The Journal of Laryngology and Otology
November 1994, Vol. **108**, pp. 1001–1004

Kikuchi–Fujimoto disease: a report of two cases and an overview

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Abstract

Kikuchi–Fujimoto disease (KFD) has been widely reported from Japan and sporadically from many parts of the world including Saudi Arabia, since its original description in 1972 but the disease remains poorly known by clinicians. In this paper we report two Saudi patients seen in Tabuk, Saudi Arabia. One was a 36-year-old Saudi man and the other a 16-year-old Saudi girl. Both presented with cervical lymphadenopathy and pyrexia. Histological examination of biospy material from both showed classical features of KFD. Other laboratory findings were unremarkable except for leucopenia. Following excision biopsy both patients recovered without sequelae. KFD is a self-limiting process of uncertain aetiology that predominantly affects young women aged 20–30 years. We review the pathology, clinical featuers and possible aetiology of this interesting disease, which may well be underdiagnosed. Increased awareness of KFD will minimize the risk of confusing this entity with malignant lymphoma or other serious conditions.

Key words: Lymphadenitis, necrotizing histiocytic

Introduction

Kikuchi–Fujimoto disease (KFD), Kikuchi's disease, or necrotizing histiocytic lymphadenitis, is a self-limiting process of uncertain aetiology that was originally described in Japan in 1972 (Fujimoto *et al.*, 1972; Kijuchi, 1972) Because it is relatively uncommon outside Japan, and the diagnosis remains a pathological one, and because the disease does not fall neatly into the responsibility of any partiuclar speciality, there is an important lack of appreciation both of the existence of KFD, and especially of its prognosis. Since many patients will present to ENT surgeons for biopsy, and since the ENT literature is sparse (Gleeson *et al.*, 1985; Garcia *et al.*, 1993), it is appropriate to attempt to heighten awareness of the disease, especially where tuberculous cervical lymphadenopathy is common, and where this diagnosis may simply be assumed to be correct without resorting to biopsy. We report on two cases diagnosed in eight years at the North West Armed forces Hospital, Tabuk, Saudi Arabia.

Case reports

Case 1

A 36-year-old Saudi male presented, in 1988, with a two-week history of painless swelling in both pre-auricular regions, the right side of the neck, and the right axilla. He was also complaining of sporadic fever, night sweats, polyarthralgia and a rash. On examination, he had a temperature of 39°C and a maculo-papular rash on his chest. Firm, non-tender, mobile, lymph nodes were present in both pre-auricular regions (4.5 × 2.5 cm), the right posterior cervical triangle (3 × 2.5 cm) and in the right axilla (3 × 1.5 cm). His haemoglobin was 12.7 g/dl, white blood cell count 2.4×10^9l, and ESR 52 mm in the first hour. Blood cultures were negative, as were serological tests for infectious mononucleosis, brucellosis, syphilis, mumps and HIV. His Mantoux test was negative, as were rheumatoid factor and antinuclear factor. His LDH, and titres for toxoplasma, CMV and EB virus, were raised. A chest X-ray and full ENT endoscopy were normal. Excision biopsy of the cervical nodes showed Kikuchi's disease. Culture of the lymph node did not grow acid-fast bacilli. Full resolution of his illness followed excision biopsy, and the patient remains well to date.

Case 2

A 16-year-old Saudi girl presented, in 1993, with an eight-week history of a painless lump in the right upper neck. For four weeks she had had cough, night sweats, malaise, and was losing weight. She had a sustained fever of around 38.5°C. There was no dysphagia, no hoarseness of voice, and no nasal or throat symptoms. She had never been hospitalized for any illness. During her illness, she had received several courses of antibiotics without response. On examination, she had a temperature of 38.5°C and looked unwell. Examination of the chest, cardiovascular system, abdomen and central nervous system was normal. Her tonsils were small and healthy, and anterior and posterior rhinoscopies and otoscopy showed no abnormalities. She had enlarged right upper deep cervical lymph nodes (5 × 5 cm) which were firm in consistency, mobile, and not tender. There was also a shotty lymphadenopathy involving the right posterior triangle. Her haemoglobin was 12.6 g/dl, white blood cell count 2.9×10^9l and ESR 17 mm in the first hour. Routine biochemistry was normal. She was Mantoux test negative, and CMV IgM negative but IgG postivie, with negative brucella and toxoplasma serology. Her chest X-ray was normal. A CT scan of the neck (Figure 1) confirmed the clinical finding of right cervical lymphadenopathy. Fine needle aspiration showed only reactive lymphoid tissue. Endoscopy under general anaesthesia was performed, including proof biopsy from the nasopharynx with frozen section, followed by excision biopsy from the upper deep certical lymph nodes. Histopathology confirmed subacute nec-

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Accepted for publication: 8 June 1994.

