

CASE REPORTS

Sinus Histiocytosis with Massive Lymphadenopathy : The First Three Cases Reported in Thailand

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Sinus histiocytosis with massive lymphadenopathy is a benign pseudolymphomatous disease first clearly established as a distinct clinicopathologic entity by Rosai and Dorfman in 1969.¹ The disease presents most often in the first decade of life with the clinical manifestations of massive cervical lymphadenopathy, fever, leukocytosis, elevated erythrocyte sedimentation rates, and hypergammaglobulinemia.¹⁻⁴ Other lymph node groups, such as axillary, inguinal, mediastinal, perihilar and retroperitoneal nodes may be affected.^{2,5,6} Extranodal sites of involvement have also been described, including upper respiratory tract, oral cavity, paranasal sinuses, salivary tissues, orbit, eye lids, skin, bone, testes, abdominal viscera and epidural space.⁷⁻²⁵ Diagnosis requires characteristic histopathological findings of lymph node or tissue biopsy showing marked dilatation of sinuses by a proliferation of benign histiocytes with prominent phagocytosis (emperipolesis) of lymphocytes, plasma cell infiltrate in medullary cords, and capsular fibrosis.^{1,2,25-27} The disease characteristically follows a protracted clinical course, with eventual spontaneous regression of the lymphadenopathy

SUMMARY Three cases of sinus histiocytosis with massive lymphadenopathy are reported in Thai children and is probably a first report in Thailand. They were clinically characterized by bilateral massive cervical lymphadenopathy. Other lymph node groups were also involved but no extranodal manifestations could be detected. Leukocytosis with neutrophilia, hypergammaglobulinemia and polyclonal gammopathy were common features. The characteristic histopathologic findings in the involved lymph nodes included pericapsular fibrosis, markedly dilatation of subcapsular and medullary sinuses which were filled with numerous histiocytes showing active phagocytosis of lymphocytes and lymphoplasmacytoid proliferation in paracortical strands and medullary cord. The disease characteristically has a benign protracted clinical course, and does not respond to either irradiation or chemotherapy. The etiology and pathogenesis of this disorder are unknown. The possible pathologic mechanisms include an abnormal response to a specific infectious process and an immune deficiency status.

and total recovery in most cases. In this report, we describe the first three cases of sinus histiocytosis with massive lymphadenopathy diagnosed in Thailand and the clinical and histopathologic findings in these patients are compared with those reported in the literature.

MATERIALS AND METHODS

Three cases which we have designated as sinus histiocytosis with massive lymphadenopathy comprise the subject of this report. All of them were admitted at the Department of Pediatrics, Siriraj Hospital Medical School, Mahidol University on April

1982, October 1982 and November 1989 respectively. In every case, the definite diagnosis was obtained by biopsy of the cervical lymph nodes. The representative sections, 5 mm thick, were properly fixed in modified millonig phosphate buffer formalin, and then processed, embedded in paraffin and sectioned at a thickness of 3 μ m. The sections

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were stained with hematoxylin and eosin (H&E), periodic acid Schiff (PAS) and methyl green pyronine (MGP) for histologic examination. Moreover, sections were also selected for immunoperoxidase (IPX) study of cells of B-lymphoid and of histiocytic origin using both indirect immunoperoxidase and peroxidase-antiperoxidase (PAP) methods. Primary antisera for immunoglobulins IgG, IgA, IgM and for kappa (K) and lambda (λ) light chains were used to detect cells of B-lymphoid origin (DAKO Co., Denmark). Primary antisera for muramidase and alpha-1-antichymotrypsin were used for cells of histiocytic origin (DAKO Co., Denmark). The IPX procedure was as described elsewhere.²⁸

