

Kikuchi-Fujimoto Disease with Cutaneous Involvement Associated with Hemophagocytic Syndrome

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Kikuchi-Fujimoto disease (KFD), or histiocytic necrotizing lymphadenitis, is a rare self-healing lymphadenopathy which typically affects young women and usually remits spontaneously with no recurrences. Hemophagocytic syndrome (HS) is characterized by non-malignant histiocytes that phagocytize normal hematopoietic cells in an uncontrolled manner and manifests clinically as a prolonged fever, palpable splenomegaly and unexplained cytopenia. To date, there have only been eight reports of KFD associated with HS in the English language literature. We report here a 14-year-old Korean boy with KFD and cutaneous involvement associated with HS. (*Ann Dermatol* 17(1) 30~34, 2005)

Key Words: Kikuchi-Fujimoto disease, Kikuchi's disease, Histiocytic necrotizing lymphadenitis, Hemophagocytic syndrome

INTRODUCTION

Kikuchi-Fujimoto disease (KFD), or histiocytic necrotizing lymphadenitis, is a benign, usually self-limited disease characterized by fever and cervical lymphadenopathy^{1,2}. Skin eruptions, usually non-specific, have been reported in 16-40% of patients with KFD³. Hemophagocytic syndrome (HS) is a histiocytic reactive process in which hematopoietic cells are engulfed by histiocytes⁴. It is characterized by histiocytic proliferation, hemophagocytosis, fever, hepatosplenomegaly, generalized lymphadenopathy, hypertriglyceridemia and hypofibrinogenemia⁴. Here we report the case of a 14-year-old boy who showed features of KFD and HS simultaneously. To our knowledge, this is only the 9th case in the English literature to show the association between the two conditions.

CASE REPORT

A 14-year-old Korean boy presented with a 3-week history of fever, malaise and progressive cervical lymph node enlargement, and a 2-week history of a generalized maculopapular skin rash. Prior to coming to our department, he had suffered from remittent fever and persistent and painful cervical lymphadenopathy. A lymph node biopsy showed a mixed infiltrate of histiocytes, plasmacytoid monocytes and lymphoid cells, with abundant karyorrhexis and necrosis, features typical of Kikuchi's disease (Fig. 1). Conservative management with antibiotics and NSAIDs failed to reduce these general symptoms, and a skin rash developed. On examination, he had a 3 × 2 cm, tender, firm cervical lymph node on the left, and hepatosplenomegaly with high fever (39°C). Cutaneous examination showed generalized, erythematous to brownish maculopapules over his trunk and extremities (Fig. 2). A skin biopsy showed a perivascular and perifollicular infiltrate of mononuclear cells and cellular debris, which stained positive for CD68 (Fig. 3), but displayed no evidence of hemophagocytosis.

Laboratory tests showed hemoglobin 8.1 g/dl, white blood cell count 2200/μl, platelet count 182,000/μl, aspartate amino transferase (AST) 2155

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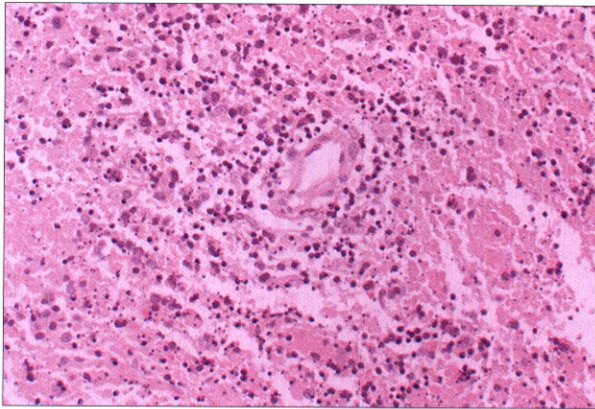


Fig. 1. Lymph node biopsy showing a mixed infiltrate of histiocytes, plasmacytoid monocytes, and lymphoid cells, with abundant karyorrhexis and necrosis, features typical of Kikuchi's disease (H&E, $\times 200$).



Fig. 2. Cutaneous examination showing generalized, erythematous to brownish maculopapules over the patient's trunk and extremities.

