CASE REPORT

Eosinophilia and multiple lymphadenopathy: Kimura disease, a rare, but benign condition

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SUMMARY

Kimura disease is a benign rare chronic inflammatory disorder of unknown aetiology. This disease is mainly endemic in Asia, although cases have also been reported in Europe and America. We describe a case in a 34-year-old Chinese man presenting with severe eosinophilia and multiple lymphadenopathy. Since our initial aim was to rule out the diagnosis of lymphoma, and given the limitations of our laboratory, we decided to perform an excision of one of the cervical lymph nodes. The histological diagnosis was consistent with Kimura disease. We review the epidemiology, the aetiology and clinical features of this entity.

BACKGROUND

Kimura disease is a benign rare chronic inflammatory disorder of unknown aetiology, characterised by generalised lymphadenopathy in the head and neck areas.¹ The nodes appear as one or several deep, non-tender and poorly circumscribed masses.¹ Patients are usually young Asian men, and sometimes present with pruritic skin lesions;² kidney involvement is often observed, and some patients may have albuminuria.³ Although imaging can be useful to rule out metastases and other malignant conditions, the definitive diagnosis is made with histological examination, and a lymph node biopsy must, therefore, be performed.⁴ Kimura disease is a rare condition in Europe and it requires a differential diagnosis mainly with lymphoma and metastases.

CASE PRESENTATION

A 34-year-old Chinese man was admitted to the hospital with cervical lymphadenopathy and eczema (pruritic urticarial papules in the upper and the lower limbs), which had gradually worsened over the last 3 months. He reported of malaise, weight loss, decrease in appetite and profuse night sweating.

Physical examination showed tender adenopathy with multiple supraclavicular, cervical, axillary and inguinal lymph node enlargement (3–5 cm in diameter). Panniculitis (raised red spots on the skin) was present on the lower limbs and the upper back region.

INVESTIGATIONS

At admission, laboratory data showed eosinophilic leucocytosis (37 410 leucocytes/mm³), with 72% eosinophils (22 090 eos./mm³). Elevated IgE (6930 IU/mm³) and IgG2 (629 mg/dL) levels were also observed, but due to the limitations of our

laboratory, when these results came back (30 days later), the diagnosis had already been made. Liver enzymes and renal function tests were normal. Peripheral blood smear showed an abnormal eosinophil count (eosinophilia).

Serology tests to rule out viral hepatitis (A, B and C), HIV, CMV, EBV and syphilis infection were negative. Antinuclear and antineutrophil cytoplasmic antibodies were normal.

The chest X-ray was normal, but CT scan showed lymphadenopathy (3–5 cm in diameter), with involvement of the cervical, retroauricular, supraclavicular and axillary areas (figure 1). We decided to perform a surgical excision of one of the enlarged cervical lymph nodes (3 cm in diameter). The pathological report described follicular and interfollicular hyperplasia, as well as eosinophils and eosinophilic microabscesses within the germinal centres (figure 2). These findings were consistent with Kimura disease.

DIFFERENTIAL DIAGNOSIS

The main laboratory finding was eosinophilia, and the main clinical feature was lymphadenopathy. Given that this was a young patient presenting with lymphadenopathy, night sweats and weight loss, our first suspicion was lymphoma or another form of malignancy. Several non-neoplastic conditions must be ruled out, including drug-induced lymphadenopathy, Kikuchi disease, angiolymphoid hyperplasia with eosinophilia (ALHE), dermatopathic lymphadenopathy, eosinophilic granuloma of lymph node, tuberculosis, sarcoidosis, systemic lupus erythematosus or other atypical infections; as well as other neoplastic conditions such as Hodgkin lymphoma, T-cell lymphoma and tumour node metastases of unknown origin, although lymphoma should be the primary consideration.¹ Since CT findings in Kimura disease and lymphoma are similar, an excisional biopsy of a lymph node is essential. The histopathological findings were consistent with Kimura disease and clinical features suggested that a diagnosis of Kimura disease might be established.

Regarding the consideration of ALHE, these two entities (ALHE and Kimura disease) can be histologically similar. However, ALHE involves superficial skin rather than subcutaneous tissue, without lymphadenopathy, and often occurs in the non-Asian population, predominantly in women.^{5 6} Moreover, minimal fibrosis and lymphoid follicles helps to differentiate ALHE from Kimura disease.⁷

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Figure 1 CT showing multiple lymphadenopathies; (A) bilateral cervical lymph nodes (2–3 cm); (B) bilateral axillary lymph nodes (4–5 cm).

TREATMENT, OUTCOME AND FOLLOW-UP

The patient received steroid treatment with prednisone 40 mg daily (0.5 mg/kg/day). Slow, but steady signs of improvement were gradually seen, and the malaise, lymphadenopathy and eosinophilia disappeared. Eighteen months of follow-up with laboratory tests revealed no abnormal findings; we found no clinical recurrence or new skin lesions, and were able to withdraw corticosteroids after 2 months of treatment.