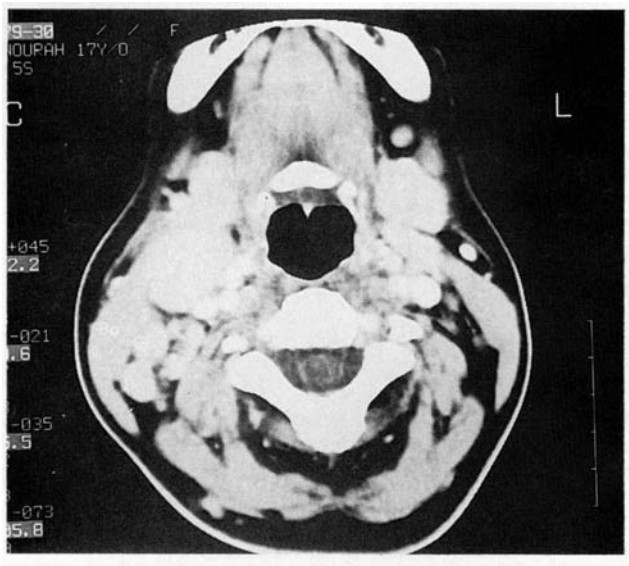

FIG. 1

CT scan of the neck with contrast *(Case 2)* showing enlarged right upper, deep, cervical lymph nodes.

rotizing histiocytic lymphadenitis. Specimen culture was negative for bacteria, including acid-fast bacilli, and fungi. She became apyrexial from the first post-operative day, and remains well and asymptomatic six months later, when her Mantoux test is also again negative.

Pathology

On gross examination the specimens received in both cases consisted of fragments of tan-coloured tissue, within which circumscribed areas of pallor were noted. Histological examination of the lymph node from *Case 1* showed tissue largely effaced by an infiltrate of immunoblasts and numerous plasmacytoid monocytes intimately associated with areas of eosinophilic necrosis. The areas of necrosis were very extensive, and contained large numbers of plump histiocytes filled with eosinophilic debris lying in a background showing karyorrhexis (Figure 2). No neutrophils were present in the areas of necrosis and no plasma cells were seen within the non-necrotic lymphoid tissue. Tissue from *Case 2* showed similar features except that the areas of necrosis were less extensive (Figure 3). No true granumlomata were noted in either, and special stains for fungi, bacteria and acid-fast bacilli were negative.

Discussion

Kikuchi–Fujimoto disease (KFD), or simply Kikuchi's disease, was first described in Japan in 1972 by Kikuchi and by Fujimoto and colleagues, independently (Fujimoto *et al.*, 1972; Kikuchi 1972). Since then over 400 cases have been reported worldwide, well over half coming from Japan (Kikuchi, 1979; Wakasa *et al.*, 1979; Fujimore *et al.*, 1981; Imamura *et al.*, 1982; Pileri *et al.*, 1982; Dorfman and Berry, 1988), and the disease has become a recognizable clinical and pathological entity. It affects women about three times as commonly as men, with a peak age of onset usually between 20 and 30 years. Cervical lymphadenopathy is by far the commonest form of presentation, especially posterior cervical, although supraclavicular, axillary and other nodes may

