รายงานผู้ป่วย

Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease): a case report and review of literature

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Abstract:

Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease): a case report and review of literature

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Sinus histiocytosis with massive lymphadenopathy (SHML) or Rosai-Dorfman disease is an unusual, benign, self-limited condition of unknown etiology which generally presents as massive bilateral cervical lymphadenopathy in children. It is differentiated from other childhood histiocytosis by its distinct character and should be kept in mind for differential diagnosis of neck mass in children because of the different treatment modalities. In this article a case of neck mass in a 10-month-old boy with diagnosis of SHML is presented. The clinical features, cytopathological characteristics of diagnosis and the treatment of disease are discussed and the literature is reviewed.

Key words: *Sinus histiocytosis with massive lymphadenopathy, Rosai-Dorfman disease, neck mass*

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บทคัดย่อ:

Sinus histiocytosis with massive lymphadenopathy (SHML)หรือ Rosai-Dorfman disease เป็นโรคที่มีลักษณะเฉพาะและพบได้ไม่บ่อย ผู้ป่วยมักเป็นเด็กและมาพบแพทย์ด้วยอาการก้อนที่คอโตขึ้นทั้งสองข้าง ซึ่งต้องวินิจฉัยแยกกับภาวะก้อนโตที่คอจากสาเหตุอื่น รายงานนี้นำเสนอผู้ป่วยเด็กชายอายุ 10 เดือน มีก้อนที่คอโตขึ้นมา 2 เดือนก่อนมาโรงพยาบาล และได้รับการตัดต่อมน้ำเหลืองตรวจวินิจฉัยว่าเป็นโรค SHML จากการติดตามผู้ป่วย 6 เดือนไม่พบความผิดปรกติใด ๆ ผู้รายงานได้อภิปราย และรวบรวมรายงานที่เกี่ยวกับโรคนี้ รวมทั้งแนวโน้มใหม่ที่ใช้ Fine needle aspiration ช่วยในการวินิจฉัยโรค

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Introduction

Sinus histiocytosis with massive lymphadenopathy (SHML) was first described by Rosai and Dorfman in 1963 as a unique clinicopathologic entity.[1] Since then many more cases have been added to the literature. In Thailand, the first three cases were reported by Siriraj Hospital in 1990.[2] The disease is characterized by massive, bilateral, cervical lymphadenopathy in children, associated with low grade fever, neutrophilia, raised erythrocyte sedimentation rate (ESR) and polyclonal gammopathy.[1] Extranodal involvement has also been described including upper respiratory tract,[1, 3] oral cavity,[1, 4] salivary glands,[5] skin,[6] eyelid and orbit,[7] abdominal viscera[8] and meninges.[1] Histologically, the involved lymph nodes show marked dilatation of sinuses with proliferation of large histiocytes and prominent phagocytosis of lymphocytes (emperipolesis), plasma cell infiltration in medullary cords and capsular fibrosis.[9-11] The exact cause and pathogenesis of this condition remain obscure.[8, 10] Although spontaneous remission is common, occasionally a progressive course with fatal outcome has been recorded.[12, 13] This report describes the clinical features, cytologic and histopathologic findings and treatment outcome of a 10-month old child with SHML. The use of fine needle aspiration cytology in diagnosis is also discussed.

Case report

A 10-month-old, full-term male infant was referred from pediatricians for the evaluation of masses at right submandibular area and the right side of neck. The parents gave a history of progressive enlargement of masses for 2 months. He had no fever or mass at other sites. On admission he was first diagnosed as cervical lymphadenitis and treated with intravenous antibiotic for one week with no response before seeking consultation.

On physical examination, he had no fever. There was a firm movable mass about 2.5 cm. over the right submandibular region and multiple small lymph nodes over the posterior triangle of the right side of neck. There were no intraoral or pharyngeal lesions. Liver and spleen were not enlarged. No lymph node at other sites of the body was palpable.

The laboratory examination revealed mild leukocytosis (12,800 cells/mm^3) with neutrophilia. Platelet count was 518,000 cells/mm.^{3} Erythrocytic feature showed moderate microcytic-hypochromic anemia with a hemoglobin level of 7.9 gm/dl and hematocrit of 25.5%. Chest x-ray was normal and a tuberculin test was negative. The mass was suspected to be a submandibular gland tumor with lymphadenopathy or massive cervical lymphadenopathy.