REPORT OF CASES

Case 1. A 9-year old Thai boy was referred from Chumporn Hospital, a provincial hospital in southern Thailand to Siriraj Hospital Medical School in April 1982 because of painless, marked enlargement of both cervical and inguinal lymph nodes for 5 months. His residence was at Tambon Chongmaikeao, Amphur Tungtakoo, Chumporn Province. He had no fever and his general condition was good. There were no intra-oral or pharyngeal lesions; the liver and spleen were not enlarged. Roentgenogram of the chest showed widening of the mediastinum, possibly due to enlarged lymph nodes. The CBC showed Hct 33%, WBC 22,300/cumm, with 75% segmented neutrophils, 20% lymphocytes, 3% monocytes and 2% eosinophils. Bone marrow examination revealed an increased number of histiocytes and eosinophils. The serum protein determination showed albumin 3.5 gm/dl and globulin 3.9 gm/dl. Repeated tuberculin tests were negative. Sputum culture and gastric washing failed to recover acid-fast bacilli. No organism could be grown from hemoculture. The lymph node biopsy from left cervical region was inter-

preted as sinus histiocytosis with massive lymphadenopathy. He was treated by irradiation of cervical lymph nodes with 1,600 cGy on each side, resulting in slight reduction in size of the lymph glands. The disease followed a stationary course, with no evidence of remission or progression during the follow-up period of 12 months. Two years later when he was last seen, the cervical lymph nodes were still rather large, although the patient remained asymptomatic. No further information could be obtained following several communications with his parents.

Case 2. An 8-year-old Thai boy presented on October 1982 with a painless, firm, slowly progressing mass on the right side of the neck of 7 months duration. He came from Tambon Nong-grad, Amphur Dankuntod, Nakornrajchasma Province in the north-eastern part of Thailand. The patient had no fever or any constitutional symptoms. The body temperature was 37.2° C. Several right cervical lymph nodes were enlarged, 1 to 4 cm in diameter, of firm consistency, movable, not tender, extending from the lower part of the ear to the right clavicle. The inguinal lymph nodes were slightly enlarged, 0.5 to 1 cm in diameter on both sides. Other physical examination was unremarkable. The CBC showed Hct 35%, WBC 19,200/cumm, with 78% segmented neutrophils, 15% lymphocytes, 3% monocytes and 4% eosinophils. Roentgenogram of the chest revealed interstitial infiltration in both lung fields. The tuberculin test 1:1000 dilution was 7 mm and 1:100 dilution was 15 mm in diameters of induration respectively. The gastric wash was negative for acid-fast bacilli and culture for tubercle bacilli was also negative. The immunoglobulin determination revealed IgG 3800 mg/dl, IgA 425 mg/dl and IgM 214.5 mg/dl. The lymph node biopsy of the right cervical lymph gland showed characteristic sinus histiocytosis with mas-

sive lymphadenopathy. The direct smear and culture from the lymph node material were negative for microorganisms. He was treated with 3 courses of weekly vincristine plus cyclophosphamide without improvement. Irradiation was then given to the affected lymph nodes with the total dose of 2900 cGy resulting in only slight reduction of the enlarged lymph nodes. He was then discharged and lost to follow up 4 months after diagnosis.

Case 3. An 8-year-old Thai boy was referred from Chumporn Hospital to Siriraj Hospital Medical School in November 1989 because of enlarged both cervical lymph glands for 6 months. He lived at Tambon Saleau, Amphur Tazae, Chumporn Province. He was treated with anti-tuberculous drugs (isoniazid, ethambutol and streptomycin) at the local hospital without beneficial effect. The lymph glands gradually increased in size bilaterally including at the left axillary nodes (Figure 1). He had no fever or other constitutional symptoms. The body temperature was 36.5° C. The liver and the spleen were not enlarged. The rest of the physical examination was unremarkable. The CBC showed Hct 34%, WBC 23,800/cumm with 74% segmented neutrophils, 9% lymphocytes, 15% eosinophils and 2% monocytes; the platelet count was 620,000/cumm. The stool examination showed many hook worm eggs. Repeated tuberculin tests were negative. The serum albumin was 3.1 gm/dl and globulin was 6.9 gm/dl. Immunoglobulin determination revealed IgG 2,500 mg/dl, IgA 400 mg/dl, IgM 195 mg/dl. The erythrocyte sedimentation rate (Westergren's method) was 92 mm per hour. Roentgenogram of the chest showed right paratracheal lymph node enlargement without pulmonary infiltration. The bone survey revealed no abnormal findings. The serological determination for viral infections revealed an Epstein-Barr antibody titer of 1:64, adenovirus titer of 1:4 and cytomegalovirus

