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Reactive Hemophagocytic Lymphohistiocytosis-Associated Kikuchi-Fujimoto Disease After a *Staphylococcus epidermidis* Cutaneous Infection

The First Case Report

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Kikuchi Fujimoto disease (KFD) is a rare condition with necrotizing lymphadenitis[1] with unclear etiology. We report the case of KFD complicated with hemophagocytic lymphohistiocytosis (HLH) after a *Staphylococcus epidermidis* infection.

A 49-year-old previously healthy woman presented to the hospital with fever of 38°C and back pain. Physical examination revealed many pustules on the bilateral axillary areas. Laboratory results were significant for an elevated C-reactive protein level of 160.6 mg/dL. Results of immunological tests including antinuclear antibody, anti–double-stranded DNA antibodies, C3, C4, antineutrophil cytoplasmic antibodies, rheumatoid factor, serum antibodies against cytomegalovirus, toxoplasma, leptospira, plasmodium, syphilis, human immunodeficiency virus, and blood cultures were all negative. Lumbar magnetic resonance imaging revealed enhancement of signals at the paraspinal quadratus lumborum and psoas muscles (Fig. A). Subsequent paraspinal muscle biopsy confirmed chronic myositis and was negative for bacillus acid-fast stain. Skin biopsy from the pustules on her axillae showed chronic dermatitis (Fig. B). Pus culture from the pustules yielded *S. epidermidis*. One week later, she had high fever of 38°C to 40°C with new-onset bilateral tenderness of cervical lymphoid nodules. Complete blood cell count results revealed leukopenia, anemia, and thrombocytopenia. The metabolic panel was significant for elevated liver enzymes, creatinine kinase, and ferritin with a slightly decreased fibrinogen. Computerized tomography illustrated lymphadenopathy (Fig. C). Bone marrow biopsy indicated activated macrophages with evidence of hemophagocytosis (Fig. D). Cervical lymph node excisional biopsy demonstrated histiocytic necrotizing lymphadenitis (Fig. E, F). Immunohistochemical study revealed condensed CD3-positive T cells with predominantly CD8-positive cytotoxic cells but a few CD30-positive T cells (Fig. G–J). CD68-positive histiocytes showed marked hemophagocytic activity (Fig. K, L). Kikuchi Fujimoto disease complication with reactive HLH was diagnosed. Pulsed methylprednisolone for 3 days, with tapering the following 7 days, was recommended, which resulted in complete resolution of her fever and lymphadenopathy and blood parameters returning to normal.

The KFD is a self-limiting condition; however, reactive HLH underlying KFD is severe and may be fatal. The confirmed diagnosis of KFD-associated HLH was mainly based on clinical and laboratory features. Screening serologic tests were negative for acute viral infections; therefore, *S. epidermidis* infection was possibly assumed as the primary pathogenic underlying cause of the condition. Dysfunction of T lymphocytes or their enhanced proliferation due to *S. epidermidis* infection via cytokine production might play an essential role in the pathogenesis of this condition.[2,3] Apoptotic mechanisms due to bacterial pathogens could predispose to KFD by enhancing the susceptibility of lymphocytes to apoptosis.[4] Bone marrow examination is recommended in patients with persistent fever, systemic symptoms, partial response with treatment, and abnormal laboratory findings of hemophagocytosis with KFD. Immunohistochemical staining features of the lymph node with the presence of predominantly CD8-positive cells and condensed CD68-positive histiocytes in histiocytic necrotizing lymphadenitis are similar to a previous report.[5] In conclusion, early recognition of HLH accompanied with KFD after an *S. epidermidis* cutaneous infection plays a crucial role in preventing fatal outcome in these patients. Paradoxal immune reactions may possibly induce the concurrent development of these unusual conditions.

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The authors declare no conflict of interest.

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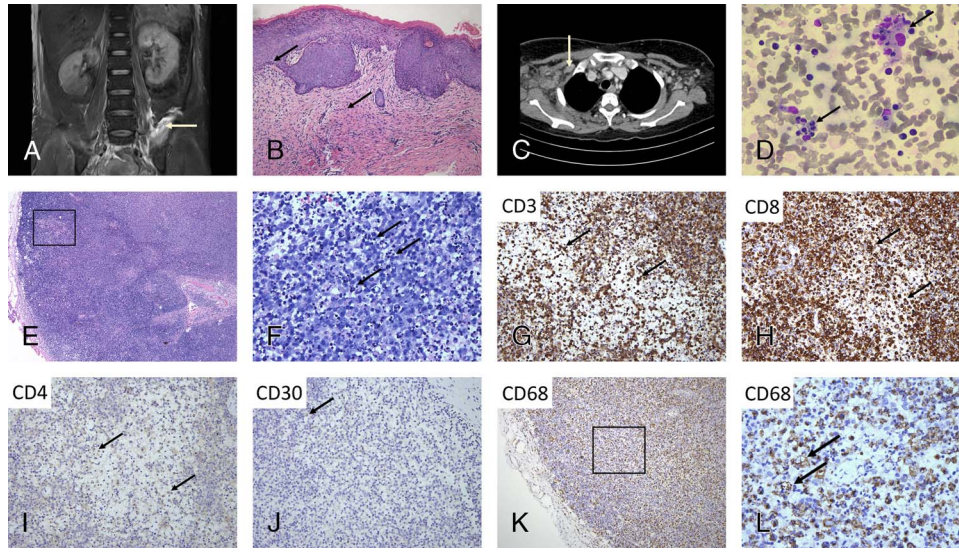

FIGURE. A, Magnetic resonance imaging showing enhancement of psoas muscles (arrow). B, The skin biopsy obtained at the infectious axillary areas showing interface dermatitis with vacuolar change, scattered lymphocytes, and some necrotic keratinocytes within the basal layer. An abundant number of mononuclear cells infiltrated the dermal layer (arrow, original magnifications ×20). C, CT image showing enlarged lymph nodes in the axillary areas (arrow). D, Bone marrow aspirate smears stained with Wright-Giemsa stain showing occasionally activated macrophages with evidence of hemophagocytosis, including engulfed granulocytes, red blood cells, and platelets (arrows). E, The enlarged cervical lymph node was biopsied. The scanned image of a hematoxylin-eosin–stained slide showing a lymph node with effaced architectures and areas of geographic and confluent necrosis. Residual normal germinal centers were identifiable on small regions of the node (square area). F, Microscopic examination showing that necrotic areas were characterized by marked apoptotic activity (arrow, original magnification ×40). G, The scanned image of an IHC-stained slide of a cervical lymph node showing an enlarged lymph node with confluent necrosis. In the background, numerous CD3-positive T cells (arrows) with predominantly CD8-positive cytotoxic T cells were identified (arrows, H). CD4-positive cells were scattered (I), and few CD30-positive cells were identified (J). K, Sheets of CD68-positive histiocytes infiltrated in the necrosis area (square area), some with plasmacytoid features and others showing marked hemophagocytic activity (L, arrows).