Case Series

Kimura’s disease: A short study of cytomorphologic features with its differential diagnosis and review of literature

Priya Sahu, DCP, DNB, Swasti Jain, MD, Manju Kaushal, MD

1Department of Pathology, ABVIMS, and Dr. Ram Manohar Lohia Hospital, New Delhi, India.

INTRODUCTION

Kimura’s disease (KD) is a rare form of chronic inflammatory disorder involving subcutaneous tissue, predominantly in the head-and-neck region along with frequent involvement of regional lymph nodes and/or salivary gland. Most cases of this disease are reported in East and Southeast Asia with male predominance.[1] It has a benign course though, recurrence is common.[2] Patients with KD can clinically mimic many benign and malignant disorders, often requiring extensive evaluation. Individually, cytomorphological features are non-specific, but the constellation of findings, that is, fine-needle aspiration cytology (FNAC), peripheral blood eosinophilia, and IgE levels, is highly characteristic to arrive at a diagnosis, especially in recurrent cases, where it may spare patients from repeated biopsies.

CASE REPORT

Herein, we report seven cases of KD with FNAC over 4 years. All the relevant history and clinical data were retrieved. FNAC was performed using 22–24 gauge needles, the dried smears were stained with Giemsa and wet-fixed smears with Papanicolaou stain. In addition, complete clinical examination and relevant investigations were done. Among the included cases, six were male and one female, aged between 16 and 42 years with a mean age of presentation at 27 years. The most common presentation was parotid...
region swelling followed by submandibular and cervical. The majority of these patients were having multiple cervical lymphadenopathies. Cytology smears from the aforementioned cases showed numerous eosinophils in a background of the polymorphous lymphoid population [Figure 1a]. Four cases revealed occasional Warthin–Finkeldey polykaryocytes (multinucleated giant cells) and three out of seven cases showed fragments of fibroblastic, collagenous stroma, and vascular proliferations [Figure 1b-d]. Based on cytomorphology, differentials were worm/filarial infestation, angiolymphoid hyperplasia with eosinophilia (ALHE), KD, and Hodgkin’s lymphoma (HL). Further, thorough screening in all seven cases did not reveal any evidence of parasite or atypical cell.

A differential count of blood showed eosinophilia in all the cases. Subsequently, quantitative estimation of IgE was performed and values were found to be raised significantly (reference range: 0.00–158.00 IU/ml). The diagnosis of KD was rendered based on cytomorphologic findings in conjunction with supportive laboratory findings (peripheral blood eosinophilia and elevated IgE). Biopsy and excision findings were correlated in five of the seven cases. One case did not undergo surgical procedure. Among these, in five cases, section showed hyperplasia of the germinal center, extensive eosinophilic infiltration, polykaryocytes (Warthin–Finkeldey type), and proliferation of thin-walled blood vessels with no evidence of malignancy. Hence, the diagnosis of KD was confirmed in these cases. However, one case on histopathological examination revealed effaced nodal architecture with prominent vascular proliferation. Sheets of cells composed of small and large lymphocytes, numerous eosinophils, and interspersed atypical mononuclear cells with vesicular nuclei and prominent nucleoli were seen. Occasional binucleate Reed–Sternberg (RS) cell was also

Figure 1: (a) Fine-needle aspiration showing polymorphous population of lymphoid cells (Giemsa, ×100), (b) interspersed Warthin–Finkeldey polykaryocyte on aspirate (Giemsa, ×100), (c) prominence of eosinophils in peripheral blood (Leishman, ×400), and (d) extensive eosinophilic infiltrate in lymph node section (H and E, ×400).
noted. With the aid of immunohistochemistry (CD15+ and CD30+), the case was finally diagnosed as HL.

