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CASE REPORT

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Skin involvement in Kikuchi's disease: an immunocytochemical and immunofluorescence study

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Abstract Kikuchi's disease (KD) is a benign self-limiting febrile illness usually affecting young women, which is manifested clinically by fever and cervical lymphadenopathy. Skin involvement in KD is very rare and is evident clinically in the form of skin rashes and nodules. We describe one such case of KD in a 33-year-old Bulgarian woman who presented with cervical and axillary lymphadenopathy and who developed a transient facial rash. Biopsy of axillary lymph nodes showed the characteristic features of KD with infiltration of the lymph node paracortex by apoptotic plasmacytoid monocytes. Biopsies of the facial skin showed two features: (1) dermal infiltration by apoptotic plasmacytoid monocytes; (2) on immunofluorescence studies of frozen sections prepared from involved and uninvolved facial skin, deposition of immunoglobulins and complement at the dermoepidermal junction and in the walls of dermal blood vessels. Such immunofluorescence findings in the skin of patients with KD have never been described. These findings suggest the presence of an autoimmune reaction as a component of KD.

Key words Kikuchi's disease · Skin involvement · Immunofluorescence study

Introduction

Kikuchi's disease (KD) was first described in Japan in 1972 [7, 11]. The involved lymph nodes show reactive hyperplasia with paracortical foci of necrosis which are devoid of polymorphonuclear leucocytes [2, 5, 7, 11, 22]. Skin involvement in KD is very rare. In this report, we describe a patient with KD who developed a facial rash. The histological, immunocytochemical and frozen section immunofluorescence findings in the facial skin biopsies are discussed.

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Clinical history

A 33-year-old Bulgarian woman, who has been living in London for the last few years, was admitted to hospital with a 5-week history of fever, fatigue and arthralgia and a 1-week history of facial rash. On examination, she was found to be severely ill, with a temperature of 39°C and had a discrete tumid erythematous rash on both cheeks, in addition to enlarged axillary and cervical lymph nodes. She had previously been well.

On investigation, she was pancytopenic with a haemoglobin of 9.3 g/dl, white blood cell count of 2.0×10^9/l and platelet count of 83×10^9/litre. The rheumatoid factor was raised on two occasions, with titres of 1/160 and 1/40. Both thyroglobulin and thyroid microsomal antibodies were raised, at titres of 1/400 and 1/600 consecutively. Chest X-ray and abdominal CAT scans were normal. The patient's symptoms suggested a clinical diagnosis of either an acute infection or acute systemic lupus erythematosus (SLE). No evidence of the following infections was found on serological screening: hepatitis B virus, parvovirus, adenovirus, cytomegalovirus, *Salmonella typhimurium* and *paratyphi*, typhus, spotted fever, brucella, psittacosis, *Borrelia burgdorferi* and lymphogranuloma venerium. Stool, urine, blood and bone marrow cultures and cultures of the biopsied lymph nodes were all negative. In relation to SLE, the renal function tests were normal, and the antinuclear antibodies and antibodies to DNA were all negative. Following 2 weeks in hospital, the patient started to improve gradually without any specific therapy and was then discharged home. There was no evidence of disease activity on follow-up.

Materials and methods

Biopsies

Biopsies included two skin biopsies of the face (one of the rash and one of the adjacent normal skin), a left axillary lymph node biopsy and a bone marrow aspirate and trephine biopsy. Half of each skin biopsy was snap-frozen, and frozen sections were prepared. All the other biopsies were processed routinely for paraffin section examinations.

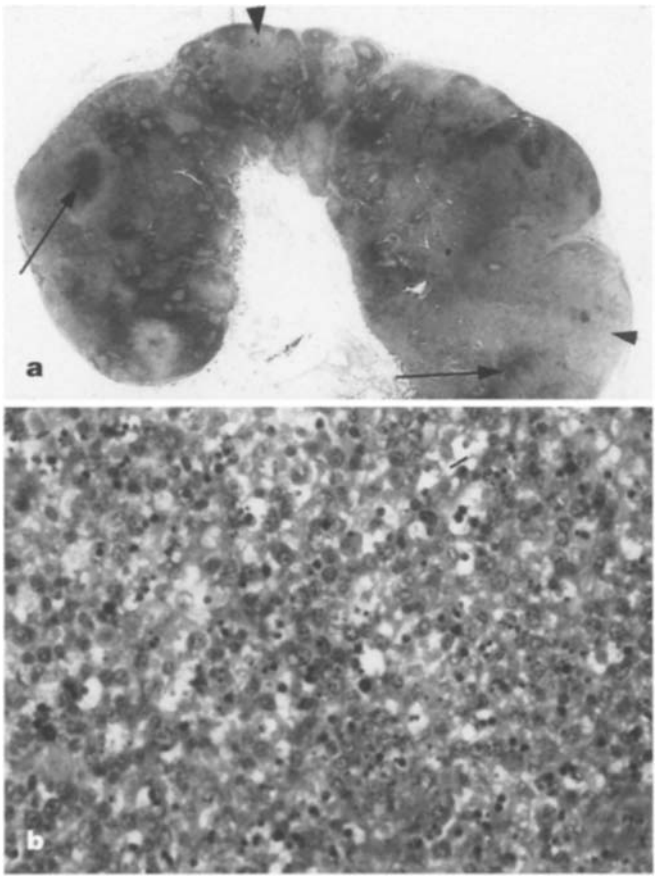

Fig. 1a, b Axillary lymph node. **a** Note the pale areas throughout the paracortex (*arrowheads*), part of which has undergone necrosis (*arrows*). **b** The necrotic areas are due to extensive apoptosis of the plasmacytoid monocytes. Note the absence of polymorphonuclear leucocytes. H&E