A fine needle aspiration at the largest mass was done. It displayed monotonous lymphoid cells, foamy macrophages and multinucleated giant cells. Cytologic report indicated a possible benign reactive lesion but malignant lymphoma could not be ruled out. So an opened biopsy was performed. At operation, there was a firm whitish-brown mass, about 3 cm. in diameter, attaching to the right submandibular gland and multiple gray-brown lymph nodes over the posterior triangle of the neck. The right submandibular gland along with some lymph nodes were removed and sent for histologic examination. Gross examination revealed normal looking submandibular gland and enlarged lymph nodes. Microscopic examination of lymph nodes showed markedly distended sinuses

and proliferation of histiocytes. The hyperplastic dilated sinuses contained histocytes, plasma cells, lymphocytes and macrophage containing phagocytized lymphocytes. (Figures 1 and 2). Immunohistochemistry gave positive result for CD68. Special stains for mycobacteria and fungus were negative.

There was no further treatment and the patient was advised to follow up monthly. At the 6th month of follow up, all lymph nodes had regressed and the patient appeared in good health.

Discussion

Sinus histiocytosis with massive lymphadenopathy (SHML) is a rare, benign histiocytic proliferation that was established as a distinct clinicopathological entity by Rosai and Dorfman in 1969.[1] It has a widespread geographic distribution. Comprehensive study of patients with SHML has been made possible through the establishment of a registry that now contains records and pathological samples from over 600 cases.[10] In Thailand, there were 3 cases reported from Siriraj Hospital in 1990[2] and to our knowledge, have been no other case reports from Thailand since then.

SHML occurs mainly in children with a male to female ratio about 2 : 1[12] Sixty two percent of patients are younger than 10 years of age, and eighty percent younger than 20 years of age.[4] Approximately 90% of patients present with massive, painless, bilateral cervical lymphadenopathy.[8, 10, 12] Other lymph node groups can be involved, including axillary, inguinal, paraaortic,and mediastinal groups. Solitary lymph node involvement is unusual.[10] In this patient, although lymph nodes presented only on right cervical area, there were many enlarged lymph node groups.

Laboratory evaluation in patients suspected of SHML are nonspecific. A mild normochromic or hypochromic microcytic anemia is present in the majority of cases (65%) as in our patient. Some patients may have red cell autoantibodies, but severe hemolytic anemia is rare. An increase in the number of peripheral blood neutrophilic cells and lymphopenia are frequently found. The erythrocyte sedimentation rate is usually elevated. Most patients (88.5% of cases) have abnormalities in serum protein levels with polyclonal hypergammaglobulinemia is most common.[1] Fever is also a prominent feature in some cases but this did not occur in our case throughout the course of the disease.[12]

Extranodal involvement has been found in 30-45% of cases occurring most commonly in head and neck.[1, 3, 12] Subsites of extranodal involvement in head and neck include 73% in upper respiratory tract with a predilection for the nasal cavity and the paranasal sinus, 50% in the orbit and 25% in the salivary gland.[3, 12] Other extranodal sites can include skin, bone, central nervous system, soft tissue and digestive tract.[1, 4, 6-8] Skin involvement is at least as common as nasal cavity and paranasal sinus involvement.[1] Two organs that stand out because of their almost universal sparing by the disorder are spleen and bone morrow.[10] Patients with extranodal disease tend to be older than patients with no extranodal sites (mean age of 40 years VS 19.7 years).[4] In this very young patient, the enlarged lymph nodes were in the submandibular area and the posterior triangle of neck with an original mistaken diagnosis as a submandibular tumor with lymphadenopathy due to the close attachment of the lymph node to the submandibular gland. Foucar et al.[14] also reported that immune dysfunction in SHML was associated with a higher prevalence of extranodal head and neck disease (up to 47%) as compared with immunocompetent individuals (22%).

For over 30 years, SHML has been a histologic diagnosis. Tissue can be obtained by opened lymph node biopsy or involved extranodal tissue that provides an adequate specimen.[15] However, recent reports indicate that fine needle aspiration cytology together with clinical clues are virtually diagnostic and can help to avoid unnecessary investigative procedures and surgical intervention.[9, 16-18] The cytologic features characteristically include three important components, atypical histiocytes, lymphophagocytosis (emperipolesis) and plasmacytosis.[18] These atypical histiocytes are characterized by well-defined cell boundaries, abundant eosinophilic cytoplasm, and round-to-oval enlarged vesicular nuclei with small nucleoli.[9, 16, 17, 19] In contrast to phagocytosis, emperipolesis is not associated with degenerative change in the "engulfed" cells. The engulfed lymphocytes and plasma cells often appear viable and are surrounded by a clear halo.