**DISCUSSION**

Kimura disease was first described by Kim and Szeto in the Chinese literature as "eosinophilic hyperplastic lymphogranuloma" in 1937 Japan.\(^3\)

It is a non-neoplastic chronic inflammatory condition, affecting mainly Asian descent with marked adult male predominance. It typically presents as a non-tender subcutaneous swelling in the head-and-neck region, predominantly in the preauricular and submandibular areas. It is associated with lymphadenopathy, blood and tissue eosinophilia, and markedly elevated serum immunoglobulin E (IgE) levels.\(^4\) Other unusual sites of involvement include the auricle, scalp, orbit, oral mucosa, and nasal sinuses.\(^2\)

The etiology of the KD is uncertain; however, various proposals have been put forth by many researchers but none of them has been substantiated. Certain findings such as predominant type 2 helper (Th2) cells and elevated granulocyte macrophage-colony-stimulating factor, tumor necrosis factor-α, soluble interleukin-2 receptor (sIL-2R), IL-4, IL-5, IL-10, and IL-13 lead to the hypothesis that an infection or toxin may trigger an

| Table 1: Differential diagnosis of Kimura disease. |
|--------------------------------------------------|
| **Differential diagnosis** | **Clinical findings** | **Peripheral blood eosinophilia** | **Serum IgE levels** | **Cytological features** | **Histological features** |
|---------------------------|-----------------------|---------------------------------|---------------------|--------------------------|--------------------------|
| Kimura disease            | Site: Deep skin, soft tissue, and lymph node | Mostly present | Elevated | Polymorphous population with markedly increased eosinophils admixed with lymphocytes, plasma cells, and occasional giant cells | Florid reactive lymphoid hyperplasia with Warthin-Finkeldey type multinucleate giant cells present, vascular proliferation and eosinophilic infiltration are minimal |
| Angiolymphoid hyperplasia with eosinophilia | Site: Superficial skin and soft tissue | Rare | Normal | Abundant spindle to plump cells in a background of a polymorphous population of inflammatory cells with many eosinophils | The proliferation of thick- and thin-walled blood vessels with hypertrophic endothelial cells |
| Parasitic lymphadenopathy | Site: Lymph nodes | Present | Elevated | Part of parasite seen with numerous giant cells, plasma cells, and eosinophils | Parasitic remnants with plenty of eosinophils |
| Eosinophilic granuloma    | Site: Bone | Absent | Normal | Characteristic Langerhans histiocytes with nuclear grooving in a background of polymorphous inflammation with eosinophils | Langerhans cells are diagnostic (CD1a and S100 positive), with prominent nuclear grooves and prominence of eosinophils and few osteoclasts |
| Hodgkin lymphoma          | Site: Lymph nodes B symptoms usually present | Rare | Normal | Reed-Sternberg cells in a background of lymphocytes, plasma cells, eosinophils, and histiocytes | Prominence of eosinophils, plasma cells with atypical RS cells |
| Angioimmunoblastic T cell lymphoma | Site: Lymph nodes B symptoms usually present | May be present | Normal | Small to medium cells with moderate cytoplasm, condensed chromatin, and often indented nuclei | Medium-sized atypical neoplastic cells, lymphoid tissue fragments with transgressing vessels in a background of reactive lymphoid cells |
| Churg–Strauss syndrome    | Site: Lungs and kidney | Present | Elevated | Eosinophilic abscesses, granulomas and Charcot–Leyden crystals | Necrotizing vasculitis and eosinophil-rich granulomatous inflammation |

RS: Reed–Sternberg
autoimmune phenomenon or lead to a type I hypersensitivity, that is, IgE-mediated reaction.\(^8\)

Understanding and consideration of this entity are important as many conditions can mimic KD clinically and radiologically such as tubercular or parasitic lymphadenopathy, Mikulicz’s disease, eosinophilic granuloma, HL, and salivary gland tumors; as in our cases.\(^9\) The diagnosis of KD is established by morphologic confirmation, that is, cytology and/or histology. Individually, cytomorphic features are non-specific and can easily be confused with conditions that show lymphocytes with prominence of eosinophils. The differentials such as parasitic lymphadenopathy, ALHE, eosinophilic granuloma, HL, angioimmunoblastic T-cell lymphoma, and Churg–Strauss syndrome should always be excluded from the study [Table 1].

In parasitic (commonly filarial) lymphadenopathy, intense eosinophilia, numerous plasma cells, and remnants of filarial worms should be seen. Sometimes, foreign body giant cell (FBGC) reaction can lead to the suspicion of the hidden parasite. The extruded sheath material of the larva may evoke this kind of reaction and if any pale eosinophilic material surrounded by FBGCs is seen, then filarial pathology needs to be considered and a vigilant search for filarial worm should be done.\(^7\)

ALHE is a very close differential to KD. It is a vascular neoplasm with distinctive benign angiomatosus subcutaneous proliferation and the absence to rare regional lymphadenopathy. FNAC shows polymorphic population, eosinophils, vascular proliferation, and vessels lined by plump endothelial cells. Peripheral blood eosinophilia and raised IgE levels are certainly not seen in ALHE.

