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Association between Kikuchi-Fujimoto disease and *Streptococcus pneumoniae* infection

Case Report

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Abstract: Kikuchi-Fujimoto disease is a rare histiocytic necrotizing lymphadenitis that affects typically young women causing fever and painful laterocervical lymphadenopathy. The etiology is unknown, but several viral infections and autoimmune diseases have been related with the disease. Bacterial infections are less frequent. Diagnosis needs for excisional lymph node biopsy that shows paracortical areas of coagulative necrosis with abundant debris, distortion of the nodal architecture, and a large amount of histiocytes at the margins of the necrotic areas. There is no specific treatment for the disease. We present the case of a young woman with Kikuchi-Fujimoto disease associated with lower respiratory tract infection by Streptococcus pneumoniae and review the literature.

Keywords: *Kikuchi-Fujimoto disease • Histiocytic necrotizing lymphadenitis • Streptococcus pneumoniae*

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1. Introduction

Histiocytic necrotizing lymphadenitis was first described in 1972 by two independent Japanese pathologists, Kikuchi and Fujimoto [1,2]. The classical presentation is in young women with fever and painful cervical lymphadenopathy and it has been referred to as Kikuchi-Fujimoto disease (KFD). Although etiology is unknown, association with several viral infections as well as autoimmune disorders has been reported. Bacterial infections like *Yersinia enterocolitica* and *Pasteurella multocida* have been associated with KFD.

We describe herein the case of a young woman with KFD and *Streptococcus pneumoniae* respiratory infection and review the features of this syndrome.

2. Case presentation

A 23 year-old woman presented to the clinic with tender right cervical lymphadenopathy, loss of appetite, caught with occasionally bloody sputum, and fever up to 40ºC. Her recent history indicated progressive painful right neck lymphadenopathy during the last month. Her past history was unremarkable. On physical exam, she had no fever, and there was right tender cervical lymphadenopathy of 0.5cm to 1cm diameter in size (Figure 1). An ORL exam was normal. The tuberculosis skin test (PPD) was negative. Routine biochemical analysis, as well as coagulation test, and urinalysis were within normal limits. ANA were positive 1/80 in the first exam and negative 2 weeks later. Angiotensin converting enzyme (ACE) level was 108 (normal range 18-55) IU/L. β-2 microglobulin level was normal. C-reactive protein: 3.12 (normal range 0-10) mg/dL, Erythrocyte sedimentation rate (ESR) 6

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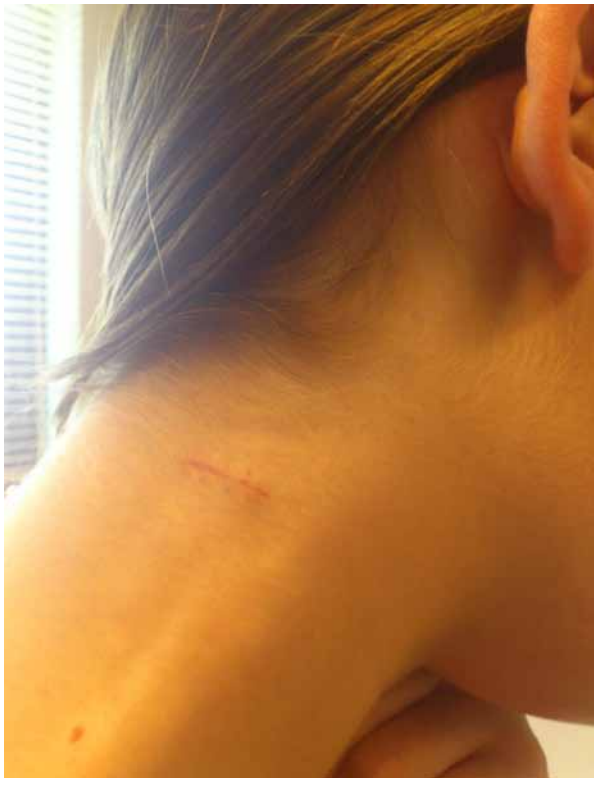

Figure 1. Painful right linear neck lymphadenopathy.

mm/hr. Peripheral blood leukocyte count was 5200 per mm^3 (neutrophils 34%, lymphocytes 54%, monocytes 6%, eosinophils 2% and basophils 1%). Haemoglobin 14.9 g/L and platelet cell count 230,000 per mm^3. Microbiological testing for *Toxoplasma gondii*, HBV, HCV, HIV, CMV, Epstein-Barr virus, *Bartonella, Treponema pallidum, Brucella, Francisella tularensis*, and *Rickettsia conorii* were negative. HSV test presented a borderline positive result, but it was negative when repeated 2 weeks later. *Mycoplasma pneumonia*e IgM negative, IgG positive. Sputum culture was negative for tuberculosis and *Streptococcus pneumoniae* was isolated. Chest radiograph was unremarkable. Fine needle aspiration cytology of the lymphadenopathy was informed as non-specific lymphadenitis. A lymph node excisional biopsy was performed and treatment with cefixime 400 mg bid was administered for 10 days. Pathological examination revealed the presence of KFD (Figures 2 and 3).

