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CASE BASED REVIEW

# Co-occurrence of Kikuchi-Fujimoto's disease and Still's disease: case report and review of previously reported cases

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**Abstract** Kikuchi-Fujimoto's disease (KFD) and adult-onset Still's disease (AOSD) are rare inflammatory conditions with some overlapping features. We encountered a 22-year-old male patient who presented with daily fevers, neck discomfort, and sore throat and subsequently developed rash, arthritis, and cervical lymphadenopathy. Biopsy of the skin rash was consistent with KFD skin involvement. Given that the patient also met criteria for AOSD, a final diagnosis of KFD/AOSD co-occurrence was made. Anti-IL-1β therapy with anakinra resulted in rapid resolution of all symptoms. A literature search identified eight more cases of KFD/AOSD. Fever, rash, arthritis, and lymphadenopathy were present in all patients. No case report demonstrated an association of rash eruption clearly associated with fever spikes. Duration of symptoms ranged from 3 weeks to 10 years. Seven patients had leukocytosis, six had anemia, and five demonstrated elevated ferritin and/or decreased glycosylated ferritin. Seven patients had elevated erythrocyte sedimentation rate (ESR), and seven had transaminitis. Eight of nine patients had no evidence of infectious disease. Autoantibodies were absent from all patients. KFD and AOSD are very rare diseases, yet they may overlap. The two conditions not only share several clinical and laboratory characteristics but also differ in characteristic ways. Given the rapid response observed with anakinra in the index patient, IL-1β likely plays a role in both diseases.

**Keywords** Kikuchi · Kikuchi-Fujimoto's disease · Overlap · Still's disease

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## Introduction

Kikuchi-Fujimoto's disease (KFD), also known as histiocytic necrotizing lymphadenitis or simply Kikuchi's disease, is a very rare, usually self-limited illness that typically affects young women. KFD was initially described in 1972 by Kikuchi and Fujimoto [1–3]. Characteristic features include cervical lymphadenopathy, fever, and an elevated erythrocyte sedimentation rate (ESR) [4]. Diagnosis is most commonly made by a lymph node biopsy revealing paracortical foci of necrosis with a histiocytic infiltrate. KFD prevalence is highest in Japan and other Asian countries, but the disease has been reported sporadically worldwide, with a female-to-male ratio of approximately 4:1. Immunogenetic predisposition may be reflected in the fact that several HLA class II genes are overrepresented in KFD patients, including DPA1*01 and DPB1*0202. These alleles occur more commonly among Asian patients, possibly contributing to the epidemiology of the disease [3]. KFD has frequently been hypothesized to be a reactive process and has been reported to occur occasionally in the setting of other autoimmune diseases, including systemic lupus erythematosus (SLE), systemic juvenile idiopathic arthritis, polymyositis, cutaneous necrotizing vasculitis, Sjogren's syndrome, hemophagocytic

lymphohistiocytosis, and catastrophic antiphospholipid syndrome. Therefore, it is important to recognize KFD not only on its own but also when it presents in association with other inflammatory conditions [3].

Adult-onset Still's disease (AOSD; also known as adult-onset juvenile idiopathic arthritis) is a rare systemic autoinflammatory condition, characterized by quotidian spiking fevers, arthritis, and salmon-colored rash typically concurrent with the fever [5]. Prevalence ranges from 1 to 10 cases/million [6]. AOSD is generally treated with corticosteroids, or more recently with anti IL-1β (canakinumab, anakinra) or anti-IL-6 (tocilizumab) therapies, as these cytokines have been implicated in AOSD pathogenesis [7–9]. Nonetheless, AOSD pathogenesis remains poorly understood.

Although both KFD and AOSD are inflammatory in nature, only a few cases of their co-occurrence (KFD/AOSD) have been reported [4, 10–13]; the rarity of each of the diseases individually makes it unlikely that their co-occurrence is a random event. To date, these cases have not been brought together for a common review. An effort to systematically examine all KFD/AOSD patients for common characteristics and/or differences would represent a useful step in understanding the co-occurrence of these diseases and might shed light on the biology of these individual diseases.

We observed a patient who suffered from KFD/AOSD, the first such case to be treated with anti-IL-1β therapy. We herein present our index case and review and analyze all KFD/AOSD patients reported to date. We further detail the clinical, pathologic, and laboratory data relating to each patient, their treatments, and outcomes. Our observations should help clinicians identify cases where there may be an overlap of these two diseases and provide insight into their common pathogenic mechanisms.

