NDT Plus (2009) 2: 370–372
doi: 10.1093/ndtplus/sfp090
Advance Access publication 17 July 2009

NDT PLUS
Nephrology Dialysis Transplantation

Case Report

Kikuchi disease preceding systemic lupus erythematosus with membranous lupus nephritis

Arvind Ponnusamy[1], Alexander Woywodt[2], Roy Reeve[3], Jyothi Kondlapudi[2] and David Lewis[1]

[1]Renal Department, Salford Royal NHS Foundation Trust, Salford, [2]Renal Unit, Lancashire Teaching Hospitals NHS Foundation Trust, Preston, Lancashire and [3]Department of Pathology, Salford Royal NHS Foundation Trust, Salford, UK

Correspondence and offprint requests to: Alexander Woywodt; E-mail: Alex.Woywodt@lthtr.nhs.uk

Abstract

Kikuchi disease (KD) is a rare form of necrotizing lymphadenitis. KD usually presents with cervical lymphadenopathy and fever in young women. It tends to run a benign course and resolve spontaneously within months. The aetiology of the disease is still unclear although a variety of infectious agents have been postulated. There is also a documented but rare association with systemic lupus erythematosus (SLE). We present the case of a young woman with biopsy-proven KD who subsequently developed SLE with biopsy-proven lupus nephritis. Nephrologists should be aware of KD as it may precede the development of SLE and lupus nephritis.

Keywords: Kikuchi disease; lupus nephritis; systemic lupus erythematosus

Introduction

Kikuchi disease (KD) is a rare cause of lymphadenopathy and fever [1]. The disease is more common in Asia and occurs more frequently in young women. It usually involves the cervical nodes [2] although it may also present with generalized lymphadenopathy. The diagnosis is made through a biopsy of affected lymph nodes. KD tends to resolve spontaneously without recurrence. The aetiology of the disease is unknown but there are several associations, notably with systemic lupus erythematosus (SLE). We present the case of a young female patient in whom KD preceded the development of SLE with renal involvement and membranous lupus nephritis.

Case

A 24-year-old Asian woman first presented with a 6-week history of being generally unwell with a flu-like illness, low-grade continuous fever, anorexia and enlarged cervical lymph nodes. She had also lost weight, but there was no history of arthralgia or night sweats. There was no history of tuberculosis. She was born in the UK and visited Bangladesh 2 years earlier. She was fit and a non-smoker, with no significant past medical or family history. The patient was on no medication. Examination revealed a mobile, non-tender group of lymph nodes measuring 2 × 2 cm in the sub-mental region of the cervical group. The remainder of the clinical examination was unremarkable. Laboratory tests revealed haemoglobin of 9.5 × 10^9/l, erythrocyte sedimentation rate (ESR) 116 mm/h with a normal white cell count and peripheral blood film. Renal function and liver function tests were normal and there was no proteinuria. Serum immunoglobulins IgA, IgG and IgM were all elevated. Immunology was all normal, including assays for rheumatoid factor, immunofluorescence (IF) for anti-neutrophil cytoplasmic antibodies (ANCA), anti-nuclear antibodies (ANA) and enzyme-linked immunosorbent assay (ELISA) for anti-double-stranded DNA antibodies (anti-ds DNA). Complement C3 and C4 were also normal. Blood cultures showed no growth. Hepatitis, toxoplasma and Epstein-Barr virus serology were negative. Ultrasound of the abdomen and chest x-ray were normal. In view of her ethnic background, symptoms and lymphadenopathy, she was also investigated for the presence of tuberculosis. Sputum was negative for acid-fast bacilli (AFB). Bronchial washings were also negative for AFB, both in stain and in culture. A diagnostic lymph node biopsy was performed. Histopathology of the specimen revealed necrotizing histiocytic lymphadenitis consistent with the diagnosis of KD. The patient was commenced on a trial of prednisolone with good response and the steroids were tapered after 3 months. The fever disappeared, as did the lymph node swelling and the patient made an uneventful recovery.

Two years later, she presented again, this time with Raynaud's syndrome of both hands. Examination was unremarkable except for bluish discoloration of the fingers of both hands and fingertip ulceration. Urine analysis revealed 4+ protein and 2+ blood with a proteinuria of 7 g/day. The creatinine clearance was normal. C3 and C4 were all low. Immunofluorescence for ANA was positive with a titre of

© The Author [2009]. Published by Oxford University Press on behalf of ERA-EDTA. All rights reserved.
For Permissions, please e-mail: journals.permissions@oxfordjournals.org

