Case Report

Parinaud Oculoglandular Syndrome as a Prominent Presenting Feature of Kikuchi-Fujimoto Disease – A Case Report and Review of the Literature

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Abstract

Kikuchi-Fujimoto disease (KFD) is an often under-diagnosed form of lymphadenitis that clinically mimics lymphoma. Ocular manifestations are rare in patients with KFD and are under-appreciated in the literature. We describe a man who presented with eye redness, blurred vision, and pain on upward gaze associated with fever, weight loss and cervical lymphadenopathy. This presentation was initially interpreted as Parinaud oculoglandular syndrome which is most often caused by infection leading to an infectious workup. Lymph node biopsy was eventually performed and showed KFD. Kikuchi-Fujimoto disease needs to be added to the list of known causes of Parinaud oculoglandular syndrome.

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Introduction

Kikuchi-Fujimoto disease (KFD) is a benign, self-limited disease of unknown etiology that is more commonly reported in Asian countries.[1] Most patients present with localized lymphadenopathy, and the diagnosis is established by lymph node biopsy. Rarely patients have generalized lymphadenopathy. Patients with KFD can have systemic symptoms and physical manifestations, most often fever, myalgia and skin eruptions, usually with spontaneous resolution. Other than skin, extranodal sites of involvement are rare.[1]

Parinaud oculoglandular syndrome (POS) is a term often used to describe patients who have the combination of conjunctivitis associated with lymphadenopathy anterior to the ear and generalized illness with fever. Patients often have ocular symptoms including pain, swelling and blurred vision. The most common causes of POS are infectious agents, such as *Bartonella henselae*. Other causes include connective tissue diseases and lymphoproliferative disorders.[2]

We report a case of a young man with no significant past medical history who presented with conjunctival erythema, pain with upward gaze, blurred vision, fever of unknown origin, weight loss and cervical lymphadenopathy. The diagnosis of POS was established and a workup for infectious diseases and lymphoma was initiated. Lymph node biopsy showed KFD. We report this case to emphasize this unusual, extranodal manifestation of KFD and to add this disease to the extensive list of causes of POS.

Case Presentation

A 24-year-old Hispanic man with no known past medical history presented with a one-week history of blurred vision and pain on upward gaze accompanied by redness in his eyes. According to the patient, there had been a daily fever up to 102^0 F, accompanied by chills, persisting for one month despite treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics. There was also diffuse cervical lymphadenopathy, first in the posterior cervical triangle, later progressing around his neck and gradually increasing in size. This was accompanied by fatigue, weight loss, occasional profound night sweats, and transient stiffness in his knees,

ankles, wrists and hands that was worst during morning hours.

On examination, his conjunctivae were diffusely injected. Ophthalmologic examination showed anterior capsular clouding and deepening of the anterior chamber. Prominent choroidal edema and corneal flare was noted. Examination of the fundi revealed relatively normal blood vessels with some tortuosity and pink nerves. Multiple, 2 x 2 cm, soft, mobile, non-tender lymph nodes were palpable in the right supraclavicular, preauricular, posterior cervical, occipital and left anterior cervical regions. There was no axillary or inguinal lymphadenopathy or hepatosplenomegaly. Examination of the musculoskeletal system revealed tenderness in several metacarpophalangeal and interphalangeal joints. The right knee was slightly swollen. There was no redness or increased temperature over any joint.

Laboratory results were significant for a low white blood cell count of 2.1 K/uL (reference range, 4.0-11.0 K/uL) with 70% neutrophils and 22% lymphocytes. Peripheral blood smear revealed a mild left-shift but was otherwise unremarkable. The erythrocyte sedimentation rate was elevated at 42 mm/hr (reference range, 1-13 mm/hr for men). His lactate dehydrogenase, aspartate aminotransferase and alanine aminotransferase levels were elevated at 2399 IU/L (reference range, 313-618 IU/L), 202 IU/L (reference range, 5-35 IU/L) and 106 IU/L (reference range, 7-56 IU/L), respectively. Autoantibodies including ANA, dsDNA and HLA-B27 were negative. Infectious disease workup revealed an elevated parvovirus IgM titer of 1:2 (reference range, negative). Magnetic resonance imaging studies of the head and neck demonstrated abnormal symmetric enhancement of both orbits and choroid with irregular enhancement surrounding the optic nerve sheath and prominent bilateral cervical lymphadenopathy. Computed tomography scan of the chest, abdomen and pelvis confirmed nonspecific bilateral lymphadenopathy, involving axillary, mediastinal, hilar and retroperitoneal lymph nodes but no hepatosplenomegaly. Synovial fluid analysis showed 10,000 white blood cells per microliter with lymphocyte predominance.