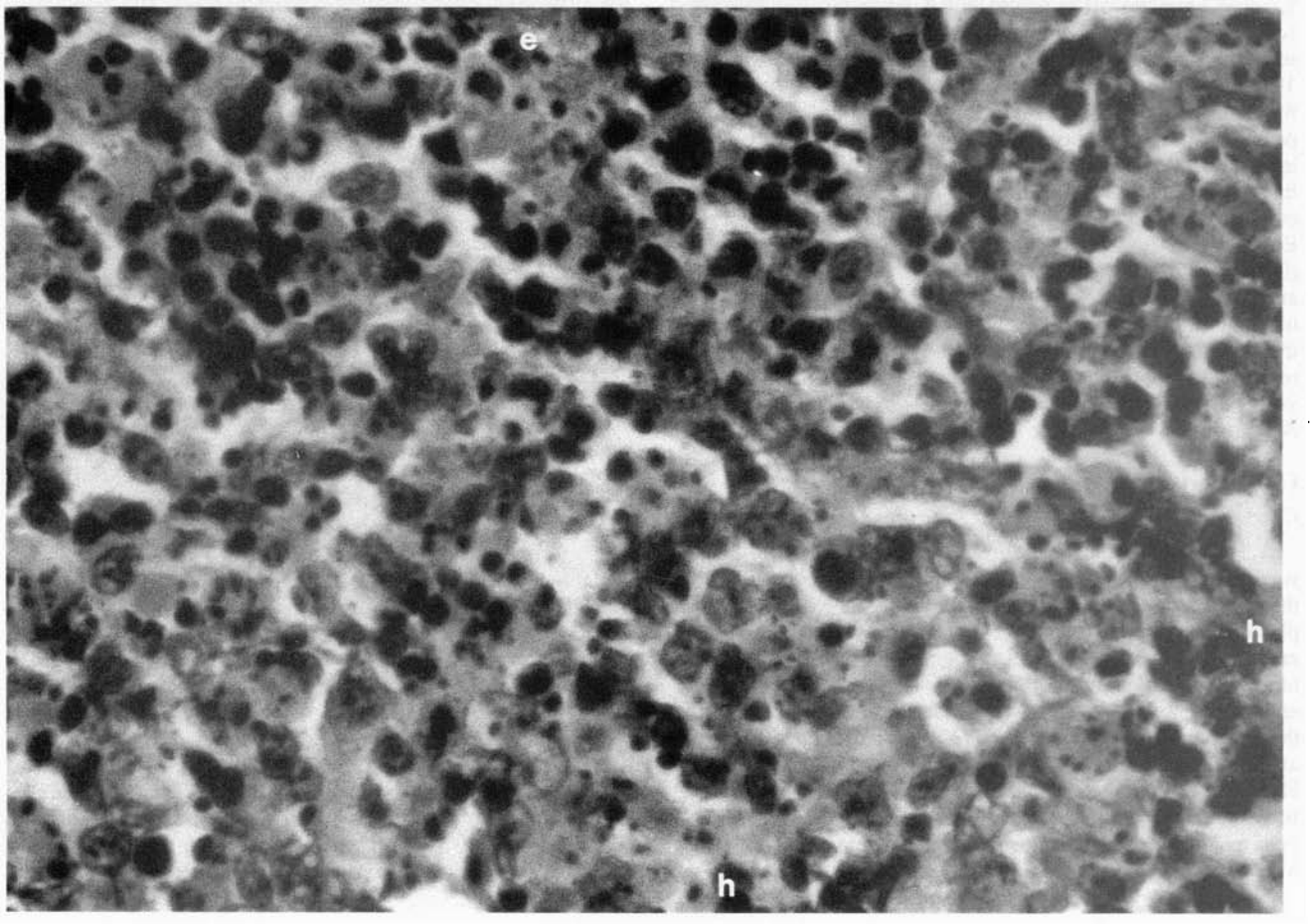

FIG. 2

Photomicrograph of lymph node *(Case 1)* showing extensive areas of eosinophili necrosis (e) and numerous plump histiocytes (h, h) (H & E; × 40).

https://doi.org/10.1017/S0022215100128749 Published online by Cambridge University Press