## Methods

We encountered and treated the index patient during routine clinical care. A PubMed literature search was subsequently conducted to identify additional cases of KFD/AOSD. Search terms utilized included "Adult-onset Still's Disease," "Still's Disease," "Kikuchi's Disease," "Kikuchi- Fujimoto's Disease," and "Histiocytic Necrotizing Lymphadenitis." Boolean searches were conducted combining the first two, Still's-related terms with the third, fourth, or fifth KFD-related terms. References so obtained were evaluated to identify case reports and/or case series. The references cited in these reports were reviewed to identify any additional cases. All identified cases were reviewed, and a comparison of the clinical and laboratory data was conducted. In addition, the different treatment options and responses were compared between the cases.

## Results

### Index case

A 22-year-old male from Bangladesh presented to his primary care physician with fever and sore throat. The patient's physical exam was unremarkable; a diagnosis of streptococcal pharyngitis was excluded by rapid antigen detection test, and the patient was discharged home. However, his fevers persisted intermittently, and 2 months later, he additionally developed painful cervical lymphadenopathy, along with an evanescent rash on the face, trunk, and legs. The rash consisted of erythematous-to-violaceous indurated papules and plaques on the forehead, temples, dorsal nose, and cheeks, a few with overlying collarettes of scale (Fig. 1a). Similar lesions were present over the right clavicular area (Fig. 1b), and patches and plaques were seen on the upper back (Fig. 1c). Tender posterior cervical lymphadenopathy was observed bilaterally (left > right), with overlying violaceous erythema (Fig. 1d). No palmar, plantar, or mucosal lesions were noted.

The patient was admitted to the hospital for evaluation, and a skin biopsy was performed. Hematoxylin and eosin staining revealed superficial and deep perivascular and periadnexal dermatitis with focal interface changes (Fig. 2a–d). Periodic

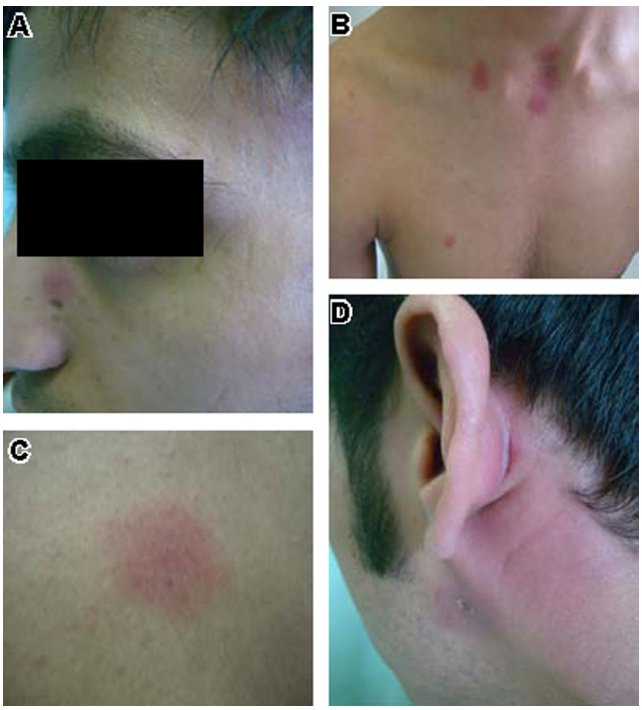


**Fig. 1** Clinical appearance of the index patient's rash. **a** Erythematous and violaceous lesions on the temple, cheek, forehead, and nose. **b** Truncal macules in the sternoclavicular and anterior chest regions, together with faint diffuse erythema over the anterior chest and right shoulder. **c** Plaque on the upper back. **d** Postauricular involvement, including swelling indicative of cervical lymphadenopathy