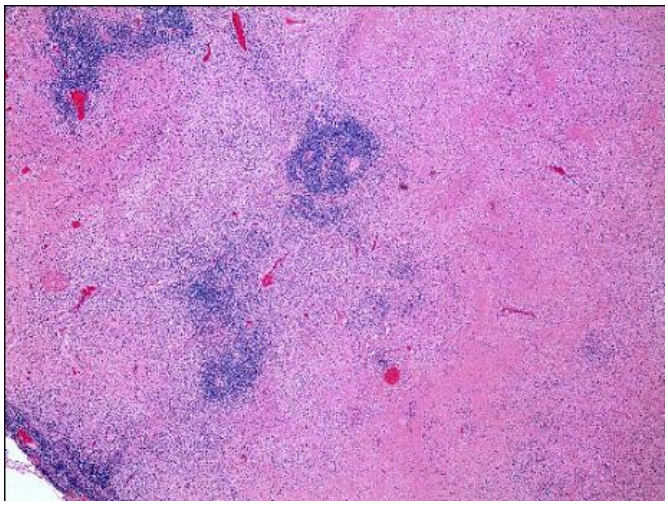

Figure 1. Low power view of a supraclavicular lymph node from the patient with Kikuchi-Fujimono disease. The paracortical area is replaced with extensive coagulative necrosis and rare foci of inflammatory cells.

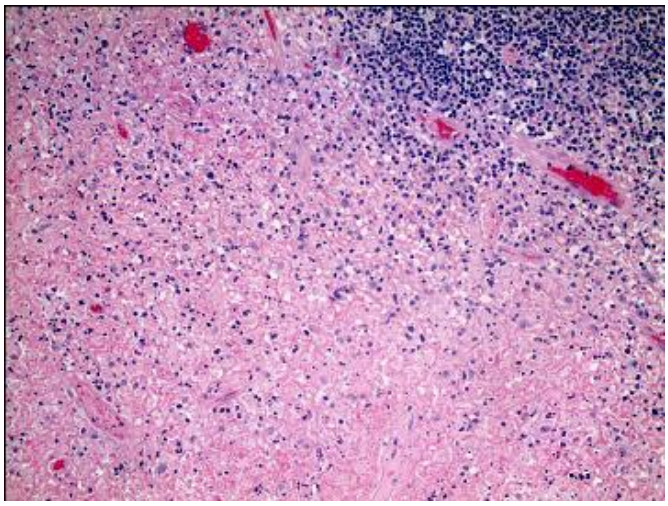

Figure 2. High power view of a supraclavicular lymph node from the patient with Kikuchi-Fujimono disease. The lesions are composed of abundant histiocytic cells, karyorrhectic debris, eosinophilic fibrinoid deposits and small lymphocytes.

A biopsy of the right supraclavicular lymph node was performed. Low power view of the lymph node demonstrated extensive necrosis with rare inflammatory cells (**Figure 1**). Upon high power examination, the paracortical area was expanded with prominent irregular and coalescing foci containing karyorrhectic debris, nuclear fragments and bright eosinophilic fibrinoid deposits. No neutrophils or eosinophils were present. Pale staining histiocytes surrounded the patchy and confluent necrotic areas and were actively engulfing and phagocytosing the aforementioned cellular debris. Plasmacytoid monocytes, immunoblasts and thrombosed blood vessels were present in viable areas of the lymph node (**Figure 2**). Based on the above findings, a diagnosis of KFD was made.

The patient was started on prednisolone eye drops to alleviate intraocular inflammation, and acetaminophen for systemic symptomatic relief. His ocular symptoms improved and the fever subsided gradually. Five days post admission, the patient was discharged with persistent lymphadenopathy and minor complaints of morning stiffness, which gradually resolved over the next several weeks. At the last follow-up, the patient was found to achieve a full recovery with no apparent ophthalmological consequence.

Discussion

Parinaud oculoglandular syndrome was initially described by Henry Parinaud, a French ophthalmologist and neurologist, in 1889; the eponymic designation was subsequently suggested by Harold Gifford, an American ophthalmologist, in 1898. The disease is characterized by conjunctivitis, retrotarsal conjunctival granulations, regional preauricular and cervical lymphadenopathy, and fever. There is no gender predilection, but the disease appears to be more frequent in children. The syndrome appears to be almost invariably triggered by infections; however, there is a continuously expanding list of causes such as connective tissue diseases and lymphoproliferative disorders.[2]

Kikuchi-Fujimoto disease is a benign, self-limited, histiocytic necrotizing lymphadenitis which is often associated with mild constitutional symptoms. Possible accompanying symptoms can range from myalgia and fever to skin eruptions, with spontaneous resolution. The disease was first described by Kikuchi and Fujimoto, independently, in 1972. It primarily affects young adults with a slight female predominance, and is most prevalent in Asia.[1] It has been reported to account for 5.7% of all pathological abnormalities in lymph node biopsies.[3] The most common presentation of KFD is cervical lymphadenopathy involving the posterior cervical triangle. Generalized lymphadenopathy or involvement of peripheral lymph nodes such as axillary, inguinal, thoracic, abdominal or pelvic lymph nodes is far less common.[1] Involvement of extranodal sites like ocular area remains extremely rare.[4-8] Therefore, the concomitant diagnosis of KFD and POS is seldom considered.

