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Case Report

Unique presentation of recurrent subdural effusions and subsequent abdominal lymphadenopathy in a patient diagnosed with Kikuchi-Fujimoto disease

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ABSTRACT

Kikuchi Fujimoto Disease, originally discovered in 1972, is a rare lymphoproliferative disorder traditionally characterized by cervical lymphadenopathy, fevers, parotid gland enlargement, and several other nonspecific manifestations. Differentials include lymphoma, other viral diseases such as Epstein-Bar Virus, as well as other autoimmune conditions such as Systemic Lupus Erythematosus. Central nervous system involvement is exceptionally rare, with manifestations including meningitis as well as subdural effusions, as presented in this case. This review will summarize a case of a 24-year-old man with recurrent subdural effusions requiring intervention, subsequent relapse with abdominal lymphadenopathy, and possible IgG4 related disease. The background epidemiology, radiology, and potential pathophysiology will be reviewed.

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Introduction

Kikuchi-Fujimoto Disease, also represented as Histiocytic Necrotizing Lymphadenitis, is a self-limiting lymphoproliferative disorder of non-specific etiology. It was first described in Japan in 1972 and traditionally had been thought to predominate in Asian populations, however more re-

cent cases suggest more variability in the affected populations [5,8]. The disease is characterized by subacute necrotizing lymphadenopathy with histology demonstrating follicular hyperplasia with a preserved architecture [5]. Patients will present with a variety of nonspecific symptoms and signs, such as fevers, rashes, fatigue, and sweating, as well as lymphadenopathy which is most prominent in the neck region.

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While there are also many manifestations of the disease, including an association with systemic lupus erythematosus, Graves disease, and other autoimmune conditions, neurologic and central nervous system complications are relatively rare within its spectrum. Furthermore, recurrence is seen in extremely rare cases. This review will present a case of a 24-year-old male with history of headaches and recurrent bilateral subdural effusions and cervical lymphadenopathy, with subsequent relapse many years later as an atypical presentation of Kikuchi Fujimoto disease with a brief review of its clinical, and diagnostic properties.

Initial presentation

A 24-year-old Filipino male initially presented outpatient to his primary care physician with complaints of headaches and visual disturbances for about 1 week. For 2 months prior to his presentation, the patient described persistent right sided facial swelling as well as painless left neck enlargement. One week prior to presentation, the patient began having intermittent, pulsatile, right temporal headaches with associated photophobia, nausea, and vomiting. He denied any fever, sick contacts, recent travel history, intravenous drug use, chills, or weight loss. He did report moderate increased alcohol consumption up to 6 beers a day with friends in recent times. The patient immigrated to the US from the Philippines 2 years prior and last visited the country 1 year prior to presentation. His review of systems and physician exam were otherwise non-contributory.

Imaging

A non-contrast CT head demonstrated a left frontal, parietal, and temporal lobe subdural fluid collection with a 4 mm rightward midline shift [1]. He was shortly sent to the emergency department for further workup and subsequent inpatient admission to Neuro ICU (Fig 1).

Initial labs were remarkable for a normal white blood cell count with 15.3% lymphocytes, with a thrombocytopenia of $119 \times 10^9/L$. The rest of his metabolic profile, including liver function tests, glucose levels, and renal function tests were unremarkable. His blood count demonstrated no other abnormalities. Further investigation with subsequent CT of the neck showed extensive deep cervical chain lymphadenopathy bilaterally with right parotid gland enlargement (Figs. 2A and B).

An MRI of the brain was deemed appropriate to further elucidate these findings, the results of which showed a 7 mm left subdural fluid collection which demonstrated findings concerning for sequelae of meningitis, without signal pattern of simple blood products (Figs. 3A, B, and C).

Patient was subsequently taken to the operating room by neurosurgery for evacuation of the collection via burr hole with drain placement; initial drainage contents demonstrated purulent foul-smelling fluid. Cultures of the fluid were negative for fungus, bacteria, and acid-fast bacilli. Notably, HIV



Fig 1 – Axial non-contrast CT scan of the head shows a crescentic low attenuating fluid collection along the left cerebral hemisphere measuring about 4 mm in maximal thickness (red arrows), with associated mild rightward midline shift of 4 mm. No other brain parenchymal abnormalities were identified otherwise. No fractures or other traumatic changes. Overlying scalp is within normal limits (Color version of the figure is available online).

serology was negative, markers for mumps IgG positive and IgM negative, syphilis negative, negative blood cultures, and QuantiFERON gold twice negative. He was initially treated empirically with Vancomycin and Meropenem. However, these were discontinued after all cultures came back negative and patient developed a short-lived rash. Patient was discharged subsequently after symptoms started to improve and after removal of intracranial drain, with plans for outpatient biopsy of right parotid gland for continued investigation. However, he was lost to follow-up and thus biopsy was not performed at that time.

