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Case report

Sinus histiocytosis with massive lymphadenopathy (Rosai Dorfman disease) in an HIV-positive patient

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Summary. We report a case of a 31-year-old HIV infected black female, who presented with asymptomatic generalized lymphadenopathy. Three particularly enlarged lymph nodes were biopsied (2 cervical and 1 axillary). The histological picture was consistent with a diagnosis of sinus histiocytosis with massive lymphadenopathy (SHML) or Rosai-Dorfman disease. Large histiocytes, positive for a variety of macrophage markers and for the S-100 protein, were observed in the distended sinuses. A few hyperplastic follicles, such as usually seen in HIV-infection-associated lymphadenopathy, were present at the periphery of one lymph node. No infections agent besides HIV could be detected by histological or microbiological analysis or by in situ hybridization. This is the first reported case of SHML associated with HIV infection. The possible relationship between the two diseases is discussed.

Key words: Lymph nodes – Histiocytes – Sinus histiocytosis with massive lymphadenopathy – HIV – Persistent generalized lymphadenopathy

Introduction

Sinus histiocytosis with massive lymphadenopathy (SHML) or Rosai-Dorfman disease was recognized as a clinicopathologic entity more than 20 years ago (Destombes 1965; Rosai and Dorfman 1969, 1972). The disease is thought to be an "idiopathic histiocytosis" of unknown aetiology occurring usually in young white or black people, with a male preponderance. Patients are most often asymptomatic and present with massive – usually cervical – lymphadenopathy. In most cases, the disease runs a benign clinical course. However, extranodal involvement and/or clinical evidence of one or more immune-associated disorders have unfavourable prognostic significance (Boman-Ferrand and Floquet 1990; Foucar et al. 1990). The diagnosis of SHML can confidently be established on histopathological grounds, since the microscopic features of this entity have been clearly outlined in the literature (Foucar et al. 1990). We report here a patient presenting with both SHML and HIV infection. To the best of our knowledge, this association has not been described to date in the literature.

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Case report

A 31-year-old HIV infected black female was referred to the Infectious Diseases Outpatient Clinic of the University Medical Center, Lausanne, because of a 1-month history of a painful, slowly enlarging lymph node in the right preauricular area. For more than a year, the patient had been known clinically to have chronic, stable, persistent, generalized lymphadenopathy (PGL) without any other signs or symptoms (stage III according to the CDC/WHO system (Centers for Diseases Control 1986)). HIV infection was thought to be heterosexually acquired in Zaire. The right preauricular lymph node was 2.5 cm in its largest diameter. It was soft, slightly mobile and without any inflammatory signs. All other lymph nodes were ≤ 1.5 cm. ENT and general physical examination were normal. Haemoglobin was 109 G/l, white cells were 5.6 G/l with a 0.772 G/l CD4-lymphocyte subset (normal: >0.5 G/l) and the platelet count was 257 G/l). ESR was 49 mm/h. Chest radiograph was normal. The right preauricular node was removed to rule out a malignant lymphoma or an opportunistic infection.

During the following 2 months, two new enlarging lymph nodes were observed: the first (2.5 cm) in the right axilla and the second (3 cm) in the left submaxillar area. Both were removed.

Eight months after the last biopsy, the patient was seen for follow-up. She was asymptomatic. No new adenopathy or enlargement of existing nodes was observed. The CD4 cell count had fallen to 0.423 G/l.

Materials and methods

The lymph nodes obtained by surgery were fixed immediately after removal in 10% phosphate-buffered formaldehyde solution and were paraffin-embedded according to conventional procedures. Consecutive sections 4 μm thick were stained using the following standard procedures: haematoxylin-eosin (H & E), Giemsa, methenamine silver stain, Gomori's silver impregnation, Ziehl-Nielsen, periodic acid-Schiff (PAS) and Gram stain.

Immunohistochemical studies were performed on paraffin sections obtained from the three lymph nodes. The three-step immunoperoxidase method (PAP) (Delsol et al. 1984) or the alkaline phosphatase technique (APAAP) (Cordell et al. 1984) were used. The primary antibodies are listed in Table 1. All antibodies were purchased from DAKO except CD15 (Leu M1), which was obtained from Beckton-Dickinson.

For *electron microscopy*, tissue from the largest lymph node (third biopsy) was post-fixed in osmium tetraoxyde and embedded in Epon. Ultrathin section were stained with uranyl acetate and lead citrate.

In situ hybridization (ISH) was done on tissue sections (third biopsy) with S35-labelled probes for Epstein-Barr virus (EBV) and human herpesvirus-6 (HHV-6).

