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Case Report

CASE REPORT

Painless lymphadenopathy, eosinophilia and nephrotic syndrome: a diagnostic challenge in an era of increased migration

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Abstract

Kimura's disease is a rare chronic inflammatory condition of unknown cause that most frequently affects Asian adults. It is characterized by painless lymphadenopathy in the head and neck region and eosinophilia, often associated with nephrotic syndrome. A young Asian male presented to our Department with œdema at the lower limbs and scrotum, retroauricular masses, eosinophilia and proteinuria. Diagnosis was reached by a combination of the clinical picture, the patient's origin and a histological examination, which revealed well-developed lymph follicles with increased numbers of eosinophils and fibrosis, a finding typical of Kimura's disease. In case of a young Asian male who is otherwise healthy, but presents head/neck masses and/or unexplained eosinophilia associated with nephrotic syndrome, consider Kimura's disease in the differential diagnosis.

INTRODUCTION

Kimura's disease is a rare inflammatory condition of unknown cause that most commonly presents as eosinophilia and painless lymphadenopathy in the head and neck region, and is often associated with nephrotic syndrome [1]. The disease has a high prevalence in young Asian adults, although all racial groups can be affected [1]. Clinical differential diagnosis should include mainly lymphomas and metastases of unknown origin. The diagnosis is confirmed by a histological examination. Histopathological differential diagnosis is extensive and includes the diseases/conditions reported in Table 2.

CASE REPORT

A 32-year-old male from Pakistan was admitted to our Department for œdema in the lower limbs and scrotum. He had no other significant past or family history. Lymphadenopathy and progressive œdemas were noticed 2–3 months before admission. A physical examination revealed œdema at the lower limbs and scrotum and the presence of retroauricular masses (3.0×1.5 cm on the right and 2.5×1.3 cm on the left). On admission, biochemical findings indicated severe hypoalbuminemia (albumin 1.2 g/dl), moderate renal failure (creatinine 2.1 mg/dl, the modification of diet in renal disease formula (MDRD) 37 mL/min/1.73 m^2, acute kidney injury stage 2) and severe eosinophilia (2.65×10^3/μl) with a normal white blood cell count. Total- and low-density cholesterol (LDL) levels were increased (322 and 266 mg/dl, respectively) with normal triglyceride levels. C-reactive protein was mildly increased (1.2 mg/dl, normal values being < 0.5 mg/dl). Serum transaminases, alkaline phosphatase, gamma-glutamyl transferase (γGT), international normalized ratio and activated partial thromboplastin time were all normal. A screening for the most common parasitic, fungal

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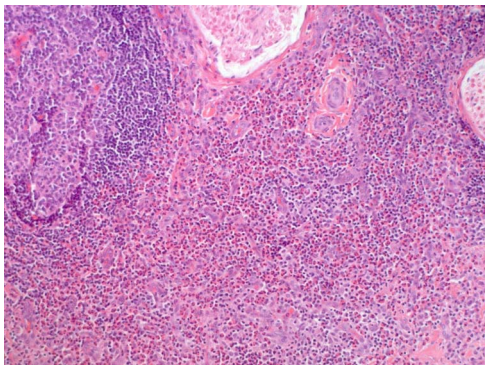

Figure 1: The inflammatory process was characterized by lymphoid follicular hyperplasia, dense collections of eosinophils as well as fibrosis sometimes causing nerve fiber entrapment (at the top and upper right corner) (H&E, ×100).

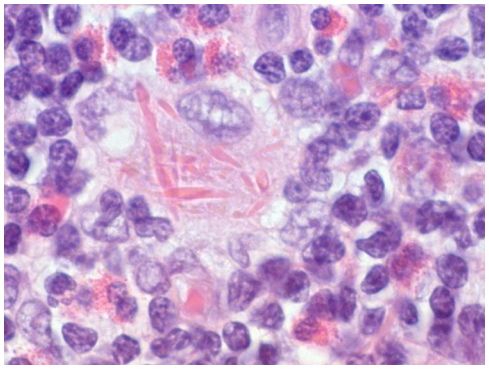

Figure 2: At high magnification, Charcot Leyden crystals may be found within macrophages (H&E, ×1000).