Follow up 1

Three months after discharge, the patient again presented to the emergency department with 3 weeks of right sided headaches, similar in quality to his prior episode. Vitals and labs were non-contributory. A CT scan of the head performed at this presentation showed development of a new right sided subdural fluid collection with mild leftward midline shift. Patient was admitted under neurosurgery and a subsequent MRI was performed which confirmed the findings. Patient was subsequently again taken to the operating room for burr hole drainage of this collection as well as biopsy of a Level V lymph node by ENT. Subsequent histologic findings from biopsy described as below (Figs. 4A, B, and C):



Fig. 2 – (A) Coronal postcontrast CT scan of the neck demonstrates multiple enlarged cervical chain lymph nodes, most prominent at levels 3 and 4 bilaterally (red arrows). Right unilateral parotid gland swelling with enlarged parotid space lymph nodes are also seen (blue arrow). Redemonstrated but partially visualized left sided subdural fluid collection (green arrow). (B) Axial postcontrast CT scan of the neck demonstrates multiple cervical chain lymph nodes most prominent at levels 3 and 4 bilaterally (red arrows), as well as within the right parotid space (blue arrow), partially shown in this slice (Color version of the figure is available online.)

Level V lymph node biopsy demonstrated a lymph node with partially preserved architecture and areas of necrosis rimmed by histiocytes. The necrotic areas demonstrated nuclear debris but with no neutrophils present. Other stains not shown: immunohistochemical stain for CD163 highlighted the histiocytes adjacent to the necrotic areas. Stains for CD3, CD10, and CD20 showed few preserved germinal centers. Stain for CD30 was negative. Stain for CD15 showed non-specific binding in the histiocytes. Special stains for mycobacteria (AFB) and fungi (GMS) were negative.

Follow up 2

Patient presented to the emergency room 5 years later with complaints of bilateral lower back pain with associated fevers, diarrhea, insomnia, anorexia, and weight loss lasting 4 weeks. Physical exam findings were remarkable for mild tenderness to palpation around the periumbilical area as well as multiple sub-centimeter, erythematous, non-blanchable skin lesions on the cheeks which persisted throughout his hospital stay. Lab-work was significant for leukopenia with hyponatremia, transaminitis with elevated LDH, and ferritin. An extensive workup was performed at this time given the rarity of a relapse of KFD, including COVID PCR, Monospot and HIV antibodies which were negative. Urinary analysis was normal with negative blood cultures, Clostridium difficile test, and hepatitis serologies. Bone marrow biopsy was negative for any form of associated lymphoproliferative disorders. Autoimmune workup, including anti-nuclear antibodies, were negative except for elevated IgG4 levels. CT of the abdomen, and pelvis was remarkable for peri-aortic infiltrative tissue with enlarged peri-aortic lymph nodes. Patient underwent an abdominal retroperitoneal lymph node biopsy which demonstrated findings again suggesting KFD.

Patient was observed inpatient with remaining work-up showing anemia of chronic disease, with the elevated LDH levels, and parotid enlargement being attributed to KFD. He was started on steroids for treatment of KFD as well as Rituximab for treatment of possible IgG4 related disease with subsequent discharge and close follow-up with Rheumatology with resolution of symptoms on subsequent visits.

Discussion

Kikuchi-Fujimoto Disease (KFD), also known as histiocytic necrotizing lymphadenitis, was first described by Masahiro Kikuchi and Y. Fujimoto et al. in 1972. It was initially thought to affect mostly young East Asian women usually under the age of 30. However, multiple cases in both male and female patients with various ethnic backgrounds as well as within the United States and other countries have since been reported [5]. Due to the rarity of the disease, it is important for radiologists, and pathologists to be aware of the entity as well as its various presentations.