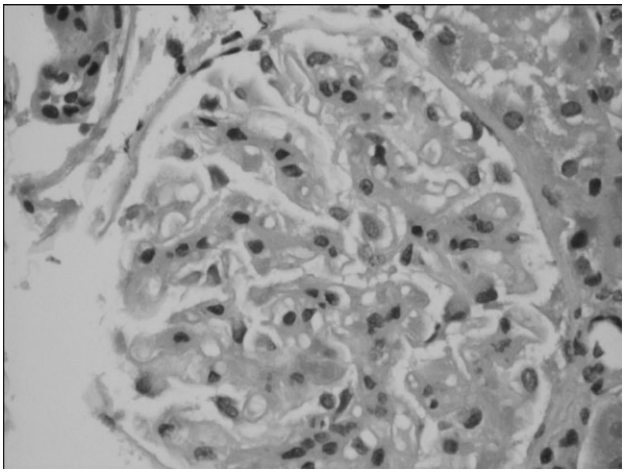

Fig. 1. Light microscopy showing thickening of the glomerular basement membrane. Glomeruli show very mild segmental areas of mesangial cell hyper-cellularity with some mesangial matrix increase, but without necrosis or crescents.

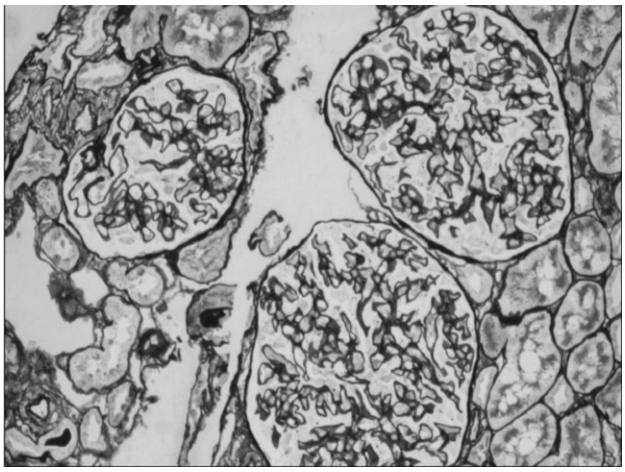

Fig. 2. Silver methenamine stain confirming diffuse thickening of the glomerular basement membrane, in keeping with membranous glomerulonephritis.

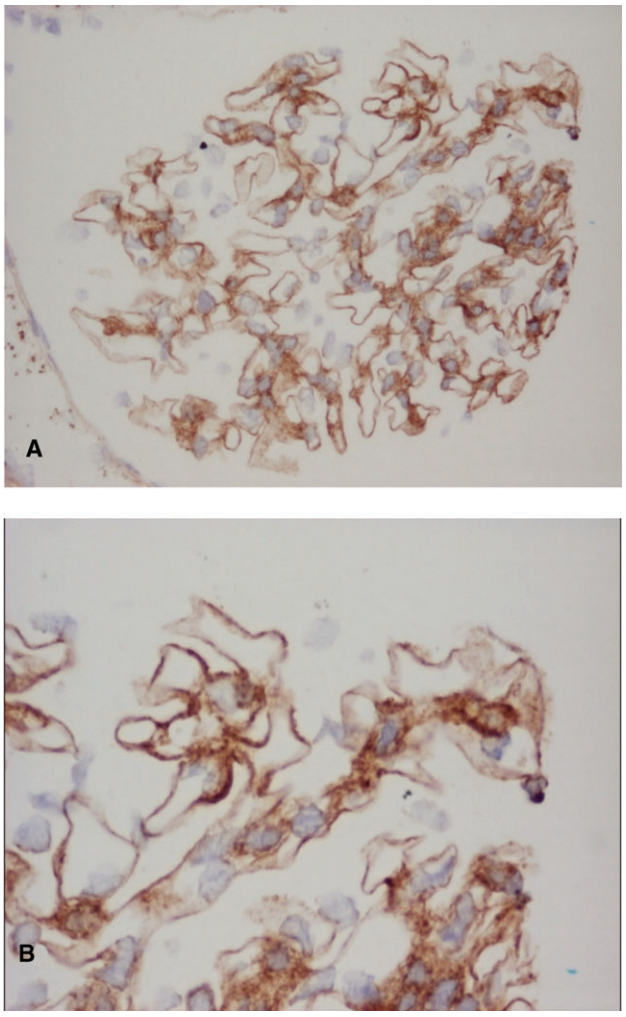

Fig. 3. Immunohistochemistry showing granular staining of the basement membrane for immunoglobulin G. (**A**) Low power field; (**B**) high power field. IgM, IgA, C3 and C1q were also all positive and electron microscopy showed subepithelial deposits (not shown).

1:1024 and a speckled pattern. Anti-ds DNA ELISA was positive at 84 U/ml. Assays for anti-RNP, anti-Sm, anti-Ro and anti-La were all positive. A diagnosis of probable SLE was made, and she was started on prednisolone 60 mg/day whilst awaiting a kidney biopsy. The kidney biopsy showed membranous glomerulonephritis in keeping with type V lupus nephritis (Figures 1–3). She was started on mycophenolate mofetil (MMF). Her most recent urine protein creatinine ratio is 230 g/mol with normal renal function while on MMF and prednisolone. There were no extra-renal symptoms of SLE and her Raynaud's had improved as well, without recent digital infarcts.