DISCUSSION

Kimura disease was first described in 1937 by Kim (China), as eosinophilic hyperplastic granuloma, and its histological description was later reported by Kimura (Japan) in 1948.² It is a rare, benign disease affecting the subcutaneous tissue and lymph nodes. Kimura disease is endemic in parts of Asia (Japan, China and Indonesia), although cases have also been reported in Europe and America in the non-Asian population, with a similar clinico-pathological presentation.⁶ There are ~300 cases in the world,^{2,4} and it occurs predominantly in men, with a male:female ratio of up to 19:1.⁴ This entity generally occurs in young and

middle-aged men. Although the aetiology is unknown, there are various hypotheses, including the excessive proliferation of lymphoid lineage, mast cells releasing interleukin-4 and interleukin-5 and causing eosinophilia and increasing IgE, and inadequate response to parasite infestation, among others.⁴

The onset of the disease is slow and progressive, and the lymph nodes often involve one or more subcutaneous masses in the head and neck areas (in up to 76% of the patient).¹ Other areas can be also affected, such as the cervical, retroauricular, inguinal and epicranial areas, eyelids, axillary area, oral cavity and nasal sinuses. Although Kimura disease affects soft tissue, non-tender, small lesions can gradually increase to solid masses, with a diameter of up to 20 cm. These nodular lesions are sometimes accompanied by itchy rashes, and there is also involvement of the salivary glands in some cases.

Eosinophilia is the most important finding and it must identified to establish a positive diagnosis. Increased levels of IgE are almost systematically observed, and TNF- α , IL-4, IL-5 and IL-3 levels may also be elevated.¹

Although Kimura disease shows a benign course, activated T cells may increase the permeability of the glomerular basement membrane and cause proteinuria, and nephrotic syndrome may even be observed (19% of all cases).^{2,3}

CT and MRI are not specific, but can rule out other soft tissue or show the presence or involvement of lymph nodes or any extralymphatic structure. A definitive diagnosis must be made by histological examination, which will eventually rule out lymphoma, as mediastinal, extrapleural, mesenteric and retroperitoneal lymphadenopathy is sometimes difficult to differentiate from lymphoma.⁸

Fine-needle aspiration cytology (FNAC) can be a good first-line method for investigating the cases of cervical lymphadenopathy; it can distinguish reactive lymphoid hyperplasia from malignant lymphoma, is a reliable and cost-effective diagnostic procedure when compared with the gold standard (excisional biopsy)⁹ and can yield a very good performance. However, as pointed out by Kapoor *et al.*,¹⁰ the role of fine-needle aspiration procedures appears to be limited in making the histological diagnosis of Kimura disease, due to occasional wrong diagnoses through misinterpretation. In order to overcome such limitations and drawbacks of the cytomorphological features, given the suspicion of lymphoma, we decided to perform an excision of one of the lymph nodes rather than FNAC.^{11,12}

When a lymph node biopsy is performed, histological examination will show lymphoproliferation, lymph node follicle hyperplasia and enlargement of the germinal centres, eosinophilic infiltration and eosinophilic microabscesses, and IgE reticular staining in the germinal centre. Immunohistochemistry

Figure 2 (A) Prominent germinal centres (arrows) and interfollicular areas with massive infiltration of eosinophils and eosinophilic microabscesses (H&E, 10 $\times$ magnification). (B) Massive eosinophilic infiltration and folliculolysis (H&E, 20 $\times$ magnification).

can be useful, and CD68, CD34, LCA and S-100 can be positive.¹

Although the natural history of this disease is non-malignant, untreated patients present with swelling subcutaneous masses, which must be treated. The definitive management remains unclear, but several treatments have been proposed, including surgical excision, radiation, systemic corticosteroids and cytotoxic agents.

Surgery can be the best choice in some cases,¹⁰ and can avoid further recurrence, but its use is probably limited to the focal variant of the condition rather than generalised lymphadenopathy. Steroid treatment has been successfully used, as shown in several case reports,¹³ but shows a high rate of recurrence after its cessation.² Nevertheless, steroids are essential if the kidney is affected.^{2,3}

Our patient underwent conservative management and the outcome was favourable with corticosteroid treatment only.

Radiotherapy has been shown to be effective in some case reports,^{14,15} with high rates of local response, when steroids have been unsuccessful. Other proposed treatments are cyclosporine,¹⁶ imatinib or cyclophosphamide.¹⁷

Overall, the prognosis is excellent and the disease has no risk of malignant degeneration.² Our patient remained asymptomatic throughout the 18-month follow-up period.

As with other case reports,^{8,18} we would like to highlight the importance of a proper differential diagnosis for lymphadenopathy. Our initial diagnostic suspicion was lymphoma; however, the histopathological features led us to the definitive diagnosis.

Learning points

- ▶ Kimura disease is a benign condition, without potential of malignancy, that mainly affects young Asian males.
- ▶ It should be taken into consideration as a differential diagnosis for generalised lymphadenopathy, and lymphoma and metastases must be ruled out.
- ▶ Eosinophilia and increased serum IgE are crucial for the diagnosis, and are the main laboratory findings; a histological examination is also required.
- ▶ The combination of surgery and corticosteroids is a good choice, although no definitive management regime has been validated to date. If there is renal involvement, corticosteroids should be the first line of treatment.

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Contributors RGC drafted the manuscript. MRB and NR-A made interesting suggestions for the final paper. OV-G took the pictures.

Competing interests None declared.

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