The pathogenesis is not clearly understood; however, it is theorized to be autoimmune in nature secondary to an immune activation against an infectious agent [1]. There are a variety of viral etiologies identified, with an unclear rea-

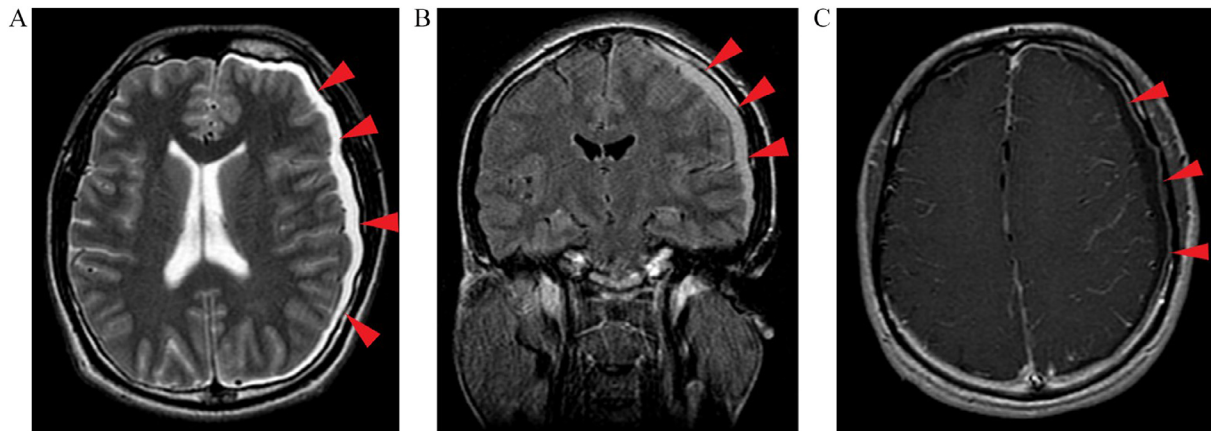


Fig. 3 – (A) Axial T2 MR image through the brain at the level of the lateral ventricles demonstrates a crescentic hyperintense collection along the left cerebral hemisphere (red arrows), measuring up to 7 mm. There is an associated mild rightward midline shift of 7 mm. The remainder of the brain parenchyma shows no abnormal T2 signal changes. **(B)** Coronal FLAIR MR image through the brain demonstrates a crescentic hyperintense collection along the frontal and temporal lobes measuring 7 mm in maximal thickness consistent with an effusion (red arrows). There is also associated 7 mm midline shift toward the right. **(C)** Axial T1 postcontrast image through the brain demonstrates nonenhancement of the extra-axial collection, however with thickening and enhancement of the overlying dura mater. Mild midline shift is also appreciated (Color version of the figure is available online.)

son as to how each of the virus types plays a role; many of these include Human Immunodeficiency Virus (HIV), Herpes, Epstein Barr, and parainfluenza, among others. Alternative explanations include an autoimmune condition which is initiated by transformation of lymphocytes from previous viral infections or other nonspecific stimuli [7]. However, it is still considered a benign disease characterized by generalized or focal lymphadenopathy potentially associated with fevers. Most commonly, involvement of the posterior cervical groups is observed. Rare manifestations include axillary and mesenteric lymphadenopathy, parotid gland enlargement, arthralgias, cutaneous rash, interstitial lung disease, and hepatosplenomegaly [2]. Overall, the disease workup will appear like that of a nonspecific viral infection; the clinical picture, radiological findings, as well as the histopathologic features under microscopy are needed in order to develop the diagnosis [6].

Both laboratory and clinical findings may mimic lymphoma, sarcoidosis, tuberculosis, Systemic Lupus Erythematosus, and HIV [1]. Example laboratory findings, many of which were also demonstrated in the present case, include elevated lactate dehydrogenase, c-reactive protein, and leukopenia, as well as elevated liver enzymes; these findings are also more commonly seen in male patients compared to females [15]. Many of these lab findings are otherwise nonspecific, however, and as a result diagnosis is usually made by tissue sampling of lymph nodes. Classic histologic features of KFD may include eosinophilic necrosis, which will be seen in the cortex of the nodes, a notable lack of granulocytes and plasma cells, the presence of immunoblasts, plasmacytoid T cells or monocytes, as well as fragments of “nuclear dust” within areas of necrosis [4]. Immunohistochemical staining can also be useful for the evaluation of the involved cells. Positive staining of histiocytes will include CD163, myeloperox-

idase, CD 68, as well as lysozyme. Lymphocytes will express traditional CD 3 and CD predominantly CD 8 compared to CD 4, as well as a small number of cells demonstrating CD 30 [5].