A review of literature identified only five other cases of KFD with ocular manifestations (**Table 1**).[4-8] Overall, there were four women and 2 men, with a median age of 20 years (range, 10-37). Four patients experienced concomitant presentation of KFD and ocular manifestation, the other two patients developed ocular disease two years after initial diagnosis of KFD. Whereas three patients including our patient depicted no disease recurrence or long-term ocular consequence, the other three patients demonstrated long-term damage to the eye.

The pathogenesis of KFD is not well-established. Viruses and autoimmune diseases have been suggested as the etiology. Exuberant T-cell-mediated immune response to a variety of stimuli, cytokine-mediated mechanisms and genetic predisposition have been proposed to play an important role in the pathogenesis of KFD.[1] It has been shown that CD8+ T-lymphocytes are the main cell population undergoing extensive apoptosis in the lymph node of KFD.[9]

Table 1. Clinical features of published cases of Kikuchi-Fujimoto disease presenting as Parinaud ouloglandular syndrome.

Author/ year (reference)	Age/ Sex	Onset of POS and KFD	Symptoms	Treatment	Outcome/FU
Hoehn, current	24/M	concomitant	reduced vision, conjunctival injection, uveitis, choroidal edema	topical steroid	unremarkable/6 months
Rocher/ 2006 (8)	10/F	concomitant	diplopia, oculomotor palsy, papillary edema, exopthalmus, ptosis, intraconical attack of apex	intravenous and oral steroid	unremarkable/6 months
Perez Alvarez/ 2005 (7)	37/F	2 years post KFD	panuveitis, vasculitis, subretinal macular infiltrate	metotrexate and prednisone	scar and mild vascular distorsion/11 months
Kim/ 2004 (6)	16/M	concomitant	conjunctival injection, reduced vision, anterior uveitis	topical steroid	unremarkable/6 months
Taguri/ 2001(5)	16/F	2 years post KFD	photophobia, discomfort, bilateral uveitis, reduced vision	topical steroid	recurrent episodes, reduced vision/ 9 months
Chavis/ 1998 (4)	32/F	concomitant	upper eylid swelling, pain on upgaze, lacrimal gland enlargement	oral steroid	dry eye/ “several months”

M, male; F, female; POS, Parinaud oculoglandular syndrome; KFD, Kikuchi-Fujimono disease; FU, follow-up

Viruses that have been shown to be associated with KFD include Epstein-Barr virus, human herpes viruses 6, human immunodeficiency virus and parvovirus B19.[1] Viral infections are preferably suggested as causative agents because of the histologic features, clinical presentation and clinical outcome with most cases having spontaneous remission. The patient described here had positive antibody titer for parvovirus B19, a virus that has been suggested to play a role in the pathogenesis of KFD. It was recently demonstrated that lymph nodes from patients with KFD showed stronger positivity for parvovirus B19 than normal controls by immunohistochemistry and *in situ* hybridization.[10] Moreover, positive parvovirus B19 antibody tests were reported in patients with simultaneous occurrence of KFD and systemic lupus erythematodes (SLE), and it was proposed that parvovirus infection might be responsible for the development of KFD as well as acceleration of SLE flare.[11,12] The suggested etiology of viral infection may support a shared pathogenesis between KFD in the lymph node and concomitant ocular manifestations.

No definitive effective treatment is available for KFD. The disease is usually self-limited. NSAIDs are often used for symptomatic relief. In case of persistent and severe symptoms, systemic steroids or hydroxychloroquine can be added. The recurrence rate of KFD is about 3% with recurrence usually occurring within a few weeks after the first episode.[9,13] Follow-up of these patients is necessary, since there has been an association with development of SLE[14,15] and lymphoma.[16]

In summary, we report a case of KFD with an unusual presentation as POS. While KFD is usually a benign, self-limited disorder, the ophthalmologic manifestations of blurred vision, pain on upward gaze, uveitis and perineural changes have to be taken seriously, as these changes may progress, if untreated, and can result in vision loss. We suggest that KFD be added to the list of differential diagnoses of POS.

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