3. Discussion

KFD is extremely uncommon with higher Japanese and Asiatic prevalence [3] but it has been described in all ethnic groups around the world. Sporadic causes have also been reported in Europe. It happens to occur

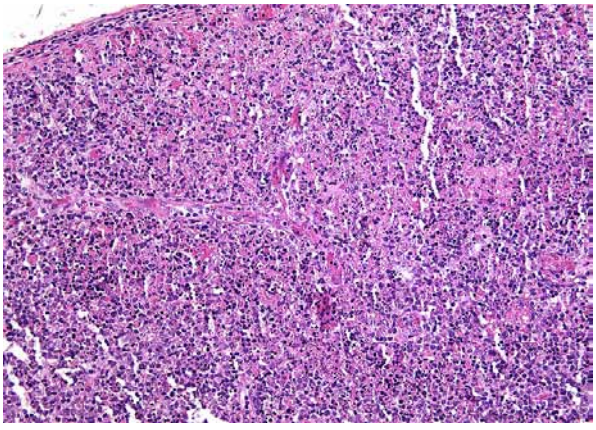

Figure 2. Multifocal necrotic lesions in the lymph node. There is prominent nuclear debris and numerous degenerated mononuclear cells evident in the necrotic lesion. Neither Reed-Sternberg cells nor granulomatous inflammation were identified (Hematoxylin and Eosin staining, ×40).

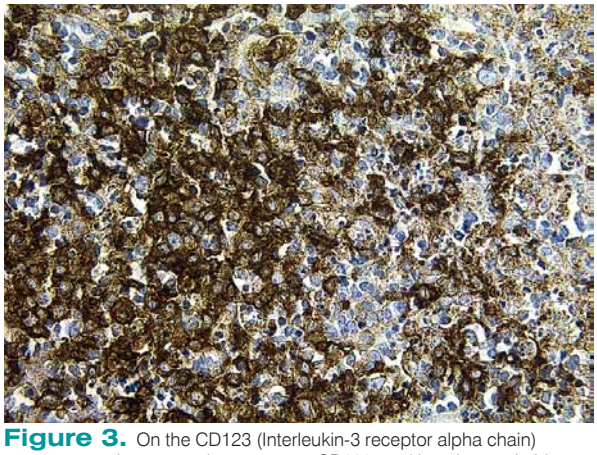

Figure 3. On the CD123 (Interleukin-3 receptor alpha chain) immunostain, numerous CD123-positive plasmocitoid monocytes are noted in the necrotic lesion. CD15, CD30, EBV and ALK-1 immunostain were negative as well as PAS and Ziehl-Neelsen immunostain.

mainly in young adults below 40 and seldom in children. Although a slight female predominance was considered, the recent literature regards it as male to female ratio 1:1 [4]. A slightly male predominance has been reported in most paediatric studies [5].

The etiology of KFD remains unknown. Literature discusses both viral and autoimmune causes as the most likely. The role for viruses like Epstein-Barr virus, human herpesvirus 6 and 8, parvovirus B-19, parainfluenza and paramyxoviruses is controversial and, unremarked [5,6]. KFD has also been reported in patients with AIDS [7]. Other infectious agents related have been *Toxoplasma gondii, Yersinia enterocolitica* and *Pasteurella multocida* [8,9].

Among autoimmune diseases, the relation to systemic lupus erythematosus (SLE) has been postulated

because of lymphocytes and histiocytes in patients with KFD show tubular reticular structures in their cytoplasm on electron microscopy like in patients with SLE [10]. Moreover, apoptotic cell death might be involved in the pathogenesis of KFD because of proliferating CD8 T-cells may be killed in the apoptotic process of this disease using Fas and perforine pathways [11]. In this sense, perforin plays an important role in lymphocyte-mediated cytolysis inducing pore formation and cell osmotic lysis. Perforin detection has been reported in lymphocytes $CD8^+$ T cells (low perforin level) and fundamentally NK cells (higher perforin level) [12]. Lupus lymphadenitis is also characterized by prominent necrosis and the presence of hematoxylin bodies, prominent plasma cells and neutrophils point to this diagnosis. Additionally, KFD can precede, postdate or coincidence with the diagnosis or SLE [13].

KFD is an acute or sub-acute condition developing over two or three weeks. The milestone is the presence of tender cervical lymphadenopathy (56%-98%) usually involving the posterior cervical triangle. Enlarged lymph nodes size ranges from 0.5 cm to 4-5 cm. About 50% of patients present painful lymphadenopathy and 1%-22% patients undergo generalized lymphadenopathy. Rarely, mediastinal, peritoneal or retroperitoneal regions can be involved [4,10,14]. Fever is present in 30%-50% of patients sometimes associated with upper respiratory symptoms, sore throat, sweets, weight loss, headache, rash, nausea and vomiting [15,16]. Rare manifestations like skin or nervous system involvement or bone marrow affection has been reported [3,17].