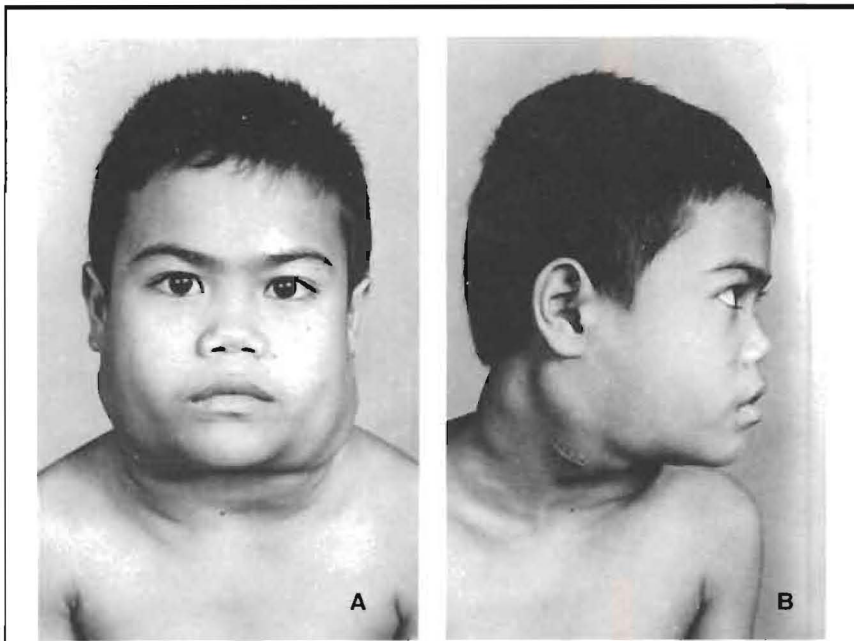


Fig. 1 (A,B) The appearance of the patient with sinus histiocytosis with massive lymphadenopathy (SHML) showing markedly enlarged cervical lymph nodes on both sides of the neck.

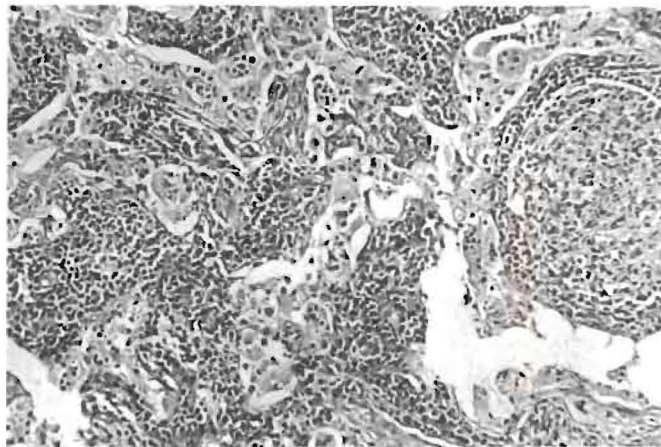


Fig. 2. Histologic section of the enlarged lymph node in SHML, showing dilatation of medullary sinuses filled with proliferation of sinus histiocytes. Paracortical strands and medullary cords showed lymphoplasmacytic proliferation. A remaining lymphoid follicle with germinal center was also noted. (H & E \times 100).

titer of 1:8. Bone marrow aspiration showed normal cellular marrow with slightly increase of lymphoblasts (8%). The cervical lymph node biopsy was

consistent with sinus histiocytosis with massive lymphadenopathy. No specific treatment was given, and he was seen again at the pediatric

hematology clinic 5 months later when persistent enlarged lymph nodes were still observed, however, he had excellent general condition without any constitutional symptoms.

