili Rosai-Dorfmanove bolesti. Utvrđen je i povišen titar antitijela na Epstain-Barrov virus. Upotrebom antireumatika i kortikosteroida nastupale su remisije bolesti, limfadenopatija je, međutim, perzistirala.

Ključne riječi: sinusna histiocitoza s masivnom limfadenopatijom, zahvaćenost zglobova

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