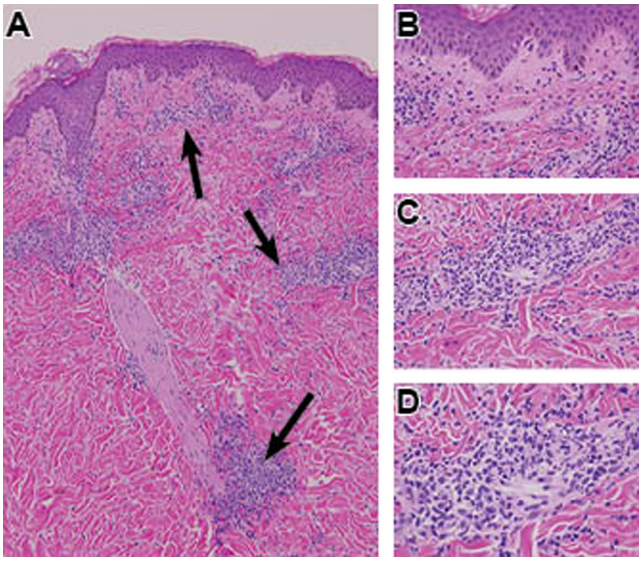


**Fig. 2** Hematoxylin and eosin staining of skin biopsy of the index patient. **a** Superficial and deep perivascular and periadnexal infiltrates (*top*, *middle*, and *bottom arrows*, respectively). **b**–**d** Magnifications of specific regions of **a** illustrating the following: **b** focal interface changes/inflammation near the dermal-epidermal junction; **c** infiltrate comprised of lymphocytes, histiocytes, and non-neutrophilic nuclear dust; and **d** enlargement of the image from **c** illustrating perivascular involvement

acid-Schiff stain revealed a normal thickness basement membrane, but a colloidal iron stain demonstrated increased deposits of connective tissue mucin (Fig. 3a). These findings were initially considered by the dermatopathology service to

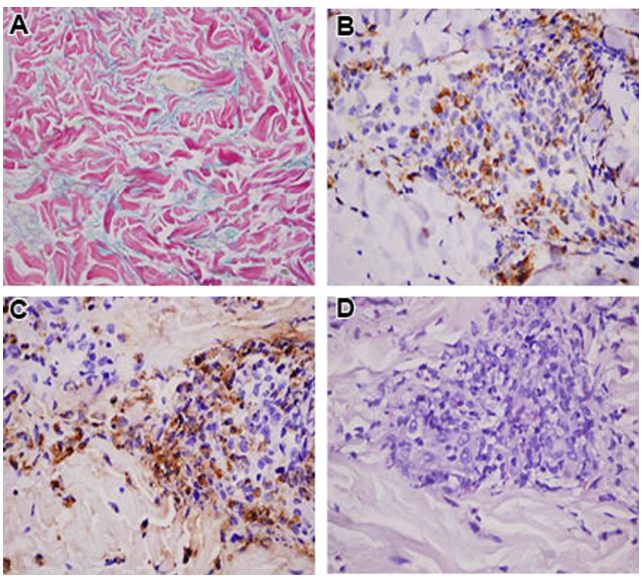


**Fig. 3** Special stains of skin biopsy from the index patient. **a** Colloidal iron stain demonstrating increased deposits of connective tissue mucin (*light blue areas*). **b** Positive immunohistochemical reaction for CD68, a marker for macrophages. **c** Positive immunohistochemical reaction for myeloperoxidase, a marker for granulocytes. **d** Negative reaction for the Leder (chloroacetate esterase) stain, a marker for neutrophils. The combination of a positive stain for macrophages, together with a marker for granulocytes (neutrophils and macrophages) and a negative stain for neutrophils, is specific for a macrophage infiltrate

be consistent with SLE. However, serologic testing failed to support a diagnosis of SLE or other autoimmune conditions (Table 2). Additional laboratory results obtained at the time included a total leukocyte count of 14,000/mm$^3$ (92 % neutrophils), serum ferritin of 451 ng/mL, aspartate aminotransferase level (AST) of 47 U/L, and alanine aminotransferase level (ALT) of 56 U/L. The erythrocyte sedimentation rate (ESR) was 20 mm/h, and C-reactive protein (CRP) concentration was 1.0 mg/dL. Contrast-enhanced computerized tomography (CT) of the neck confirmed the presence of scattered, mildly enlarged cervical lymph nodes; a cervical lymph node biopsy was performed, but the specimen obtained was considered inadequate for pathologic interpretation. CT scanning of the abdomen and pelvis, as well as a transthoracic echocardiogram, revealed no relevant abnormalities. The patient was discharged on ibuprofen 800 mg as needed.