Pathological Features

Since the morphologic characteristics of this disease were virtually identical in all three cases, they will be described as a group.

The specimen from the biopsy of the cervical lymph node was a greyish white, oval-shaped mass, measuring $2 \times 1 \times 1$ cm. On serial sectioning, a homogeneous greyish white cut surface was noted, the capsule was distinct about 1 mm in thickness.

On histologic examination, the enlarged lymph node had a thick fibrous capsule. The normal lymph node architecture was disturbed by markedly diffuse dilatation of subcapsular and medullary sinuses which were filled up with a large number of histiocytes (Figure 2). Strikingly, many of these histiocytes showed active phagocytosis. Almost all of the phagocytic vacuoles in their cytoplasm contained small lymphocytes (Figure 3). Twenty to thirty phagocytosed lymphocytes were commonly found in one histiocyte (emperipolesis).²⁹ In addition, lymphoplasmacytoid cells, plasma cells, neutrophils, erythrocytes or even eosinophilic bodies of dead cells were occasionally seen in these phagocytic vacuoles. However, some histiocytes contained only foamy cytoplasm. These foamy histiocytes could be found throughout, particularly at the subcapsular region.

Paracortical areas were compressed by the dilated sinuses to be irregular strands comprising mainly plasma cells. Small indistinct lymphoid follicles with or without germinal centers were seen within some medullary cords both in the central and peripheral portions of the lymph nodes. Blood vessels were not prominent, most of them were capillaries

or venules. No evidence of necrosis or granuloma was found.

By immunoperoxidase study, histiocytes were strongly positive for anti-muramidase and alpha-1-anti-chymotrypsin, and plasma cells were positive for all cytoplasmic immunoglobulins including anti-K, anti- λ light chains, anti-IgG, anti-IgA and anti-IgM.

DISCUSSION

Sinus histiocytosis with massive lymphadenopathy (SHML) is a rare, well recognised pseudolymphomatous benign disorder occurring mainly in children and young adults. Approximately 365 cases have been registered at a case registry center and there are at least 130 articles reporting observations about this disorder.³⁰ Fifty-six percent of reported patients reside in the United States, Canada, or western Europe, but reported cases from such places as mainland China, the Soviet Union, central Africa, Japan, and the Caribbean region emphasize the disease's global distribution. Of patients in the USA whose race was specified, 49.0% were black, 46.2% were white, and 4.8% were Oriental. To our knowledge, there is no previous report of this disorder from Thailand. Our three cases therefore appear to be the first reported cases of SHML in Thai children. The mean age of our patients was 8 years. The age of registry patients in USA at onset of SHML had a skewed distribution, with a mean of 19.7 years and an SD of 20.4 years.³⁰ Somewhat more male than female patients have been identified, with a male-female ratio of 1.4:1. All of our three cases were male. The disease is characterized by massive bilateral painless cervical lymphadenopathy, fever, leukocytosis with neutrophilia, elevated erythrocyte sedimentation rate, and hypergammaglobulinemia.² Thirty percent of the patients show evidence of extranodal disease, and half of the extranodal sites are in the upper