Eosinophilic granuloma is common in the younger age group, usually involving bone and less commonly affecting the lymph nodes and soft tissue. FNAC shows predominantly accumulations of histiocytes with a remarkable population showing nuclear grooving (Langerhans cells), variable number of scattered eosinophils, neutrophils, lymphocytes, and giant cells.\(^8\)

HL enters the list of differential diagnoses given the presence of a remarkable number of eosinophils at times but the large binucleate cells (RS cells) with prominent inclusion-like nucleoli are characteristic in a polymorphous background. Furthermore, positivity for immunohistochemical markers such as CD15 and CD30 in these atypical cells substantiates the diagnosis of HL.\(^9\) Other lymphoproliferative disorders such as T-cell lymphoma may have a polymorphic population of lymphoid cells with prominent eosinophils but the presence of atypical cells guides toward the diagnosis.

Churg–Strauss syndrome usually presents with multisystem involvement such as allergic rhinitis, asthma, and hemoptysis. However, a limited form may present with lymphadenitis where eosinophilic abscesses are seen surrounded by granulomas along with scattered Charcot–Leyden crystals. Histologically, there is evidence of small-vessel vasculitis and the diagnosis is confirmed by the presence of c-ANCA antibody against neutrophils.\(^8\)

For the initial diagnosis, though, it is prudent to perform an excisional biopsy for confirmation; FNA cytologic evaluation may be useful in the diagnosis of recurrent lesions in Kimura’s disease. The prognosis of KD is excellent and has no potential for malignancy, however, recurs locally and wax and wanes over time.\(^1\) Multiple treatment methods have been offered for KD with variable responses, including surgical excision, radiotherapy, and medications including corticosteroids, cyclosporine, cyclophosphamide, and loratadine.\(^9\) A maintenance dose is often required to prevent disease relapses.

**CONCLUSION**

We reiterate that increased awareness of this entity is imperative as it can be underdiagnosed in our geographical location. The individually cytomorphological features are non-specific, but the constellation of findings (FNAC, peripheral eosinophilia, and raised IgE levels) is highly characteristic to arrive at this diagnosis. It may spare the patient from repeated biopsy examinations, especially in recurrent cases, and also prompt the clinicians to institute appropriate management.

The Warthin–Finkeldey type polykaryocytes had 3–30 nuclei and prominent nucleoli with ill-defined cytoplasmic borders. Their nuclei were arranged in grapevine or ring-shaped clusters. As these polykaryocytes could also be found in lymph nodes and extranodal tissues of both reactive and neoplastic lymphoid disorders, polykaryocytes themselves are clinically non-specific. However, the morphologic features of the Warthin–Finkeldey type giant cells are quite different from the foreign body type or Langhans’ type giant cells. When the characteristic cytologic features of Kimura’s disease such as a significant number of eosinophils in a background of lymphoid cells with a proliferation of vessels and endothelial cells are also observed in the smear, it is possible to suggest this diagnosis in the appropriate clinical settings.

**COMPETING INTERESTS STATEMENT BY ALL AUTHORS**

No conflicts of interest.

**AUTHORSHIP STATEMENT BY ALL AUTHORS**

Priya Sahu- Data collection, analysis and drafting. Swasti Jain- Data collection and analysis. Manju Kaushal- Concept of the work and execution.
ETHICS STATEMENT BY ALL AUTHORS
This is a retrospective study and proper permission was taken from the patients.

LIST OF ABBREVIATIONS (IN ALPHABETIC ORDER)
ALHE - Angiolymphoid hyperplasia with eosinophilia
ANCA - Antineutrophil cytoplasmic antibodies
CD - Cluster of differentiation
FBGC - Foreign body giant cell
FNAC - Fine needle aspiration cytology
HL - Hodgkin's lymphoma
Ig - Immunoglobulin
IL - Interleukin
RS - Reed Sternberg

EDITORIAL/PEERREVIEW STATEMENT
To ensure the integrity and highest quality of CytoJournal publications, the review process of this manuscript was conducted under a double-blind model (the authors are blinded for reviewers and vice versa) through an automatic online system.

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