Four months later, the patient was readmitted for ongoing fevers, fluctuating rash, neck discomfort, and new-onset polyarthritis of the wrists, ankles, knees, and shoulders. The patient reported that his fevers now occurred almost daily but were not consistently concurrent with the expression of the rash. Physical examination confirmed synovitis of the hands, knees, and ankles. Autoantibodies continued to be absent, and radiographic studies of the involved joints revealed no abnormalities. Serum transaminase levels remained only mildly elevated. However, his ESR was now 119 mm/h, CRP was 14.2 mg/dL, and serum ferritin was 2,052 ng/mL. Blood cultures and serologic testing were negative for possible infection (Table 2). A bone marrow biopsy revealed no evidence of malignancy, hemophagocytic lymphohistocytosis, or other specific abnormality. Positron emission tomography confirmed only the presence of small hypermetabolic lymph nodes in the bilateral neck, axillae, and mediastinal, hilar, abdominal, and pelvic regions. The surgical team again considered lymph node biopsy, but deferred given the small size of lymph nodes. Instead, review and additional immunohistochemical stains were performed on the prior skin rash biopsy. In addition to the focal interface changes and connective tissue mucin seen previously (Fig. 3a), non-neutrophilic nuclear dust was now recognized in several sections (Fig. 2c, d). Observed within the perivascular and periadnexal infiltrate were many histiocytes positive for CD68 (Fig. 3b) and myeloperoxidase (Fig. 3c) but negative for chloroacetate esterase (Leder stain, Fig. 3d; a mast cell marker) and CD34 (not shown).

Based on the re-evaluation of the skin biopsy, as well as the patient's initial presentation with localized cervical lymphadenopathy, a diagnosis of KFD was now assigned. Ibuprofen at the maximum standing dose (800 mg three times daily) was initiated, but the patient continued to experience persistent daily fevers and evanescent rash. Given that the patient now also met criteria for AOSD (arthritis, fever, transaminitis, diffuse lymphadenopathy, and negative ANA/RF, along with the characteristic elevation in ferritin [5]), a diagnosis of KFD/

AOSD overlap was rendered, and a trial of anti-IL-1β therapy using anakinra was initiated. Within 24 h, the patient's fevers, rash, cervical pain, and arthritis resolved completely. His laboratory abnormalities also resolved within days of treatment. At a 3-month follow-up visit, the patient remained on anakinra and remained asymptomatic with complete resolution of laboratory abnormalities, synovitis, rash, fevers, and lymphadenopathy.

## Review of previously reported cases

Our directed literature search yielded eight additional reports of KFD/AOSD. All cases were reviewed with regard to age, sex, and race/ethnicity, along with the presence of fever, rash, arthritis, lymphadenopathy, and duration of symptoms. Patient characteristics, including those of the index case, are summarized in Table 1. The patients' ages ranged from 14 to 47. Fever was present in all patients. Rash was also present in all patients, ranging from urticarial lesions (two patients) to non-pruritic erythematous papules (three patients). Arthritis was present in all cases, ranging from small joint involvement to knee and ankle involvement. Lymphadenopathy was present in all patients. Three patients had only cervical involvement, whereas six of nine had disseminated lymphadenopathy. Duration of symptoms ranged from 3 weeks to 10 years. A review of the laboratory and pathologic findings was also performed (Table 2). Evaluation for infection was negative in eight patients; the ninth patient tested positive for HSV 1 and 2 IgM by serum ELISA, although a skin biopsy of his rash was negative for HSV by PCR and culture. Autoantibodies were absent from all patients' sera.

Lymph node biopsies were performed successfully in eight patients, and all were interpreted as consistent with KFD. Our index patient underwent attempted lymph node biopsy, but the sample was insufficient. Nevertheless, our index case did have a skin biopsy that was consistent with KFD [14]. In particular, immunohistochemical staining of the skin biopsy showed an abundance of histiocytes positive for CD68 and myeloperoxidase, a finding seen in the lymph node biopsies of patients with KFD. This finding was also documented in a review of 16 cases of cutaneous lesions in KFD [15–17].

A review of the reported treatment options and outcomes was conducted and is summarized in Table 3. Six patients treated initially with glucocorticoids experienced marked improvement or complete resolution of their signs and symptoms of both AOSD and KFD. The index patient was the only one treated with anti-IL-1β therapy; he experienced a rapid and complete resolution of his fever, arthritis, rash, and lymphadenopathy accompanied by a rapid normalization of inflammatory markers and transaminitis. These improvements were observed in the absence of glucocorticoid therapy.

