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Subacute cutaneous lupus erythematosus onset preceded by Kikuchi-Fujimoto disease

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ABSTRACT Kikuchi-Fujimoto disease (KFD) is an uncommon clinicopathological entity characterized by fever and lymphadenopathy, predominantly involving cervical lymph nodes, accompanied by chills and leukopenia. The diagnosis relies primarily on the presence of typical morphological features in the swelling lymph nodes. KFD can occur as a benign and self-limiting lymphadenopathy, but it can sporadically precede, postdate or coincide with the diagnosis of systemic lupus erythematosus (SLE). The authors report a case of subacute cutaneous lupus erythematosus (SCLE) in a 42-year-old female preceded by prolonged fever, anemia, leukopenia, and cervical necrotizing lymphadenopathy. About two months later, the patient developed facial and scalp plaques suggestive of lupus skin disease. Histologic and immunologic investigations lead to the diagnosis of SCLE. It is not clear whether KFD associated with lupus skin disease are true KFD or a histopathologic feature of SLE.

Introduction

Kikuchi-Fujimoto disease (KFD) or histiocytic necrotizing lymphadenitis is a rare, benign, and self-limited disorder characterized by regional cervical lymphadenopathy, mild fever, and night sweats. It has a worldwide distribution, with higher prevalence among young Asian females [1]. Recognition of KFD is crucial especially because it can be mistaken for lymphoma, tuberculosis or even, for carcinoma. Prognosis is favorable with spontaneous recovery occurring in 1 to 4 months. Treatment is symptomatic and includes analgesics-antipyretics, non-steroidal anti-inflammatory drugs and, rarely, corticosteroids.

KFD can occur isolated, or associated with severe and autoimmune diseases including mixed connective tissue diseases and systemic lupus erythematosus (SLE). In particular KFD can precede, postdate or coincide with the diagnosis of SLE [2]. Here we report a case of necrotizing lymphadenitis preceding the occurrence of subacute cutaneous erythematosus lupus (SCLE) in a 42-year-old woman.

Case report

A 42-year-old Moroccan female was admitted to the hospital with fever lasting one month, night sweats and left cervical lymphadenopathy. Laboratory exams showed leukocytes 3300/mm^3, erythrocytes 4.370.000/mm^3, hemoglobin 12.7 g/dl, thrombocytes 156.000/mm^3, LDH 843U/l (normal values: 230-460). Other laboratory findings were all within normal ranges. Serologic investigations excluded viral, bacterial and parasitic infections, including syphilis and cytomegalovirus, Epstein-Barr virus, HIV, *Rickettsia coronii*, Brucella spp, *Salmonella typhi*, *Salmonella paratyphi*, toxoplasma, *Leishmania donovani* infections. Blood and throat cultures were negative. QuantiFERON TB Gold (ESAT-6, CFP-10, TB7.7 antigens) was negative. Chest X-ray was normal. Chest computed tomography (CT) showed multiple, small-sized bilateral hilar and mediastinal lymphadenopathies. Abdominal CT revealed additional small interaortocaval, para-aortic mesentheric and iliac lymphadenopathies. Due to the presence of multiple lymphadenopathies, a bone marrow biopsy was performed to exclude a lymphoma. Bone marrow examination was considered normal. Histology showed a mild reactive T lymphocytosis, consisting of a regular number of interstitial lymphocytes which showed mainly a CD3+, CD 20- phenotype. Bronchial aspiration with microbiologic cultures for *Mycobacterium tuberculosis* were negative. A cervical lymph node biopsy was performed. The lymph node structure was completely effaced by diffuse necrotic areas with abundant karyorrhectic debris (Figure 1); the search for DNA of *Mycobacterium tuberculosis* was negative. A mediastinal lymph node biopsy and a liver biopsy showed normal histological findings. At this time a definitive diagnosis was not available. After two months new laboratory investigations showed a leukocyte count of 3830/mm^3, erythrocytes 3360000/mm^3, Hgb 9,2 g/dL, thrombocytes 353.000/mm^3, AST 44 U/I, ALT 45 U/I, LDH 138 U/l. Since the patient developed recurrent papulo-squamous lesions on her scalp, ears, face, and trunk, she was referred to the dermatology department.