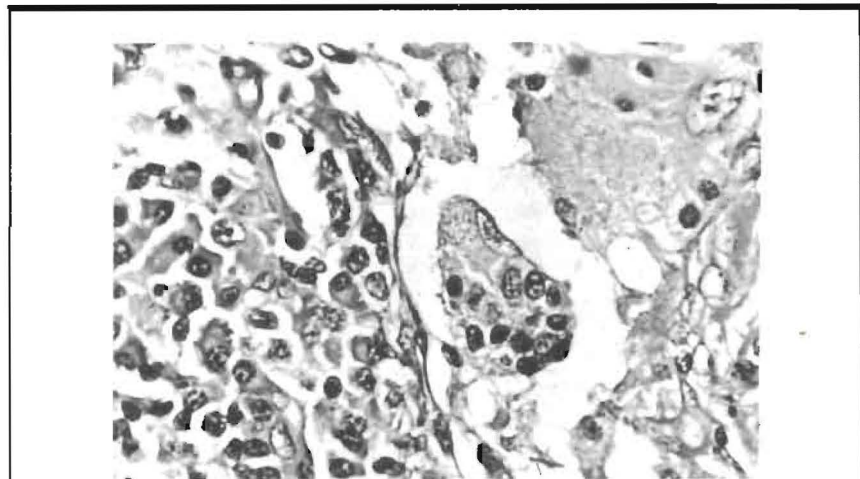


Fig. 3 High power appearance of the lymph node section in SHML showing phagocytic vacuoles containing viable lymphocytes in one sinus histiocyte (emperipolesis). Proliferation of plasma cells in medullary cord was also distinct. (H & E, x 450).

aerodigestive tracts.⁷⁻¹² The course of the disease is protracted and relatively unaffected by various modes of therapy. Eventually, the lymphadenopathy and other symptoms regress, although it may take several years for this to occur. The general condition of the patient is often remarkably well during the course of the disease. All of our three patients had the clinical manifestations compatible with this disease. All of them had massive painless cervical lymphadenopathy but they had no fever or any extranodal involvement. Leukocytosis with neutrophilia was clearly demonstrated in all three cases without evidence of bacterial infections. Elevated gamma globulin in the first case and the elevation of all three classes of immunoglobulins (IgG, IgA and IgM) in the other two cases suggested polyclonal gammopathy which is characteristic of this disease. The definitive diagnosis depends on histopathologic findings of the enlarged lymph nodes. The basic abnormality is the markedly dilatation of subcapsular and medullary sinuses with the proliferation of sinus histiocytes with abundant pink

cytoplasm, sometimes resulting in complete effacement of the nodal structure and marked infiltration of plasma cells in the medullary cords. The most characteristic feature of SHML is the presence of histiocytes with active cellular phagocytosis. The presence of well-preserved lymphocytes and occasionally of other hematopoietic cells within the cytoplasm of the sinus histiocytes is a constant finding.^{1,2} Its significance is not clear. It may represent phagocytosis by the histiocytes or active cytoplasmic penetration by the lymphocytes, a phenomenon known as emperipolesis.²⁹ The plasma cells and the lymphocytes in the medullary cords have different classes of immunoglobulins (polyclonal plasma cell proliferation) corresponding to the polyclonal hypergammaglobulinemia.³¹ These findings were clearly demonstrated in the lymph node biopsy of our patients by the immunoperoxidase staining showing cytoplasmic immunoglobulins of IgG, IgA and IgM. More recently, the demonstration that the histiocytic cells in SHML are S100 protein positive has provided a unique feature that may be of aid in establishing

the diagnosis in suspected cases.³²⁻³³

The clinical course of sinus histiocytosis with massive lymphadenopathy is variable. Most patients manifest an indolent course with remissions and exacerbations. Spontaneous remission is possible, usually ensuing within the first few years after diagnosis. Persistent disease for 5 or more years occurs in approximately one third of patients.²⁻⁴ All of our patients had persistent cervical lymphadenopathy for long periods of time up to 2 years in the first case. Chemotherapy and irradiation have no beneficial effects, as was true in case 1 and case 2. There is a mortality rate of approximately 7%, but the fatal outcome is unrelated to duration or extent of disease or to therapy.⁴ However, there is a significant (70%) relationship between death and evidence of an immune dysfunction.^{4,13} Pathogenesis of sinus histiocytosis with massive lymphadenopathy is unknown. The spectrum of the clinicopathologic severity seen in this disease, however, seems to indicate that it lies between benign reactive lymphoreticular hyperplasia and lymphoma. Two major pathologic mechanisms have been proposed as possible causes of SHML: a specific infectious process and an immune deficiency status.² There are several features of SHML which are strongly suggestive of an infectious etiology. The appearance of localized lymphadenopathy in a previously healthy individual, accompanied by fever, leukocytosis with neutrophilia, elevated erythrocyte sedimentation rate, and hypergammaglobulinemia, spontaneously receding after a variable length of time, is certainly consistent with this interpretation. However, attempts to document an infectious etiology by microscopic examination, cultures, and other laboratory tests have been uniformly unsuccessful. Although, high titers of antibodies against Epstein-Barr virus have been detected in some cases of SHML,³⁴ the significance of this finding remains to be estab-