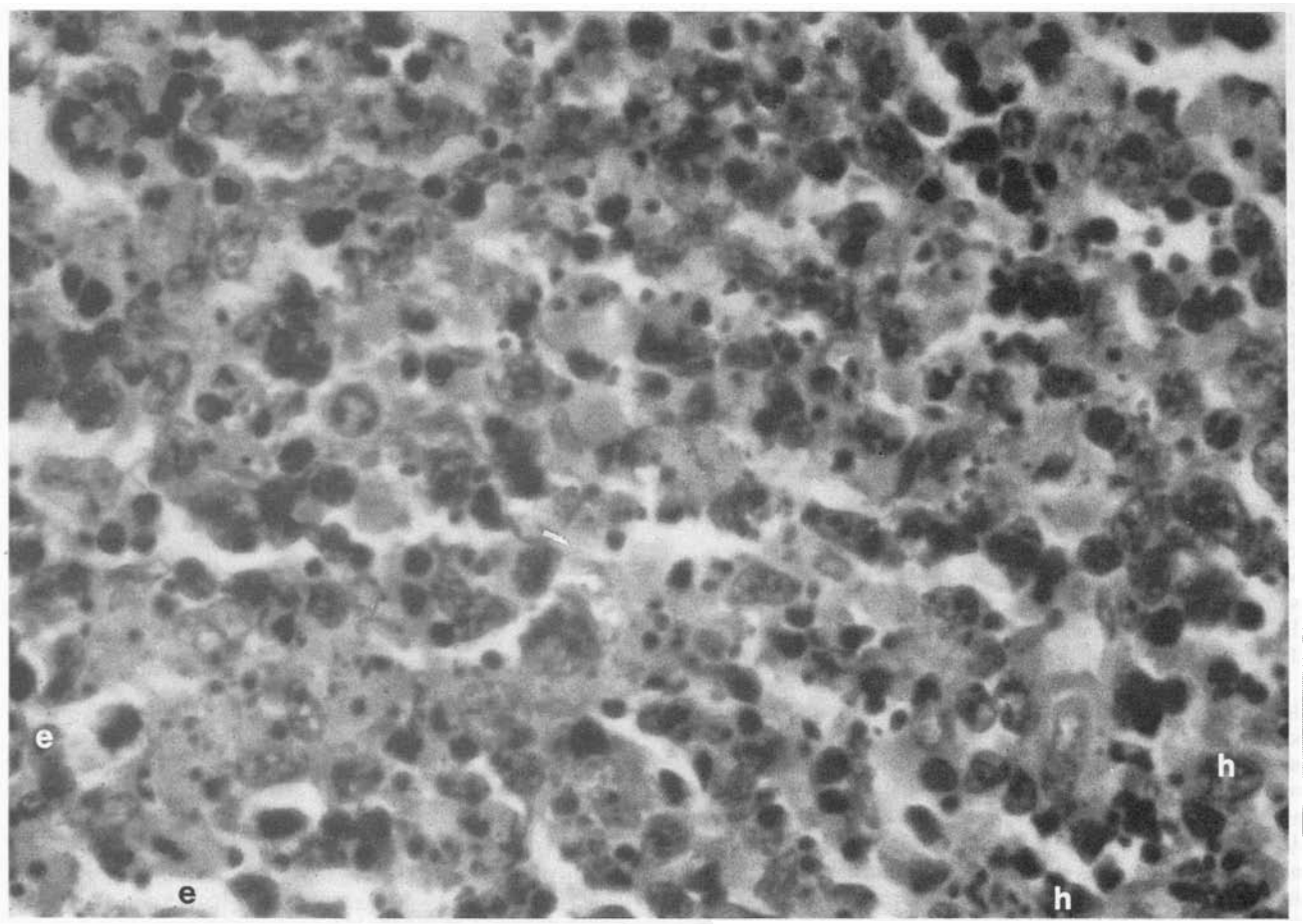

FIG. 3

Photomicrograph of lymph node *(Case 2)* showing areas of eosinophilic necrosis (e, e) and numerous plump histiocytes, but a complete absence of neutrophils and plasma cells (h, h) (H & E; × 40).

be involved. The nodes may be mildly painful or tender. The other main symptoms are fever and malaise, sometimes with weight loss, nausea and vomiting, and there may be a prodromal influenzal or upper respiratory illness. Patients have typically been given more than one course of antibiotics without response before diagnosis. Splenomegaly occurs in less than 10 per cent, often as part of a generalized lymphadenopathy, and there is very occasional hepatomegaly. Spontaneous complete resolution often occurs rapidly after excision biopsy, but may take a month or more. Occasional patients have an illness lasting many months, or may relapse years later. One, with very widespread disease, died (Chan *et al.*, 1989), possibly from myocarditis, but the fears of some authors of progression to systemic lupus erythematosus or malignancy have turned out to be ill-founded. The mechanism of resolution is not understood but it may well be that the excised nodes form the active centre of a pronounced, necrotizing immunological reaction, and that removal is actually beneficial. It is interesting to note that nodes remaining after the open biopsy resolve along with the symptoms.