IU/l, alanine aminotransferase (ALT) 573 IU/l, alkaline phosphatase 799 IU/l (normal, 40-120 IU/l), total bilirubin 2.3 mg/dl (normal, 0.2-1.2 mg/dl), direct bilirubin 1.1 mg/dl, lactate dehydrogenase (LDH) 9790 IU/L (normal, 120-250 IU/L), ferritin 1564.9 ng/ml (normal, 20-320 ng/ml), fibrinogen 109 mg/dl (normal 200-400 mg/dl) and cholesterol 143 mg/dl (normal, <240 mg/dl). The patient was positive

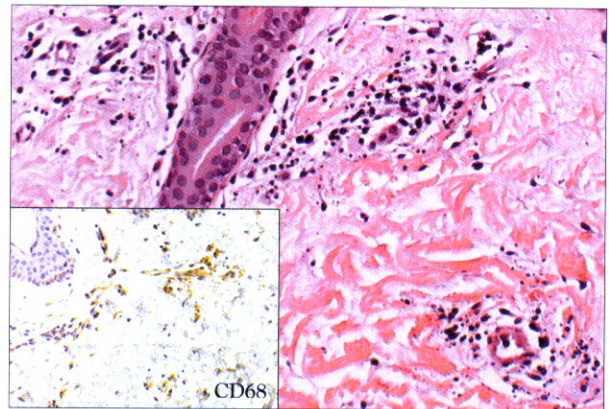


Fig. 3. Histopathologic results of a skin biopsy included a perivascular and perifollicular infiltrate of mononuclear cells and cellular debris with no evidence of hemophagocytosis (H&E, $\times 200$). Inset: much of the infiltrate was clearly immunostained with antibody to CD68 ($\times 200$).

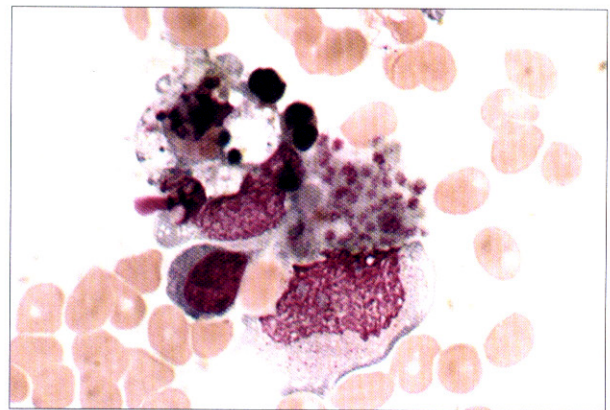


Fig. 4. Bone marrow aspirate showing histiocytes engulfing erythrocytes (hemophagocytic histiocytes). (Wright Giemsa stain, $\times 1000$).

for latent infection with cytomegalovirus (CMV; IgG 35 AU/ml; IgM negative), Epstein-Barr virus (EBV; viral capsid antigen IgG 1.9 OD ratio, IgM negative; nuclear antigen IgG positive) and rubella virus (IgG 77 IU/ml; IgM negative), but negative for antinuclear antibodies. Family history was noncontributory. Clinical findings, including prolonged remittent fever and palpable splenomegaly, and abnormal laboratory findings, including bicytopenia, hypofibrinogenemia and elevated ferritin (above 1000 ng/ml) and LDH (above 1000 IU/l) levels, were very suggestive of hemophagocytic syndrome. Bone marrow examina-

tion showed relatively hypocellular marrow containing a high percentage of well-differentiated histiocytes (13.2%) and prominent hemophagocytosis (Fig. 4). Induction with dexamethasone and etoposide was started. After 1 week, a marked improvement of the skin rash and other symptoms was observed, and the patient was treated continuously with cyclosporin A.

DISCUSSION

Kikuchi-Fujimoto disease (KFD), or histiocytic necrotizing lymphadenitis, is a rare self-healing lymphadenopathy first reported in 1972 as a distinct clinicopathological entity of unknown etiology^{1,2}. It mainly affects young adults, mostly women, and is clinically characterized by cervical lymphadenopathy, high fever, occasional leucopenia and liver dysfunction³. Other symptoms may include weight loss, diarrhea, nausea, vomiting, thoracic pain, myalgia, arthralgia and skin rashes.

Although 16-40% of patients with KFD have been reported to have skin eruptions, no specific skin changes in KFD have been described³. Well-documented skin lesions have included urticarial, morbilliform, rubella-like or drug-eruption-like rashes, facial erythema, generalized erythema and papules, plaques and nodules, leukocytoclastic vasculitis, erythema multiforme, papulopustules and even eyelid edema⁵⁻⁷. In most cases, the lesions were located on the face, upper trunk or extremities.