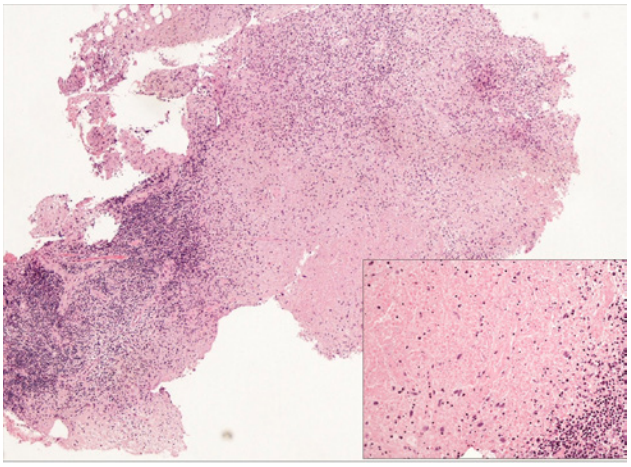

Figure 1. Lymph node showing evident loss of architecture with widespread apoptosis and necrosis (inset, at high power). [Copyright: ©2014 Di Lernia et al.]

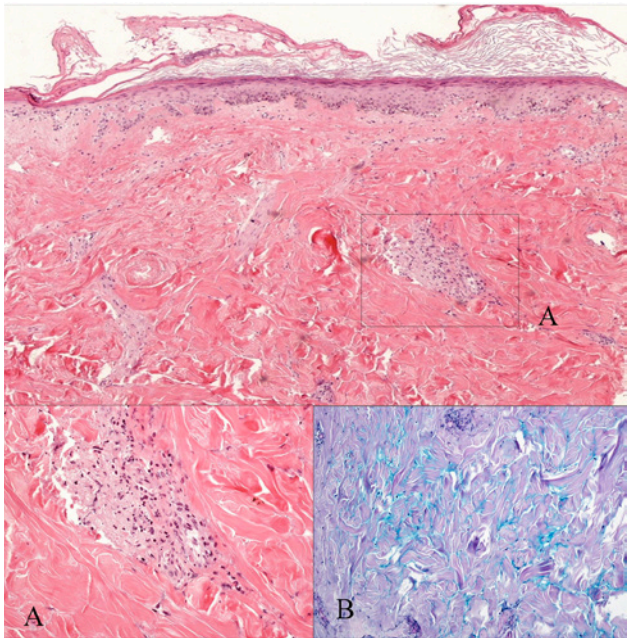

Figure 2. At low power, the epidermis is hyperkeratotic and the basal membrane is focally thickened. The dermis shows scattered aggregates of granulocytes (A). Interstitial mucin deposits are highlighted with Alcian PAS stain (B). [Copyright: ©2014 Di Lernia et al.]

Skin examination showed papular and scaly plaques on the face, the scalp, the V-area of the neck, upper chest, back and shoulder in a photodistributed pattern. No malar rash was noted. Skin lesions were biopsied with a presumptive diagnosis of lupus.

At histology, the epidermis was thinned and displayed focal parakeratosis and vacuolar degeneration of basal keratinocytes, with occasional cytoid bodies. The dermis showed conspicuous interstitial mucin deposits, dense perivascular and perifollicular lymphocytic infiltrates with interface dermatitis (Figure 2) and superficial nuclear debris with karyorrhexis. Direct immunofluorescence failed to demonstrate immunoglobulin or complement deposits along the dermo-epidermal junction or around the vessels. Immunologic serum investigations showed absence of antinuclear antibodies, antibodies (anti)-LA/SS-B, anti-ds DNA, anti-phospholipids, anti-pANCA, anti-Jo1, anti-Scl-70, anti-RNP. Antibodies anti-Ro/SS-A (E.I.A) were 59 (normal value: 0-10), ENA (E.I.A) 18.7 (normal value: 0-3). The patient's complement levels were low with C3 71 mg/dL (normal values: 88–201 mg/dL), C4 5 mg/dL (normal values: 16–47 mg/dL). On the basis of clinical, laboratory and histology findings, a diagnosis of SCLE was made.