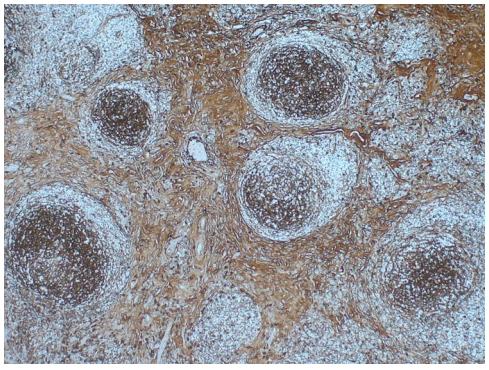

Figure 3: Deposits of IgE in the germinal centers (IgE-immunostain ×40).

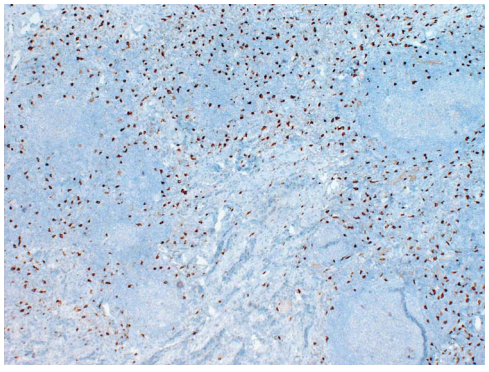

Figure 4: C-kit (CD117) immunostain showing numerous mastocytes between lymphoid follicles (×100).

and viral infections was negative. Immunoglobulin E (IgE) levels were increased (19.000 U/ml). Urinalysis showed specific weight 1.026 and 4+ proteinuria; red blood cells (80 cells/μl) and one hyaline crystal were present in the urine sediment. A 24-h proteinuria count showed proteinuria in the nephrotic range with a striking amount of 19 g/24 h. In order to characterize the renal damage, we proposed the patient to undergo a renal biopsy, which he unfortunately rejected. However, he agreed to undergo resection of one of the retroauricular masses. In the meanwhile, we had also performed a total body computed tomography scan, which was normal. Initially, the patient was treated with water and salt restriction as well as a daily intravenous infusion of human albumin 20% and furosemide 40 mg for five days inducing only a mild reduction of the œdema and a small increase in serum albumin (1.2 → 1.3 g/dl).

Since the highest diagnostic priority was to rule out lymphoma and metastases of unknown origin, excisional biopsy was preferred over fine-needle aspiration cytology [2]. After performing the resection of the right retroauricular mass, we started treatment with high doses of methylprednisolone (~ 1 mg/kg/-day, 80 mg/day) resulting in a striking clinical improvement in the œdemas and a reduction in the eosinophil count as well as diminished proteinuria.

The patient was discharged after 11 days of hospitalization with improved biochemical findings consisting of a normal eosinophil count (0.2×10^3/μl), decreased 24-h proteinuria levels (3.2 g/24 h), normal renal function (creatinine 0.9 mg/dl) and a mild improvement in serum albumin levels (1.8 g/dl). He was dismissed with a recommended therapy of high oral methylprednisolone dose (40 mg/day) to be tapered slowly while waiting for the histological result. The histological examination revealed well-developed lymph follicles with increased numbers of eosinophils and fibrosis (Fig. 1); the presence of Charcot Leyden crystals within macrophages (Fig. 2); deposits of IgE in the germinal centers (Fig. 3) and numerous mastocytes between the lymphoid follicles (Fig. 4). The combination of the clinical presentation, the histological result and the geographic origin of the patient indicated Kimura's disease.

At 1-month follow-up, the patient was in good clinical condition, with no œdema or lymphadenopathy, a normal eosinophil count and a marked improvement in his serum albumin levels (3 g/dl). In addition, his 24-h proteinuria count had considerably decreased (250 mg/day) while he was still on tapering corticosteroid treatment. At 3-month follow-up and after withdrawal from corticosteroid treatment, his clinical and laboratory findings were stable, with normal serum albumin levels and a normal 24-h proteinuria count. At 2-year follow-up, the patient had remained completely healthy (Table 1).