Histopathologically, lymphadenitis in KFD is characterized by a proliferation of immunoblasts, lymphocytes, and histiocytes, a large amount of nuclear debris and an absence of neutrophils and granulomata⁸. Skin biopsies of patients with KFD and cutaneous involvement have demonstrated variable histopathologic findings, including nonspecific superficial and deep perivascular infiltrates, papillary dermal edema and vacuolar changes with necrotic keratinocytes at the dermal-epidermal junction, as well as a patchy infiltrate of lymphoid cells, histiocytes and nuclear debris, findings similar to those observed in lymph node biopsies^{3,6,8}. Dermal infiltrates consisting of histiocytic cells, so called plasmacytoid monocytes, and karyorrhectic debris were positive for CD68^{5,8}. In our case, the histopathological findings in skin showed a perivascular and perifollicular infiltrate of CD68 positive histiocytic

cells and nuclear debris, consistent with a diagnosis of KFD.

The cause of KFD remains unknown, although apoptosis may play an important role in its pathogenesis⁹. In KFD, cytotoxic T lymphocytes may act as apoptotic effectors as well as target cells, while histiocytes may enhance apoptosis^{5,9}. The perforin and Fas pathways of cytotoxic T cells have been implicated in the increased apoptosis observed in patients with KFD⁹. A viral pathogenesis for KFD is suspected because of the self-limiting clinical course of this disease and the lack of a neutrophilic response. Among the viruses thought to be involved are EBV, CMV, human herpes virus type 6, parvovirus B-19 and type I human T-cell lymphotropic virus¹⁰⁻¹². Although the association between KFD and infectious agents may vary sequentially in time, viral infection may act to "trigger" this condition. In the case presented here, latent infection by CMV, EBV and rubella virus was detected.

Autoimmune mechanisms have also been suggested in the pathogenesis of KFD^{1,7}, primarily because of its association with connective tissue diseases such as SLE, adult Still disease and mixed connective tissue disease^{11,13-14}. It is possible that more than one etiologic agent can provoke this immune response in susceptible individuals.

Hemophagocytic syndrome (HS), or hemophagocytic lymphohistiocytosis, is a rare, rapidly progressive, and potentially fatal disorder of activated histiocytes⁴. Diagnosis of HS requires the presence of five criteria: fever of unknown etiology for 7 or more days, palpable splenomegaly, unexplained cytopenia affecting at least 2 cell lines, hypertriglyceridemia or hypofibrinogenemia and histopathological evidence of hemophagocytosis^{4,15}. Other abnormal findings have been documented, including abnormal liver function tests, coagulopathy, low natural killer cell activity, cerebral spinal fluid pleocytosis and neurological involvement^{4,15}. Our patient fulfilled the diagnostic criteria for HS.

HS has been described in the context of an autosomal recessive familial syndrome, in various malignant diseases, mainly of lymphoid origin, and in association with viral and other infections, including infection with parvovirus B19, herpes simplex virus, varicella zoster virus, EBV, CMV, influenza virus, coxsackie viruses, adenoviruses, fungi, parasites, rickettsia and *Mycobacterium tuberculosis*^{15,16}.

To date, eight cases of HS combined with KFD

have been reported in the English language literature¹⁶⁻²². Cutaneous lesions were described in only two cases, one as an erythematous rash and the other as a generalized maculopapular rash^{16,21}. Skin biopsies were not performed on these patients, so the diagnosis of cutaneous lesions is unclear. Cutaneous eruptions in HS have been reported to occur in 6% to 65% of cases, with a transient, non-specific, generalized maculopapular eruption being the most common cutaneous finding²³. Skin biopsy findings are not diagnostic and have been described as lymphohistiocytic perivascular infiltrates in the reticular dermis without epidermal changes or vasculitis²³. Histopathologic findings of our patient were more likely those of KFD than of HS.

Although the mortality rate of patients with HS has been reported as 20-42%, childhood HS associated with KFD seems to be less aggressive and have a better prognosis than adult HS²⁴. The recognition of its association with KFD is therefore very important in devising a therapeutic strategy. It is noteworthy that HS and KFD may both be initiated by viral infection. Furthermore, defects in the perforin gene, which appears to be important in controlling activated immune activity and has been implicated in KFD, have been detected in approximately 20% of unrelated patients with familial HS²⁵. Pathophysiological overlap suggests that both diseases may form a single entity with a spectrum of illness, ranging from localized KFD to generalized HS¹⁹.

In summary, we have described a case of KFD associated with HS, which assumed a relatively benign course. Dermatologists should keep in mind that cutaneous manifestations may be seen in both diseases, and that awareness of the various types of cutaneous presentations and histopathologic findings can assist in diagnosis.

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