In this patient, careful cytologic review of the FNA specimen revealed good correlation with the histologic appearances, with scattered lymphocytes intermixed with histiocytes, multinucleated giant cells and macrophages containing phagocytized lymphocytes (Figure 3), as reported in a previous study.[18]

In the histopathologic study, the lymph nodes are usually matted together with prominent capsular fibrosis as seen in this patient.[11, 17] The germinal center is rarely visible. The sinuses of the lymph nodes are expanded by a polymorphous cellular infiltration with numerous large and distinctive Rosai-Dorfman cells (RD). (Figure 1 and 2) The RD cells have round-to-oval, medium-to-large nuclei with a vesicular chromatin pattern. The cytoplasm is abundant with pale eosinophilic staining. Phagocytized lymphocytes are present in the cytoplasm of most RD cell (lymphophagocytosis or emperipolesis).[10, 16] (Figure 2) Although not pathognomonic, these features are of great diagnostic importance.[10] In immunohistochemistry studies, the RD cells are strongly positive for s-100 protein and markers of macrophage lineage such as CD68, the antigen commonly detected in cells with phagocytic activity[10, 16] as in our case. The result of immunohistochemistry studies can help the diagnosis by excluding other diseases.

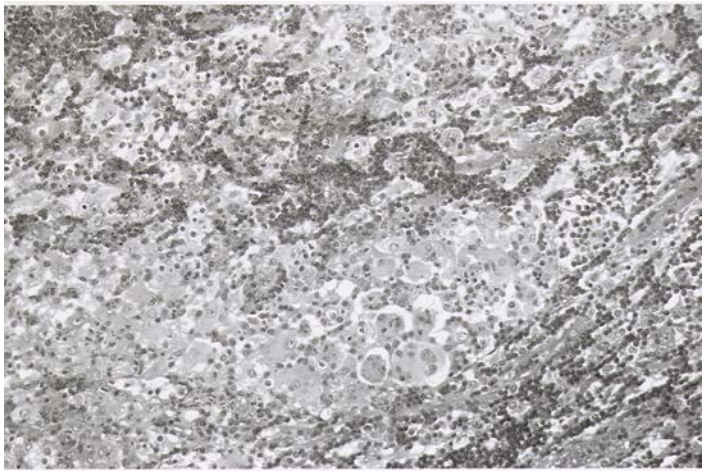

Figure 1 Lymph node showing markedly distended sinuses and proliferation of histiocytes

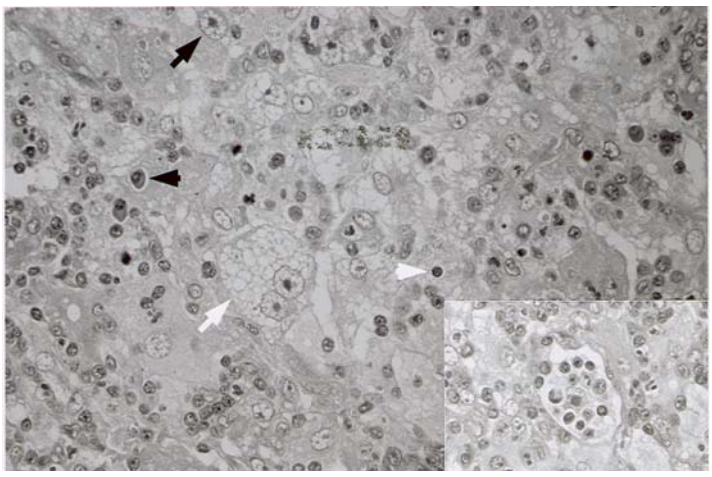

Figure 2 Dilated sinuses containing histiocytes (black arrow), plasma cells (black arrow head), lymphocytes (white arrow head), lipid-laden macrophages (white arrow) and macrophages containing phagocytized lymphocytes (inset)

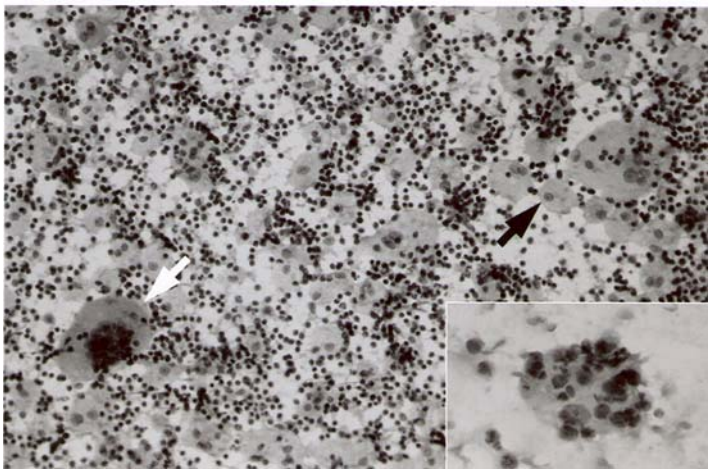

Figure 3 Specimen from fine needle aspiration revealing scattered lymphocytes intermixed with histiocytes (black arrow), multinucleated giant cells (white arrow) and macrophages containing phagocytized lymphocytes (inset)