The Central Nervous System (CNS) can also be affected in very rare cases, resulting in spontaneous subdural hematomas or aseptic meningitis [9]. Few cases in the literature have been reported with manifestations of KFD in involved portions of the meninges or the CSF space, and even fewer cases with recurrent subdural fluid collections which manifest as empyema, hematomas, or effusions, as shown in the present case workup. While the causality of the effusions is still unclear, theories may include a similar pathophysiology to that of proposed reasoning behind Epstein Barr or other leukemic malignancies [10]. Our literature review demonstrated a variety of causes of spontaneous subdural hematomas and/or effusions, however non-Hodgkins Lymphoma was demonstrated to be a rather recurrent or relatively more common etiology among others. While lymphoma may have a different pathophysiology compared to KFD, a proposed mechanism in which a hematoma resulting from infiltration of the tumor into dural veins with subsequent obstruction, stasis, and rupture of the capillary net may also be considered for KFD [11]. Furthermore, upon analysis of CSF fluid, lymphocytic pleocytosis may be present along with elevated glucose, and protein levels [3]. In cases of aseptic meningitis, the etiology is thought to represent an autoimmune response with infiltration of the neural parenchyma by lymphocytes. [7]. CNS involvement may lead to significant morbidity and mortality, in a disease that is otherwise known to manifest with more benign processes.

The presenting case also demonstrated a biopsy-confirmed relapse of KFD few months following the initial presentation as well as 5 years following the initial presentation, which is uncommon for this disease; such occurrences have only