lished from studies of a larger number of cases with appropriate controls. The second major possibility is that SHML is the expression of an abnormal immunologic response. A broad spectrum of immunologic abnormalities such as arthritis, auto-immune hemolytic anemia, Wiskott-Aldrich syndrome, glomerulonephritis, and systemic amyloidosis, has been identified in approximately 10% (23 out of 220 cases) of SHML.³¹ In 18 of the 23 cases examined in that report, SHML preceded or occurred simultaneously with the immunologic abnormality. These findings strongly suggest that there is an association between SHML and clinically significant immune dysfunction. Furthermore, ten of the 23 SHML patients who had associated immunologic abnormalities died and in many cases the cause of death could be linked to the immune dysfunction.³¹ None of our three cases in the present report had clinical evidence of immunologic abnormalities. However, detailed immunologic evaluation has not been done in our patients. A more thorough evaluation of SHML patients for evidence of immunologic abnormalities may better define both the mechanisms of this rare disease and its clinical spectrum.

REFERENCES

- Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy: A newly recognized benign clinicopathological entity. *Arch Pathol Lab Med.* 1969; 87 : 63-70.
- Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy: A pseudolymphomatous benign disorder: Analysis of 34 cases. *Cancer* 1972; 30 : 1174-88.
- Lampert F, Lennert K. Sinus histiocytosis with massive lymphadenopathy: Fifteen new cases. *Cancer* 1976; 37 : 783-9.
- Foucar E, Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy: An analysis of 14 deaths occurring in a patient registry. *Cancer* 1984; 54 : 1834-40.
- Becroft DMO, Dix MR, Gillman JC, *et al.* Benign sinus histiocytosis with massive lymphadenopathy: Transient immunological defects in a child with mediastinal involvement. *J Clin Pathol* 1973; 26 : 463-9.
- Marsh WL, McCarrick JP, Harlan DM. Sinus histiocytosis with massive lymphadenopathy: Occurrence in identical twins with retroperitoneal disease. *Arch Pathol Lab Med.* 1988; 112 : 298-301.
- Sanchez R, Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy. An analysis of 113 cases with special emphasis on its extranodal manifestations. *Lab Invest.* 1977; 36 : 21-2.
- Foucar E, Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy: Ear, nose and throat manifestations. *Arch Otolaryngol* 1978; 104 : 687-93.
- Stankiewicz JA, Lotan AN, Ratajczak HV. Sinus histiocytosis with massive lymphadenopathy and subglottic stenosis. *Ear Nose Throat J.* 1987; 66 : 440-3.
- Okada K, Lee MO, Hitomi S, Nagayama Y, Noma S. Sinus histiocytosis with massive lymphadenopathy and tracheobronchial lesions: CT and MR findings. *J Comput Assist Tomogr.* 1988; 12 : 1039-40.
- Carpenter RJ, Banks PM, McDonald TJ, Sanderson DR. Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease): Report of a case with respiratory tract involvement. *Laryngoscope* 1978; 88 : 1963-9.
- Bankaci M, Morris RF, Stool E, *et al.* Sinus histiocytosis with massive lymphadenopathy: Report of its occurrence in two siblings with retropharyngeal involvement in both. *Ann Otolaryngol.* 1978; 88 : 327-31.
- Foucar E, Rosai J, Dorfman RF. The ophthalmologic manifestations of sinus histiocytosis with massive lymphadenopathy. *Am J Ophthalmol.* 1979; 87 : 354-67.
- Stopak SS, Dreizen NG, Zimmerman LE, O'Neil JF. Sinus histiocytosis presenting as an epibulbar mass. A clinicopathologic case report. *Arch Ophthalmol.* 1988; 106 : 1426-8.
- Karcioglu ZA, Allam B, Instler MS. Ocular involvement in sinus histiocytosis with massive lymphadenopathy. *Br J Ophthalmol.* 1988; 72 : 793-5.