The patient was given prednisone 25 mg per day and hydroxychloroquine. Skin lesions improved rapidly and healed without scarring. The dosage of corticosteroids was gradually tapered without relapse of skin lesions. After

38-month follow up the patient is free of skin and systemic symptoms. Now she is taking hydroxychloroquine 400 mg/day. Laboratory investigations are all within normal value, except for persistent complement deficiency in C3 and C4.

Discussion

The etiology of KFD is unknown and controversial. The viral origin remains still a hypothesis that has not definitely been proven. Common presentation signs are acute symmetrical painful swelling of predominantly cervical lymph nodes, fever and systemic signs. The nature of the clinical and pathophysiological relationships between KFD and SLE remains a matter of debate, in particular whether KFD can be considered an atypical manifestation of SLE [3].

Both conditions share the predilection for young females and similar clinical features, including lymphadenopathy, mainly in the cervical lymph nodes, fever, arthralgia, and leukopenia [4].

Histopathologic findings of KFD are crucial in characterization of this condition. Diagnosis is generally made upon on pathological examination of the excised lymph nodes. Typical morphological features include apoptotic necrosis in paracortical areas with abundant karyorrhectic debris, infiltration of histiocytes, CD123+ plasmacytoid dendritic cells, CD8+ T cells, and the absence of neutrophils [5]. Lupus lymphadenitis (LL) is characterized by prominent necrosis, strikingly similar to that described in patients with KFD. Some histological findings, such as the presence of hematoxylin bodies, prominent plasma cells and neutrophils support the diagnosis of LL [6]. However histology alone may be not enough to distinguish between KFD and LL [7].

When KFD occurs with skin involvement, there are two major possibilities. The first one is a SLE with cutaneous and lymph-node involvement, mainly if histopathology of skin lesions show interface dermatitis [8]. In this case KFD may in fact be a histopathologic characteristic of SLE supporting the hypothesis that KFD is a rare manifestation of SLE [3]. The second one is benign, self-limited KFD with transient cutaneous involvement. Extra-nodal involvement in KFD is uncommon; skin manifestations are observed in 5–30% of patients [9]. Various skin lesions, such as urticaria-like erythematous papules, nodules, plaques, and indurate lesions, have been reported. In addition, also lupus-typical skin manifestations, as malar rash and photosensitivity, have been observed [10]. In such cases, histopathology of skin lesions usually show lymphohistiocytic infiltrates accompanied by non-neutrophilic karyorrhetic debris, similar to those observed in the involved lymph nodes.

In our patient a necrotizing lymphadenitis preceded the onset of lupus skin disease. The lymph node biopsy showed extensive necrosis suggesting the possibility of LL, however aggregates of nuclear debris or so-called hematoxylin bodies were not found. Laboratory findings were unremarkable except for neutropenia, anemia and elevated LDH. Two months later our patient developed a SCLE. She presented leukopenia and photosensitivity, but she did not fulfill ACR (American College of Rheumatology) criteria for the diagnosis of SLE. However, since we have a 38-month follow-up, a clinical evolution of our patient's SCLE toward SLE in the future cannot be definitely excluded.

SCLE has exceptionally been reported in association with KFD [11]. KFD may be the initial diagnosis in patients who go on to develop SLE later on. A lag time of 10 months to 3 years has been observed between the diagnosis of KFD and the subsequent onset of SLE [12]. Pathological features of KFD and LL show significant overlap. Thus patients with necrotizing lymphadenitis should be monitored long term for SLE. It is suitable to test for autoimmune disease repeatedly even if ANAs are initially negative.

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