The lack of specific diagnostic investigations makes diagnosis in the clinical stage very difficult. The ESR and C-reactive protein are normally raised, amd many patients have a low white blood count, the remainder nearly all being normal. The diagnosis can really only be made on histological examination, where the findings may be variable, but normally include (Chamulak *et al.*, 1990; Nathwani, 1991):

(a) patchy irregular areas of eosinophilic necrosis, which may vary considerably in extent;
(b) pronounced fragments of nuclear dust scattered through the areas of necrosis;
(c) absence of neutrophils in the areas of necrosis;
(d) almost total absence of plasma cells in the involved nodal tissue, a feature which helps in the histological differentiation of this condition from the lymphadenopathy of systemic lupus erythematosus;
(e) clusters of plasmacytoid T-cells;
(f) numerous immunoblasts within the node tissue.

Previous reports relevant to Saudi Arabia include Turner *et al.* (1983) (presumably included in Dorfman and Berry, 1988); Khan (1990) (included in Morad *et al.*, 1992); Kutty *et al.* (1991); and Smith *et al.* (1992). It is of particular interest that all the tuberculin test quoted in these papers (five by Kutty and his co-workers; two in this paper) were negative, although tuberculosis (and cervical tuberculous lymphadenopathy) is very common in Saudi Arabia. BCG vaccination has only been in routine use in Saudi Arabia for about 12 years, and both our patients had probably not been vaccinated. Surprisingly, the remaining literature contains only sparse results of tuberculin testing: Gleeson *et al.* (1985) one; Unger *et al.* (1987) one or two; Rudniki *et al.* (1988) one; Bowness and Dutoit (1988) one; all of which were negative with the striking exception of 19 positive results in the 21 patients reported by Fujimori *et al.* (1981) a finding ascribed to universal compulsory BCG vaccination in Japan. Whether therefore this is really significant in general, or specifically as an indication that the Japanese form of the disease is different from that found elsewhere, is uncertain.

The aetiology of the disease is unknown. Various infections have been postulated to be causal, but no support has been found for any one agent being a common cause, let alone the sole cause. Overlap with, or similarity to, systemic lupus erythematosus (Imamura *et al.*, 1982; Dorfman and Berry, 1988) has been a source of confusion, but others have looked for evidence of autoimmunity, and failed to find it. Likewise, there has been no evidence in favour of malignancy. Some have fallen back on a pos-

https://doi.org/10.1017/S0022215100128749 Published online by Cambridge University Press

tulated single hyperimmune reaction pattern to a wide variety of aetiological agents, whether infectious, chemical, physical or neoplastic (Chan *et al.*, 1989; Garcia *et al.*, 1993). This seems at variance with the relatively well-defined clinical syndrome, and the excellent prognosis, even if the diagnosis is still a completely histopathological one.

The not infrequent influenzal or upper respiratory prodrome, the frequent finding of fever and raised indices of inflammation, the relatively brief nature of the disease, the localized predilection for cervical lymph nodes (often unilateral), and for young women, and the occasional disseminated illness and/or relapse up to many years later, all strongly suggest an infective process. The frequent leucopenia suggests a virus, but none has been cultured or seen on electron microscopy, where only tubulo-reticular structures (which may be nonspecific) have been found (Imamura *et al.*, 1982). Although individual cases have been pregnant, had AIDS, or Still's disease, there is no good evidence of predisposition by reason of immune suppression. In the light of this, the reported negativity of the Mantoux tests noted in Saudi Arabia, and in other countries where tuberculosis is common, is of interest, as is the contrast with Japan, where Mantoux testing is nearly always positive in KFD, presumably by reason of their longstanding policy of compulsory BCG vaccination. Contrarywise, the disease is very common in Japan, but rare elsewhere.

All in all, the likeliest cause would seem to be a normally very localized infection, presumably entering by the fauces, rapid cure being accelerated by excision biopsy. Occasional relapses are presumably due to prolonged dormancy of the infective agent. The lack of person-to-person spread, and of an obvious source, and the relative great excess of cases reported from Japan, might possibly be explained by an unusual animal source, such as from eating raw fish. If so, the fulfilment of Koch's postulates would be an obvious target for a research effort which is made difficult by the fact that diagnosis comes only at the time of histological examination. In the shorter term, better understanding of the disease and its prognosis by a wide range of practitioners will be greatly beneficial in itself.

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https://doi.org/10.1017/S0022215100128749 Published online by Cambridge University Press