Table 1 Differential diagnosis of SHML

Disease	Pathologic features
- Granulomatous lymphadenitis	Epithelioid histiocyte, caseous necrotic background, intracellcular organisms
- Sinus histiocytosis	Loose clusters of histiocytes, reactive lymphocyte with germinal centers
- Hodgkin's disease	Typical Reed- sternberg cells
- Malignant histiocytosis	Atypical and malignant looking histiocytes
- Large cell lymphoma	Monotonous atypical lymphoid cells
- Eosinophilic granuloma	Prominent eosinophil infiltrate, large neoplastic histiocytes
- Hemophagocytosis syndrome	Hemophagocytosis with prominent platelets and red blood cell phagocytosis
- Metastatic carcinoma	Malignant epithelial cells
- Metastatic melanoma	Malignant melanocyst with prominent nucleolus

For extranodal sites, the characteristic pattern of alternating pale and dark areas can be seen at low magnification. There are often dilated spaces similar to the dilated sinuses of actual lymph nodes filled with many RD cells (pale stained area) alternating with lymphoid tissue rich in plasma cells (dark stained area) with scattered reactive germinal centers.[10] However, the fibrosis is usually greater in extranodal sites, and the number of diagnostic cells tends to be less than in nodal involvement.[1, 10, 12]

The differential diagnosis, both clinically and pathologically, contained a number of entities that required different modes of treatment. While lymphomatous or leukemic involvement of lymph nodes is the most important clinical differentiation, SHML must be distinguished pathologically from reactive histiocytosis to malignant diseases (Table 1).

The etiology of the diseases is still unknown, although rare cases have been reported to be associated with high titer of infective agents such as Epstein-Barr virus, Klebsiella sp. and recently Human Herpesvirus 6.[1, 12, 16, 20] However, attempts to document an infectious etiology by microscopic examination, cultures and others laboratory tests have been ultimately unsuccessful.[2] Some researchers believe that SHML is the expression of an abnormal immunologic process. Bonetli et al. showed that phagocytized lymphocytes in SHML are

helper inducer T-cell.[21] A broad spectrum of immunologic abnormalities such as arthritis, autoimmune hemolytic anemia, glomerulonephritis and systemic amyloidosis have been identified in approximately 10% of cases.[2] These provide evidence that SHML is a manifestation of disordered immunity but specific immune abnormality is still unknown.

SHML is considered to be an indolent, selflimited diseases.[10] Several extranodal sites usually accompanied by multiple nodal diseases seem to be associated with more protracted clinical course.[1] On the basis of the clinical course of the disease, patients can be subdivided into 1) those who undergo a complete and spontaneous remission such as the present case ; 2) those with a chronic course, marked by remission and exacerbations ; 3) those with persistent stable disease; 4) those with progressive disease ; and 5) patients who die with disseminated nodal disease and/or involvement of many extranodal organ systems and/or involvement of unusual sites (kidney, lower respiratory tract).[10] The overall mortality rate is about 7%.[4]

Most patients require no treatment and there is no ideal treatment for SHML.[12, 22] Our patient also had spontaneous remission after open biopsy without any further treatment. However, patients with extensive or progressive disease do need treatment. The major indication for surgery other than biopsy is life-or function-threatening obstruction.[3, 21] Radiotherapy has been used with limited success.[8, 22] For disseminated nodal or extranodal disease, a combination of vinca alkaloid, an alkylating agent (vinblastine sulfate, chlorambucil or cyclophosphamide), and corticosteroids are the most effective regimens. But the result is not as good as in malignant histiocytic diseases with response rate only about 53%.[22] Recent study showed that systemic methotrexate and mercaptopurine may be of value.[13]

Finally immunologic abnormalities (autoimmune hemolytic anemia, identification of rheumatoid factors, antinuclear antibodies, positive lupus erythematosus preparations), widespread involvement especially kidney, liver, and respiratory tract, and associated of anemia with neutrophilia, lymphocytopenia or elevated erythrocyte sedimentation rate are poor prognostic signs.[10]

Conclusion

SHML is a rare benign disorder primarily affecting children with no known etiologic factors. Progressive cervical adenopathy is the most consistent features. Many patients also have extranodal disease especially in head and neck region, and a head and neck surgeon may ultimately be called upon to establish tissue diagnosis as in our case. With more experience, diagnosis of SHML can be made from aspiration cytology and other clinical clues that help to avoid unnecessary investigative procedures and surgical intervention. Treatment is expectant, and these patients should have long- term follow-up to assess for extrinsic compression and extranodal manifestations that may require surgical or medical treatment to preserve organ function. It is important for clinicians managing head and neck problem to be aware of this entity, its variable presentation and the role of various treatment modalities.

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