**Table 1** Reported cases of KFD/AOSD: clinical characteristics

| Reference | Age, gender, race/ethnicity | Fever | Rash | Arthritis | Lymphadenopathy | Duration of symptoms |
|---|---|---|---|---|---|---|
| Cousin et al. [4] | 32, M, Caucasian | Present | Non-pruritic, indurated, erythematous papules on the face, ears, and trunk | Right ankle, left knee | Cervical, axillary, inguinal | 8 months |
| Lyberatos [11] | 18, M | Present | Present | Bilateral knees | Generalized | 4 months |
| Lyberatos [11] | 47, F | Fever spikes in the evening | Present | Symmetrical fleeting arthritis in the upper extremities | Cervical, axillary | 4 years |
| Ohta et al. [10] | 41, M, Japanese | Present | Non-pruritic erythematous papules on the face | Bilateral hands, knees, and wrists | Cervical, axillary, inguinal | 1 year |
| Ohta et al. [10] | 14, F | Daily spiking fever | Non-pruritic rash on trunk and proximal upper extremities | Wrists | Cervical | 3 weeks |
| Ohta et al. [10] | 19, M, Japanese | Daily spiking fever | Present | Proximal interphalangeal joints bilaterally | Generalized | 1 year |
| Garazzi et al. [13] | 24, F, Indian | Fever spikes in the evening | Urticarial lesions on the face and trunk | Proximal, interphalangeal, and distal interphalangeal joints bilaterally; wrists, knees, ankles, and temporomandibular joints | Cervical | 10 years |
| Miura and Yamamoto [12] | 21, F, Japanese | Present | Urticarial facial erythema on the bilateral cheeks; brownish plaques on the upper back, linear erythema on the lower extremities | Diffuse arthralgias documented | Cervical | Not reported |
| Index case | 22, M, Bangladeshi | Fever spikes in the evening | Papules and plaques on the face and right clavicular area; patches and plaques on the back | Hands, knees, ankles | Initially cervical, then diffuse | 8 months |

**Table 2** Reported cases of Kikuchi's disease (KD) associated with Still's disease: review of laboratory and pathologic findings

| Reference | Leukocyte count | Anemia | Hyperferritinemia | ESR | Transaminitis | Evaluation for infection | Evaluation for serologies/ autoantibodies | Lymph node biopsy consistent with KD | Other characteristics |
|---|---|---|---|---|---|---|---|---|---|
| Cousin et al. [4] | 12,500/mm$^3$ (80 % neutrophils, 16 % lymphs, 4 % monocytes) | Absent | Present | Elevated | Absent | Negative, including syphilis, streptococcus, toxoplasmosis, mycoplasma, brucella, *B. burgdoferi*, parvovirus, Hep B and C, HSV 1, 2, and 6, CMV, leptospirosis, rickettsia all ruled out. IgM HSV detected by ELISA. HSV PCR done on skin biopsy was negative | Negative, including ANA, anti-dsDNA antibodies, and RF | Present | Presented with rash on the face, ears, and trunk suggestive of subacute lupus erythematosus |
| Lyberatos [11] | 28,000/mm$^3$ | Present | Not reported | Not reported | Present | Negative | Negative | Present | Course complicated by DIC, pericarditis, renal failure, and progressive severe anemia |
| Lyberatos [11] | Not reported | Not reported | Not reported | Not reported | Normal liver biopsy | Negative | Negative | Present | Sore throat and neck stiffness |
| Ohta et al. [10] | 4,300/mm$^3$ | Present | Not reported | 45 mm/h | Present, mild | Negative | Increased c1q noted | Present | Sore throat, splenomegaly |
| Ohta et al. [10] | 19,900/mm$^3$ | Not reported | 24,680 ng/mL | Elevated | Present | Negative | Negative | Present | Sore throat, hepatomegaly |
| Ohta et al. [10] | 9,800/mm$^3$ | Not reported | Not reported | Elevated | Present | Negative | Initial evaluation negative, xerostomia later diagnosed as Sjogren's syndrome based on salivary gland biopsy | Present | Hepatosplenomegaly |
| Garazzi et al. [13] | 18,000/mm$^3$ (neutrophil predominant) | Hgb 10.6 g/dL | Normal | 80 mm/h | Not reported | Negative | Negative, including ANA, anti-dsDNA antibodies, and RF | Present | Sore throat, 1.5-fold increase in serum LDH level |
| Miura and Yamamoto [12] | 20,800/mm$^3$ | Not reported | 2,349 ng/mL | 64 mm/h | Present | Negative, including EBV, parvo B19, CMV, and rubella | Negative | Present | Presented with lupus-like facial erythema |
| Index case | 19,000/mm$^3$ (92 % neutrophils) | Absent | 2,052 ng/mL | Elevated | AST 47 U/L, ALT 53 U/L | Negative, including EBV IgM, parvo B19, CMV, syphilis, bartonella, brucella, borrelia, histoplasma, mycoplasma, tuberculosis, leptospirosis, streptococcus, ehrlichiosis, *Rickettsia rickettsii*, hepatitis B and C, HSV, coxsackievirus, HIV, HSV 1 and 2 | Negative including ANA, RF, anti-CCP, dsDNA, Ro, La, Scl-70, Smith, RNP, and aCL antibodies; negative cANCA, pANCA, cryoglobulins, lupus anticoagulant, C3, C4, IgA, IgM, IgE, IgG, IgG4, and ACE levels WNL | Biopsy specimen not adequate | Initially presented with sore throat and neck stiffness |