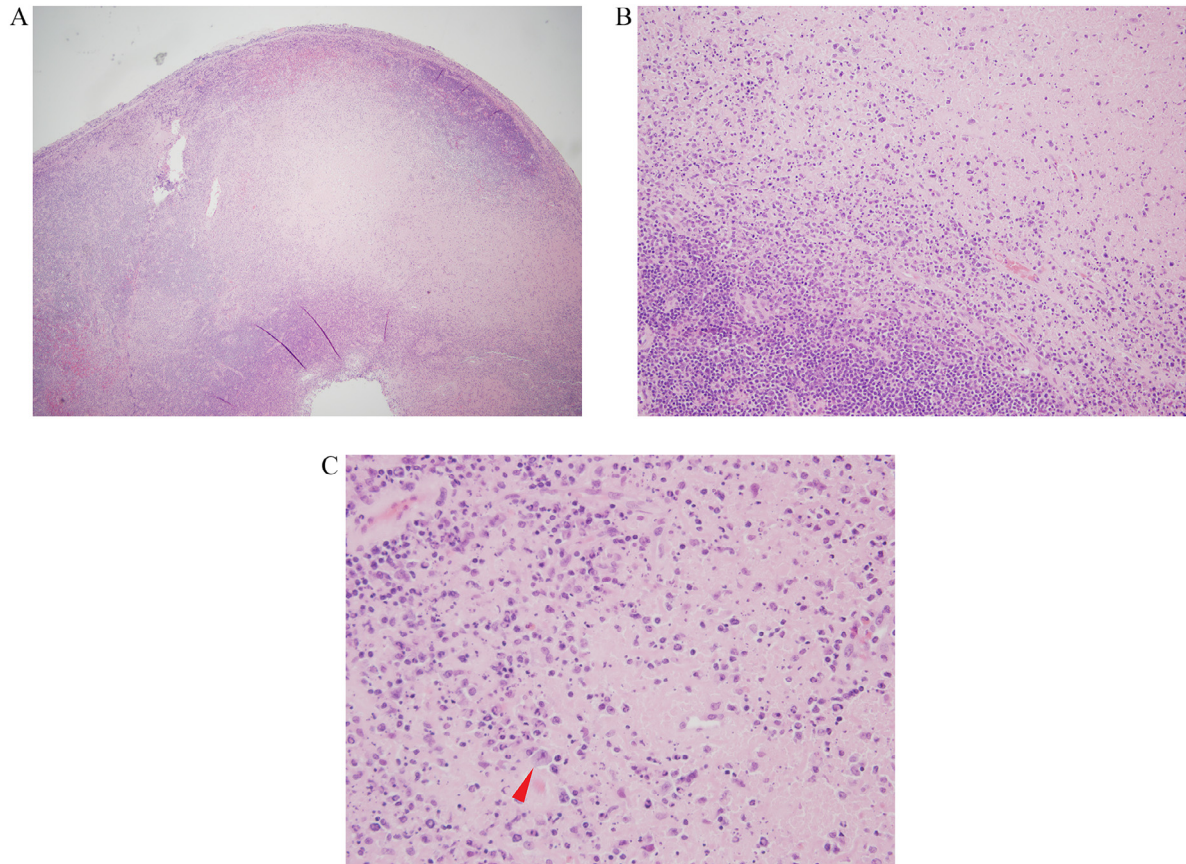


Fig. 4 – (A) Hematoxylin Eosin stain at 40x magnification of biopsied level V lymph node with altered architecture and areas of necrosis. (B) Hematoxylin Eosin stain at 200x magnification of biopsied level V lymph node with altered architecture and areas of necrosis. At this higher magnification, necrotic cellular debris is evident effacing the normal lymph node architecture. (C) Hematoxylin Eosin stain at 400x magnification of biopsied level V lymph node with altered architecture and areas of necrosis. Histiocytes (red arrow) and inflammatory cells are evident at this magnification (Color version of the figure is available online.)

been documented in sporadic cases [12]. Furthermore, a possible association with IgG4-related disease can be considered given the elevated levels during the patient's third hospital stay. IgG4 related diseases is a systemic inflammatory condition which manifests through various signs and symptoms as well as pathologic processes, such as lymphoplasmacytic infiltration of the pancreas resulting in sclerosing pancreatitis, sialadenitis, lung disease, as well as various skin manifestations, among other various presentations [14]. Elevation of serum IgG4 has high sensitivity but also low specificity for the diagnosis of IgG4-RD, with reports showing sensitivities up to 90%, but with specificities only up to 60% [14]. Furthermore, while the elevated levels of IgG4 (1.54 g/L) raises concerns for such a disease process, they are less than the 5 g/L which would generally raise the likelihood of the entity [16]. Histologic findings in IgG4 related disease generally include polyclonal lymphoplasmacytic infiltrate rich with IgG4 plasma cells as well as storiform fibrosis in the affected organs [16]. Lymph node biopsies in the presenting case were not stained for IgG4+ plasma cells due to the lack of typical morphologic patterns expected in IgG4-related diseases, including stori-

form fibrosis, as well as the overall lack of specificity in the instance of positive staining [16]. The presence of elevated IgG4 in the present case may be nonspecific, however, no studies have been shown to potentially link KFD, and IgG4-related disease processes.

The presence of the patient's erythematous skin nodules on the cheeks may be an indirect sign of a Human Herpes Virus 8 [HHV8] viral infection, the characteristic Herpes virus form linked with Kaposi sarcoma. There is no current and definitive infectious etiology linked with KFD, however, in a 1998 study by Huh, et al., 26 cases of confirmed KFD were evaluated for viral DNA containing HHV8 through PCR and southern blot analysis, with 6 of those cases demonstrating positive viral loads [13]. While the present case demonstrated a negative infectious workup including other etiologies for Kaposi Sarcoma such as HIV, a thorough workup for the patient's skin lesions including potential biopsy was not performed during his inpatient stay, and his symptoms improved over the course of follow-up outpatient visits.

While the present case required the evacuation of the subdural effusions in 2 different periods of time, KFD is usually

seen as a self-limiting illness which requires treatment with analgesics or antipyretics as needed. Our case aims to outline potential serious central nervous system findings of KFD which may need to be addressed promptly as they may result in high morbidity and mortality, and to raise awareness to consider KFD in the differential diagnosis for cervical lymphadenopathy.

Conclusion

Kikuchi Fujimoto Disease, or Histiocytic Necrotizing Lymphadenitis, is a lymphoproliferative disorder with unknown etiology however is theorized to be related to an autoimmune or infectious insult to the body. This case summarizes a rare presentation of recurrent subdural effusions as a manifestation of KFD, as well as recurrent adenopathy elsewhere in the body many years later. No definitive reason has been elucidated as to why recurrence may occur in these individuals, nor are there affirmed associations with other processes such as IgG4-related disease as suggested in the presented case. Nevertheless, as always, awareness of possible presentations is crucial for the development of a complete differential for both the radiologist, and clinician.

Declaration of Competing Interest

I certify that I have answered every question and have not altered the wording of any of the questions on this form.

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