Briefly, deparaffinized sections were incubated in 0.2 N hydrochloride acid for 10 min, washed in PBS and digested with 0.1% pronase in a 0.2% glycine/PBS buffer. The probe consisted of 200 µg labelled viral probe and 100 µg herring sperm DNA in 20% dextran-sulfate 2 × SSC and 50% formamide. Slides were denatured at 90° C and then hybridized at 42° C overnight. Washing steps in decreasing concentrations of SSC were performed. The sections were then processed for autoradiogaphic development. As negative controls, HSB2 cells not infected with HHV-6 versus HSB2 cells infected with HHV-6 as positive controls were used. BJAB cells and tissue sections proven to be EBV negative (tonsils from patients with negative serology for EBV) served as negative controls for EBV-ISH. Positive controls were Raji cells as well as tissue sections of EBV-positive endemic Burkitt's lymphomas. The 8.7 kB *Hin*dIII fragment (pZVH-14, kindly provided by the laboratory of R.C. Gallo, Bethesda), the pHD5 of HHV-6 (kindly provided by R.W. Honess, London) and the *Bam*HIW and H fragments of EBV (kindly provided by H. Wolf, Munich) were used as probes. The sensitivity of EBV detection by this technique ranges from 20 to greater than 60 copies per cell using radioactive-labelled probes (Sixbey et al. 1984). ISH with biotinylated probes was done for herpes simplex 1/2 (HSV 1/2), human papilloma virus (HPV) 16/18, 31/32 and cytomegalovirus (CMV) as described previously (Borisch et al. 1988). Negative and positive controls for the non-radioactive detection consisted of tissue sections known to be negative for the virus researched as well as infected and uninfected cell lines. The sensitivity is usually lower than the radioactive detection and ranges from 60 to greater than 80 copies per cell.

Table 1. Immunohistochemical analysis of the histiocytes

Antibodies	Percentage of positive cells
Pan-macrophage	
CD 68 (KP1)	< 10%
Mac 387	> 50%
Macrophage-associated	
Lyzozyme	< 10%
Alpha-1-antitrypsin	< 10%
Alpha-1-antichymotrypsin	> 50%
CD15 (Leu M1)	0%
Immune accessory cells	
S-100 protein	> 50%
Activation	
CD30 (BerH2)	0%
Pan-B cell	
L26	0%
4KB5	0%
Pan-T cell	
CD45RO (UCHL1)	0%

Results

Histological examination of the three lymph nodes revealed marked distension of the lymph-node sinuses, which appeared to be filled by large histiocytes (Figs. 1, 2). The histiocytic cells exhibited a round, often nucleolated nucleus and an abundant pale cytoplasm, in which some entire lymphocytes or plasma cells were to be seen (emperipolesis) (Fig. 3). Large sheets of mature plasma cells were present in the lymphoid cords between the dilated sinuses. Rare microabscesses were observed. The lymph-node capsule was fibrotic (Fig. 1). Neither lymphoma nor Kaposi's sarcoma were seen. No microorganism could be detected by the various special stains used.

At the periphery of the largest node (left submaxillar area), some residual follicles were observed that exhibited hyperplastic germinal centres with narrowed mantle zones, as is usually described in PGL. In some of the follicles, small foci of haemorrhage were present.

The *immunohistochemistry* results are summarized in Table 1. They were identical for the three lymph nodes. The large histiocytes were found to be positive for a variety of macrophage markers. They exhibited a diffuse cytoplasmic positivity for the S-100 protein, which usually stains Langerhans cells.