DISCUSSION

Kimura's disease has only rarely been reported in Europe [3, 4]. However, in an era of globalization and increased migration, practitioners should always take 'imported diseases' into consideration if clinically suspected.

Kimura's disease should always be included in the differential diagnosis whenever there is a constellation of painless head or neck masses, eosinophilia and nephrotic syndrome in an

Table 1: Improvement of laboratory findings with high doses of methylprednisolone and follow-up

	Before treatment	At discharge	Follow-up		
			1 month	3 months	2 year
Methylprednisolone (mg)	–	40	24	–	–
24-h proteinuria (g)	19	3.2	0.25	0.15	–*
Serum albumin (g/dl)	1.2	1.8	3	4	4
Eosinophils ($\times 10^9$/l)	2.65	0.2	0.1	0.1	0.1

*At 2 year's follow-up, the patient did not have a 24-h proteinuria count; however, the urine test revealed no trace of proteins.

Table 2: Histopathological differential diagnosis of Kimura's disease

Disease/Condition	Histopathological characteristics
Tumors	
Hodgkin lymphoma	Reed-Sternberg/Hodgkin cells and/or their variants
Angioimmunoblastic T-cell lymphoma	Atypical lymphocytes with pale to clear cytoplasm
Langerhans cell histiocytosis	Langerhans cells
Florid reactive follicular hyperplasia	Usually lacking eosinophilic infiltrates in germinal centers and eosinophilic microabscesses
Angiolymphoid hyperplasia with eosinophilia (ALHE)	Cutaneous vasoproliferative disease; no tissue deposition of IgE
Other lymphoadenopathies	
Castleman disease (hyaline-vascular variant)	Small hyaline-vascular follicles and capillary proliferation
Dermatopathic lymphadenopathy	Interdigitating dendritic cells, with pale indistinct cytoplasm and macrophages containing brown melanin pigment
Drug reaction lymphadenopathy	Necrosis +/−; (history of exposure to antiepileptics)
Parasitic lymphadenitis	Detection of remnants of parasites
Lymphadenitis in Churg-Strauss granulomatosis	'Ring- or C-shaped' palisading granulomas surrounding reactive germinal centers or areas of necrosis

otherwise healthy young man, especially if Asian. A practitioner should make a clinical differential diagnosis to rule out, above all, lymphomas and metastases of unknown origin. Histopathological differential diagnosis is extensive. Table 2 lists the diseases/conditions that need to be differentiated from Kimura's disease and their key histopathologic characteristics [5].

Kimura's disease is often associated with glomerulonephritis (GN) and nephrotic syndrome, and the renal involvement usually occurs simultaneously with the cutaneous lesions. However, there have been reported cases where nephrotic syndrome occurred prior to any other clinical manifestations [6]. Even though membranous GN has been described as the most common histological lesion associated with Kimura's disease, mesangioproliferative GN and minimal change GN may also be the culprits behind the nephrotic syndrome in Kimura's disease [7]. Unfortunately, our patient did not give his consent to undergo renal biopsy, which could have allowed us to further characterize the renal disease.

The two peculiar characteristics of this case report are: (i) the very high proteinuria level (19 g/24 h) compared to other Kimura's disease cases that were complicated by nephrotic syndrome reported in literature (19 g/24 h is about twice the maximum value usually reported in literature) [8] and (ii) the complete healing of the patient (at 2-year follow-up) with only a high dose corticosteroid treatment (∼1 mg/kg/day), which was progressively decreased and then discontinued 3 months after diagnosis. Most Kimura's disease cases present with frequent relapses or go into remission with long-term corticosteroid therapy [9].

Presently, there is no consensus regarding the ideal treatment of a relapsing Kimura's disease, so various treatments have been used including corticosteroids [9], non-steroidal anti-inflammatory drugs [10], cytotoxic drugs [11] and a surgical excision of the masses [12]. Since Kimura's disease is a benign condition that tends to recur, treatment choices should not be too aggressive in cases of a recurrence in order to minimize treatment-induced side effects.

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CONFLICT OF INTEREST STATEMENT

None declared.

SIGNED INFORMED CONSENT

Obtained.

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ETHICAL APPROVAL

Not applicable.

GUARANTOR

Dr. Javier Rosada had full access in the data and is the guarantor of this work.

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