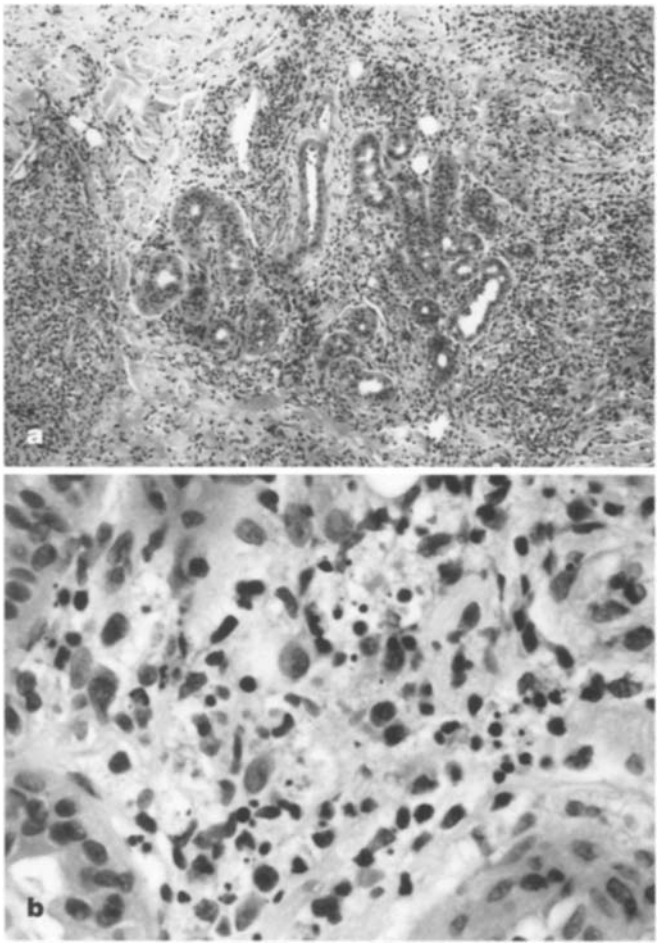

Fig. 2a, b Facial skin. **a** The reticular dermis shows a prominent mononuclear cell infiltrate, most marked around skin adnexa and blood vessels. **b** The infiltrate is composed mainly of plasmacytoid monocytes, which exhibit prominent apoptosis and are closely related to skin adnexa (*left*) and blood vessels (*right*). H&E

Immunocytochemistry

Immunocytochemistry was carried out on paraffin sections of the lymph node and skin biopsies using the avidin–biotin complex technique. The antibody panel included antibodies to B lymphocytes (CD20, MB2, κ and λ light chains), T lymphocytes (CD45RO, CD3, CD4, CD8, CD43), macrophages (CD68, Mac387), S-100 protein and factor VIII-related antigen.

Immunofluorescence staining was carried out on 5-μm-thick frozen sections prepared from the two facial skin biopsies, using the indirect immunofluorescence technique. The panel included polyclonal antibodies to IgG, IgM, IgA, fibrinogen, C3 and C1q.

Pathological findings

Axillary lymph node biopsy

The biopsy specimen consisted of a group of enlarged and matted lymph nodes measuring 8 × 3.5 × 2.5 cm, of which the largest node measured 2 cm in greatest dimension. The cut surface of the lymph nodes was pale in colour and homogeneous, with tiny foci of darker tissue. There was expansion of the lymph nodes cortex by secondary lymphoid follicles with active germinal centres. There was also expansion of the lymph node paracortex by a mixture of T lymphocytes (stained positive for CD45RO, CD43, CD3 and either CD4 or CD8). The paracortex of all the lymph nodes showed large areas of necrosis (Fig. 1a) which consisted of apoptotic plasmacytoid monocytes (Fig. 1b). Plasmacytoid monocytes expressed macrophage markers (CD68, Mac387), and some of them were also stained for CD4 and CD43 antibodies. The same areas contained a few scattered eosinophils, B and T lymphocytes, plasma cells and phagocytic histiocytes and were devoid of polymorphonuclear leucocytes.