Discussion

KD is a rare but recognized cause of pyrexia and lymphadenopathy of an unknown origin. The initial two cases were described in Japan and the disease is felt to be more common in Asia. For example, in a Korean study of 147 patients who underwent a biopsy for lymphadenitis, KD was the leading diagnosis in 34.7% of cases [3]. KD is less common elsewhere although it has now been described throughout the world and in all ethnic groups. In this regard, a study in the United States described the ethnic origin of 75% of cases as Caucasian [4]. Symptoms of the disease include headache, anorexia, nausea, vomiting, skin lesions and hepato-splenomegaly [5]. In a large series of 244 patients fever (35%), lymphadenopathy (100%) and high ESR (40%) were the most common manifestations [5]. Routine laboratory tests are usually normal except for leucopaenia. The main pathological feature is the presence of necrosis in cortical and para-cortical regions of affected lymph nodes [6]. KD is generally benign with a recurrence rate of 3% while fatalities are uncommon [7]. There is no established treatment, although corticosteroids and a variety of immunosuppressant drugs have been used in severe cases. The cause of KD is unclear as reviewed in

detail elsewhere [8]. Suffice to say that Epstein-Barr virus, toxoplasma, cytomegalovirus, Yersinia enterocolitica, the human immunodeficiency virus, varicella-zoster virus and human herpesvirus-6 have all been implicated. An autoimmune aetiology has also been suggested, chiefly because of the association of KD with lupus. SLE may occur years after the diagnosis of KD [9]. The association remains rare in that in Dorfman's seminal report, only 2 out of 108 patients with KD subsequently developed SLE [4]. However, fatal cases have been described as well [10]. The differentiation between KD and SLE is often difficult [11] not least as lymphadenopathy is seen in more than half the patients with SLE. Histological examination of lymph nodes in SLE also shows areas of necrosis, but the presence of haematoxylin bodies, abundant plasma cells and granulocytes points towards a diagnosis of SLE [4]. These features were all absent in our case and the lupus serology was normal; hence, our initial diagnosis was KD. In some cases, however, the histology may be indistinguishable. Skin involvement similar to SLE is occasionally seen in patients with KD (5–30%). Clinical symptoms of KD and SLE are also similar but the management differs. Steroid monotherapy may be indicated in refractory cases of KD, whereas more intense immunosuppression is usually indicated in SLE.

Conflict of interest statement. None declared.

References

1. Bosch X, Guilabert A, Miquel R *et al*. Enigmatic Kikuchi-Fujimoto disease: a comprehensive review. *Am J Clin Pathol* 2004; 122: 141–152
2. Kapadia V, Robinson BA, Angus HB. Kikuchi's disease presenting as fever of unknown origin. *Lancet* 1989; 2: 1519–1520
3. Joon Young S, Hee Jin C, Sae Yoon K *et al*. Disease spectrum of cervical lymphadenitis: analysis based on ultrasound-guided core-needle gun biopsy. *J Infect* 2007; 55: 310–316
4. Dorfman RF, Berry GJ. Kikuchi's histiocytic necrotizing lymphadenitis: an analysis of 108 cases with emphasis on differential diagnosis. *Semin Diagn Pathol* 1988; 5: 329–345
5. Kucukardali Y, Solmazgul E, Kunter E *et al*. Kikuchi-Fujimoto disease: analysis of 244 cases. *Clin Rheumatol* 2007; 26: 50–54
6. Hsueh EJ, Ko WS, Hwang WS *et al*. Fine-needle aspiration of histiocytic necrotizing lymphadenitis (Kikuchi's disease). *Diagn Cytopathol* 1993; 9: 448–452
7. Chan JK, Wong KC, Ng CS. A fatal case of multicentric Kikuchi's histiocytic necrotizing lymphadenitis. *Cancer* 1989; 63: 1856–1862
8. Parappil A, Rifaath AA, Doi SA *et al*. Pyrexia of unknown origin: Kikuchi-Fujimoto disease. *Clin Infect Dis* 2004; 39: 138–143
9. Vila LM, Mayor AM, Silvestrini IE. Therapeutic response and long-term follow-up in a systemic lupus erythematosus patient presenting with Kikuchi's disease. *Lupus* 2001; 10: 126–128
10. Lin SH, Ko WS, Lee HS *et al*. Kikuchi's disease associated with lupus-like syndrome—a fatal case. *J Rheumatol* 1992; 19: 1995–1996
11. Kuo TT. Kikuchi's disease (histiocytic necrotizing lymphadenitis). A clinicopathologic study of 79 cases with an analysis of histologic subtypes, immunohistology, and DNA ploidy. *Am J Surg Pathol* 1995; 19: 798–809

Received for publication: 19.6.09; Accepted in revised form: 25.6.09