16. Marion JR, Geisinger KR. Sinus histiocytosis with massive lymphadenopathy : Bilateral orbital involvement spanning 17 years. *Ann Ophthalmol.* 1989; 21 : 55-8.
17. Friendly DS, Font RL, Rao NA. Orbital involvement in "sinus" histiocytosis, a report of four cases. *Arch Ophthalmol.* 1977; 95 : 2006-11.
18. Lazar AP, Esterly NB, Gonzalez-Crussi F. Sinus histiocytosis clinically limited to the skin. *Pediatr Dermatol.* 1987; 4 : 247-53.
19. Suster S, Cartagena N, Cabello-Inchausti B, Robinson MJ. Histiocytic lymphopagocytic panniculitis. An unusual extranodal presentation of sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease). *Arch Dermatol.* 1988; 124 : 1246-9.
20. Thawarani H, Sanchez RL, Rosai J, Dorfman RF. The cutaneous manifestations of sinus histiocytosis with massive lymphadenopathy. *Arch Dermatol.* 1978; 114 : 191-7.
21. Walker PR, Rosai J, Dorfman RF. The osseous manifestations of sinus histiocytosis with massive lymphadenopathy. *Am J Clin Pathol.* 1981; 75 : 131-9.
22. Sartoris DJ, Resnick D. Osseous involvement in sinus histiocytosis with massive lymphadenopathy. *Eur J Pediatr.* 1986; 145 : 238-40.
23. Foucar E, Rosai J, Dorfman RF, Brynes RK. The neurologic manifestations of sinus histiocytosis with massive lymphadenopathy. *Neurology* 1982; 32 : 365-71.
24. Carey MP, Case CP. Sinus histiocytosis with massive lymphadenopathy presenting as a meningioma. *Neuropathol Appl Neurobiol.* 1987; 13 : 391-8.
25. Song SK, Schwartz IS, Strauchen JA, *et al.* Meningeal nodules with features of extranodal sinus histiocytosis with massive lymphadenopathy. *Am J Surg Pathol.* 1989; 13 : 406-12.
26. Ngendahaya P, Roels H, Quatacker J, *et al.* Sinus histiocytosis with massive lymphadenopathy in Rwanda : Report of eight cases with immunohistochemical and ultrastructural studies. *Histopathology* 1983; 7 : 49-63.
27. Sanchez R, Sibley RK, Rosai J, *et al.* The electron microscopic features of sinus histiocytosis with massive lymphadenopathy : A study of 11 cases. *Ultrastruct Pathol.* 1981; 2 : 101-19.
28. Taylor CR. Immunoperoxidase techniques. Practical and theoretical aspects. *Arch Pathol Lab Med* 1978; 102 : 113-21.
29. Ioachim HL. Emperipolesis of lymphoid cells in mixed cultures. *Lab Invest* 1965; 14 : 1784-94.
30. Foucar E, Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy : Current status and future directions. *Arch Dermatol.* 1988; 124 : 1211-4.
31. Foucar E, Rosai J, Dorfman RF, Eyman JM. Immunologic abnormalities and their significance in sinus histiocytosis with massive lymphadenopathy. *Am J Clin Pathol.* 1984; 82 : 515-25.
32. Weisenburger DD, Lipscomb HL, Daley DT, *et al.* Immunologic studies of sinus histiocytosis with massive lymphadenopathy (SHML) *Lab Invest* 1986; 54 : 68.
33. Miettinen M, Paljakka P, Haveri P, *et al.* Sinus histiocytosis with massive lymphadenopathy : A nodal and extranodal proliferation of S-100 protein positive histiocytes? *Am J Clin Pathol* 1987; 88 : 270-7.
34. Lober M, Rawlings W, Newell GR, Reed RJ. Sinus histiocytosis with massive lymphadenopathy. Report of case with elevated EBV antibody titers. *Cancer* 1973; 32 : 421-5.