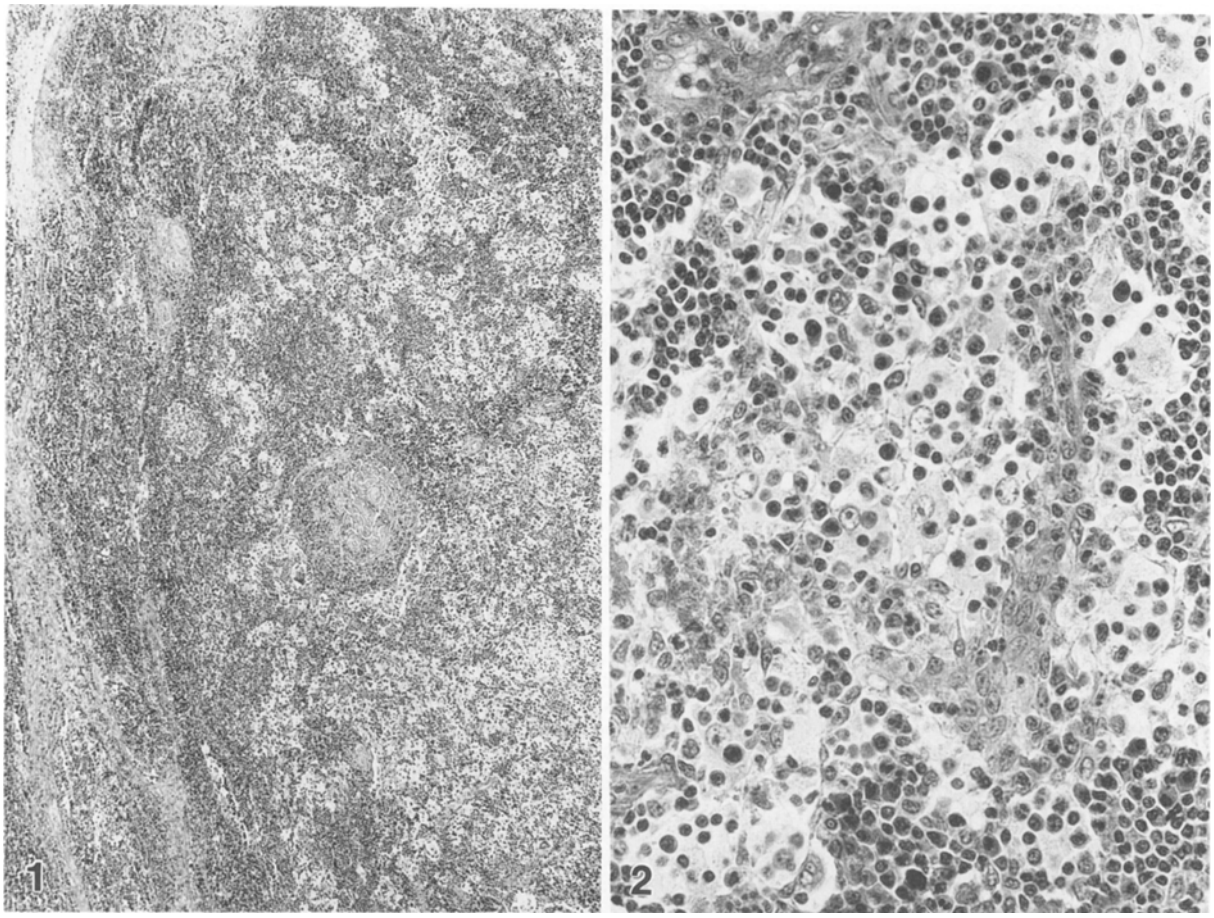
Electron microscopy failed to detect any viral particle. There were no Birbeck granules. Extensive *microbiological analyses* failed to reveal any bacteria, mycobacteria, virus or parasite.

Using *ISH*, we failed to detect any signal for the viruses tested (EBV, HHV-6, HSV 1/2, HPV and CMV). The diagnosis for the three lymph node biopsies was SHML (Rosai-Dorfman disease).

Discussion

This asymptomatic HIV-positive patient, who was known clinically to have had stable PGL for 1 year, presented with asymmetrical, enlarging cervical and axillary lymph nodes. The most prominent histological feature of these lymph nodes was the extreme sinus distension associated with a massive histiocytosis diagnostic of SHML. This finding explained the recent and asymmetric lymph-node enlargement. The presence of a few residual follicles with hyperplastic germinal centres and narrowed mantle zones at the periphery of one lymph node suggests that SHML was superimposed on PGL.

The pathogenesis of SHML is still unknown. SHML probably results from an immunological disturbance associated with a chronic, but non-specific, infectious state (Foucar et al. 1990; Ngendahayo et al. 1983). SHML might reflect an alteration in the process by which histiocytes contact T-lymphocytes for antigen presentation (Bonetti et al. 1987; Mir et al. 1985; Weisenburger et al. 1986). To date, no microorganism has been definitively incriminated, although various microbiological agents have been suspected. EBV seems to be the favourite can-