Skin biopsies

Biopsy of the facial rash showed diffuse cellular infiltration of the middle and deep dermis (Fig. 2a). This infiltrate was composed predominantly of apoptotic plasmacytoid monocytes and was primarily of perivascular and periadnexal distribution (Fig. 2b). A few small B and T lymphocytes, phagocytic histiocytes, eosinophils and

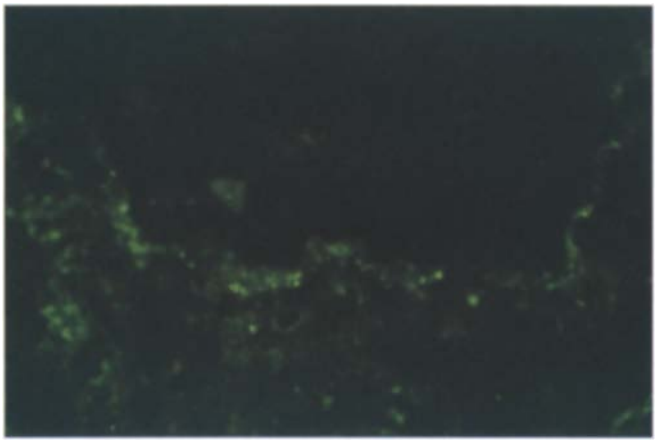

Fig. 3 Immunofluorescence staining of the facial rash. Linear staining for IgM of basement membrane of epidermis

plasma cells were also present in the dermis. Polymorphonuclear leucocytes were completely absent. The upper dermis showed oedema only. There was no evidence of vasculitis and no features of discoid lupus were seen; the epidermis was completely normal with normal basement membrane. Biopsy of the uninvolved facial skin showed normal histology.

Immunofluorescence staining of frozen tissue sections of the facial rash biopsy (Fig. 3) showed granular deposition of IgG, IgM, C3 and C1q at the dermoepidermal junction as well as deposition of IgG and IgM in the wall of dermal blood vessels. IgM and C3 were also deposited around hair follicles and sweat glands. There was scattered deposition of IgA and IgM throughout the dermis. Fibrinogen deposition was noted in some epidermal cells and walls of blood vessels. Immunofluorescence staining of the normal skin showed similar immunofluorescence staining pattern: there was conspicuous deposition of IgM and C1q at the dermoepidermal junction and IgM and IgG in the wall of blood vessels. Staining for IgA and C3 was negative. Keratinocytes of the upper granular layer were positively stained for fibrinogen.

Bone marrow aspirate and trephine biopsy

The findings were normal and no plasmacytoid monocytes were seen.

Discussion

Up to 30% of patients with KD are known to develop transient rashes during the first few weeks of the disease onset [17]. These rashes may mimic rubella or drug-induced eruptions [17] and, when the face is involved, the rash may have a "butterfly" appearance [4]. In spite of this high incidence, skin biopsies have been obtained in only a handful of cases of KD [8, 14, 17, 19, 20]. In these cases, skin involvement was manifested clinically as skin erythema, papules or nodules; biopsies of these lesions showed dense dermal infiltration by plasmacytoid monocytes with apoptosis; the density and extent of the infiltration suggested a diagnosis of lymphoma in these biopsies. In one of these published cases, KD was diagnosed following the demonstration of apoptotic plasmacytoid monocytes in a skin biopsy, in the absence of any lymph node enlargement [6]. The findings of dermal infiltration by apoptotic plasmacytoid monocytes in our case conforms with skin involvement in KD.

Immunofluorescence studies on frozen sections of skin biopsies from KD patients have not previously been published, and our case represents the first of its type in this respect. The immunofluorescence staining of frozen sections prepared from both facial skin biopsies (one from the area of rash and the other from normal-looking adjacent skin) showed, as detailed above, granular deposition of complement and different immunoglobulin subclasses at the dermoepidermal junction, around adnexal structures and in the walls of blood vessels. This immunofluorescence staining pattern documents the presence of an autoimmune response in KD. Furthermore, the finding of immunoglobulin deposition in the uninvolved skin, as mentioned above, suggests that this autoimmune response is not limited to skin areas that are infiltrated by plasmacytoid monocytes.

The aetiology of KD is still unknown. A viral aetiology has long been suspected [18], and many patients with KD have been found to have raised antibody titres to a variety of pathogens; these included Epstein-Barr virus, cytomegalovirus, herpes virus, parvovirus, varicella, toxoplasma and brucella [12, 13, 16]. Some patients have raised serum levels of alpha interferon, which further supports the presence of an acute infectious process as part of KD [18]. However, studies using electron microscopy [3, 10] and molecular biology [1, 9, 15, 21] have failed to demonstrate the presence of direct infection of lymph nodes involved in KD.

Serological investigations of our patient demonstrated a rise in gamma globulins and C-reactive proteins. There was also a rise in rheumatoid factor and antithyroid autoantibodies. These findings, as well as, the immunofluorescence findings in the skin biopsies are suggestive of the involvement of immunological mechanisms in the development of KD. The clinical course of KD, the disappearance of symptoms without any specific treatment and the recurrence of the disease (in some patients) are in agreement with this concept. In addition, the constant presence and apoptosis of plasmacytoid monocytes in lymph nodes involved in KD is consistent with their being the target cells of an immune attack. Whether the immune response in KD is initially sparked off by an infectious agent or whether it represents some underlying intrinsic defect of T cell immunity remains to be resolved.

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