Laboratory results are non-specific and include anaemia, elevated immunoglobulin levels, little rise in erythrocyte sedimentation rate, leukopenia, relative lymphocytosis, presence of atypical lymphocytes in peripheral blood films, being predominantly $CD8^+$ T-cells [18]. Antinuclear antibodies and rheumatoid factor are generally negative [19].

Diagnosis is made upon an excisional biopsy of the involved lymph nodes. There are paracortical areas of coagulative necrosis with abundant karyorrhetic debris, distortion of the nodal architecture, and large numbers of histiocytes at the margins of necrotic areas [20]. Histopathologic features can be classified in three stages: 1.- Proliferative, with the expression of various histiocytes, plasmacytoid monocytes and lymphoid cells containing karyorrhetic nuclear fragmentes, and eosinophilic apaptotic debris. 2.- Necrotizing, that shows a degree of coagulative necrosis. 3.- Xanthomatous, with a predominance of foamy histiocytes [21]. Immunohistochemically, there is an expression of CD68 antigen by the histiocytic component and a prevalence of $CD8^+$ cytotoxic cells in the lymphoid component [22]. It also has been suggested that $CD8^+$ cytotoxic T cells simultaneously undergo apoptosis and proliferation in KFD and co-express immature dendritic cell phenotypes including CD123 [23]. Recently, it has been reported than PET could be useful to differentiate benign disorders like KFD from malignant lymphoma but most cases required surgical biopsy for a final diagnosis [24].

Recently immunohistology, gene analyses and immunology have improved KFD diagnosis. In this sense, the alpha-chain of the interleukin-3 receptor (IL-3RA or CD123) is expressed in various sources from hematopoietic cells such as fetal liver, cord blood, bone marrow and peripheral blood [25].

Dendritic cells (DCs) consist of two subpopulations according to separate differentiation pathways: myeloid-derived DCs and plasmacytoid DCs. It has been reported a higher average of CD123-positive plasmacytoid DCs in lymph nodes of patients with KFD as compared with lymph nodes of patients with reactive lymphadenitis, Hodgkin lymphoma, T cell lymphoma and B cell lymphoma [26]. These plasmacytoid DCs are one of the major producers of type I interferon that is known to protect a host against the invasion of viral pathogens [27]. From a genetic point of view, DNA released from nuclear debris in the inflamed lesion could stimulate the release of myeloperoxidase from leucocytes and some CD123 positive macrophages can express myeloperoxidase in KFD [23]. Expression of interferon-stimulated genes is up-regulated in peripheral blood mononuclear cells as well as in involved lymph nodes of KFD patients. The evaluation of the level of mRNA expression is useful in order to distinguish KFD from other diseases that also express interferon-stimulated genes like malignant lymphoma and leukemia [27,28]. Additionally, NK cells can interfere with the adaptive immune response by killing immature DCs. This NK cell-mediated cytotoxicity induces an antigen-specific adaptive immune response that involves not only $CD8^+$ T cells and CD4+ T cells but also antibodies [12].

Differential diagnosis includes non-Hodgkin's lymphoma (there is an atypical reactive immunoblastic component very common in KFD that can be mistaken for lymphoma), tuberculosis, SLE, plasmacytoid T-cell leukemia, Kawasaki's disease, lymphogranuloma venereum, sarcoidosis, myeloid tumor, signet-ring carcinoma and metastatic adenocarcinoma [3]. Lymphoid forms of leukemia are CD68 negative [22]. Regarding to sarcoidosis, our patient had a high level of ACE, but the pathological examination was not suggestive of the disease and besides, it is well known that young people have higher levels of ACE without pathological significance [29]. Association with bacterial infection has been described previously, especially with *Yersinia enterocolitica*

and *Pasteurella multocida* [9]. To our knowledge, this is the first association between KFD and *Streptococcus pneumoniae* infection. KFD is a self-limiting condition that resolves spontaneously within 1 to 4 months. No standard of specific treatment has been recommended and sometimes, specific treatment for an associated infection, like in our patient, is administered. Recurrence has been reported in 3%-4% and SLE may happen to occur some years latter [10,30]. Lymph nodes tenderness and fever is treated with analgesics, antipyretics, NSAIDs, and sometimes steroids with or without associated intravenous immunoglobulin especially in severe extranodal involvement or generalized clinical course [31]. Recognition of KFD is crucial because its clinical course and treatment differ dramatically from other diseases affecting lymph nodes. Bacterial infections as cause of KFD are rare but probably more frequent than thought. This case illustrates a patient with KFD associated to pneumococcal infection being the first case reported to our knowledge. Clinical follow-up of KFD is necessary for emergence of SLE or other connective tissue disorders.

Conflict of interest statement

Authors state no conflict of interest.

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