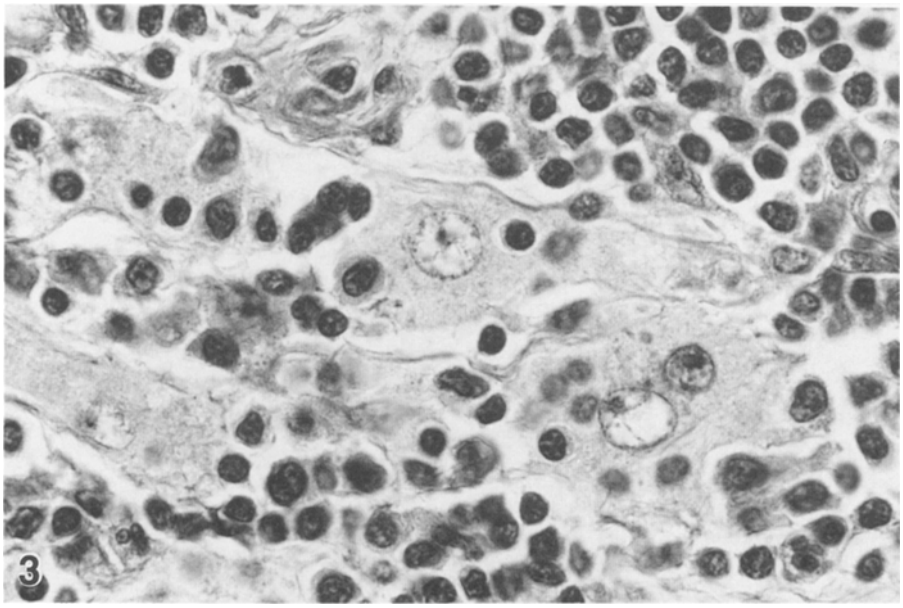


Fig. 1. Overview of the Rosai-Dorfman lesion (third lymph-node biopsy). The expanded sinuses compress the intersinusoidal lymphoid tissue, which is reduced to thin columns. Capsular fibrosis is also seen. H & E, ×165

Fig. 2. Marked distension of the lymph node sinuses, which are filled by large histiocytes, intermingled with lymphocytes and plasma cells. Sheets of mature plasma cells are to be seen in the intersinusoidal tissue. H & E, ×300

Fig. 3. Large sinus histiocytes exhibiting emperipolesis. These cells have a round, pale nucleus with a small nucleolus. H & E, ×750

didate in the literature (Boman-Ferrand and Floquet 1990; Foucar et al. 1990). In our patient, however, we could not identify any infectious process besides HIV infection. No EBV signal could be detected in the lymphoid tissue tested by ISH.

The nature of the histiocyte involved is still a matter of debate. Our immunohistochemical results show a peculiar phenotype with both macrophage and Langerhans cell features. According to Eisen et al. (1990), SHML histiocytes may correspond immunohistochemically to true activated macrophages. However, a phenotype closer to the T-zone histiocyte or Langerhans cell has been described in some studies (Bonetti et al. 1987; Miettinen et al. 1987; Sacchi et al. 1990; Weisenburger et al. 1986). According to the recent and fluid concept of the mononuclear phagocyte and immunoregulatory effector

(M-PIRE) system (Foucar and Foucar 1990), it is possible to think that the SHML cell corresponds to an intermediate or a hybrid cell between a macrophage and an immunoregulatory tissue histiocyte.

Although reactive histiocytosis with haemophagocytosis (Brynes and Gill 1990) and even a single case of malignant histiocytosis (Sayler and Craven 1990) have been described in HIV-positive patients, the combination of SHML and HIV infection, as in our case, has never been reported. The fact that this combination is apparently so rare would argue in favour of a fortuitous association. Some arguments, however, support the hypothesis of a relationship between SHML and HIV infection. Immune-mediated diseases, associated with or preceding SHML, are not rare. About 12% of the SHML patients reported by Foucar et al. (1990) had clinical evidence of one or more immune disorders.

In addition, some cells of the so-called M-PIRE system have been incriminated in the pathogenesis of HIV-associated lesions. The function of these cells may be defective in terms of antigen-processing. Damage to follicular dendritic cells, which present HIV antigen to B-cells in the lymph node. They are thought to play a significant role in the pathogenesis of PGL (Brynes and Gill 1990; Piris et al. 1987). Monocytes, phagocytes, multinucleated cells and microglia are known to be involved in the pathogenesis of AIDS dementia complex (Cho and Sharer 1990). Kupffer cells and bone-marrow mononuclear cells might be target cells in hepatic and haematological HIV-associated disorders (Housset et al. 1990; Sun et al. 1989). The natural history of SHML in the HIV-infected patient is totally unknown. The prognosis of SHML might be worsened by the presence of an immune-associated disorder. Whether or not SHML really represents a HIV-associated disease and should be included in the CDC/WHO classification system remains to be determined.

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