**Table 3** Reported cases of Kikuchi-Fujimoto's disease (KFD) associated with Still's disease: review of treatments and response

| Reference | Age, sex, race | Treatment | Response |
|---|---|---|---|
| Cousin et al. [4] | 32, M, Caucasian | Acyclovir/valacyclovir | No response |
| | | Steroids | Marked improvement |
| Lyberatos [11] | 18, M, race not reported | Steroids | Asymptomatic at 3 months |
| Lyberatos [11] | 47, F, race not reported | Aspirin | Asymptomatic |
| Ohta et al. [10] | 41, M, Japanese | NSAIDs | No response |
| | | Steroids | Marked improvement |
| Ohta et al. [10] | 14, F, Japanese | Steroids | Marked improvement |
| Ohta et al. [10] | 19, M, Japanese | Indomethacin/aspirin | Partial response |
| | | Intramuscular gold | Initial but transient benefit for arthritis |
| | | Steroids | Improvement |
| Garazzi et al. [13] | 24, F, Indian | NSAIDs | Initial but transient benefit |
| | | Methotrexate | Good effect |
| Miura and Yamamoto [12] | 21, F, Japanese | Steroids | Successful treatment |
| Index case | 22, M, Bangladeshi | Anakinra | Asymptomatic at a 3-month follow-up |

## Discussion

We reviewed nine cases of KFD/AOSD and observed several commonalities. All had fever, rash, arthritis, and lymphadenopathy, findings that can independently occur in either KFD or AOSD alone [3, 5]. However, these findings may also serve to distinguish KFD/AOSD from either entity individually. For example, in isolated KFD, no more than 30 % of patients have been reported to have a rash. Therefore, the fact that all of the KFD/AOSD patients had rashes would be atypical for KFD alone [4]. Conversely, none of the KFD/AOSD cases demonstrated the classic temporal association of rash and spiking fever that is considered characteristic of AOSD [5]. Importantly, the clinical appearance of our index patient's rash was typical for KFD but atypical for AOSD, as the AOSD rash is typically composed of thin pink papules. Persistent plaques have recently been reported in AOSD, findings also not seen in our patient's case [18]. Thus, the reported patients with KFD/AOSD demonstrated several clinical features that were typical for KFD, but not for AOSD alone.

Conversely, patients with concurrent KDF/AOSD had other features that were typical for AOSD, but atypical for KFD alone. Most of the patients with KFD/AOSD had generalized rather than isolated cervical lymphadenopathy. Additionally, the leukocytosis and markedly elevated ferritin levels that were observed in most of the KFD/AOSD patients would be atypical for KFD alone [3, 19]. Arthritis is a feature of AOSD, but not typically of KFD (in which arthralgias are more common), and the equal sex distribution of the nine cases (5 M:4 F) is more typical of AOSD than KFD [3, 20, 21]. Perhaps because of the complexity of their cases, and the need to consider and rule out other conditions (neoplasia, infection, autoimmune and autoinflammatory diseases, atrial myxoma, sarcoid, etc.), patients with KFD/AOSD had symptom durations of at least 4 months before receiving a diagnosis—longer than the typical duration for isolated KFD, but common for AOSD (see Table 2).

The presence of histologic skin findings that were consistent with KFD, but inconsistent with AOSD only, further supported a diagnosis of concurrent KFD/AOSD in our index patient. In 2010, Kim et al. published criteria for the diagnosis of cutaneous lesions of KFD based on two major criteria and two minor criteria. Our index patient met the major criteria with the presence of karyorrhexis and lack of neutrophils, as well as most of the minor criteria including (1) infiltration of reticular dermis or subcutaneous fat tissue with inflammatory cells, (2) presence of interface dermatitis, and (3) the histiocyte as the dominant inflammatory cell (defined by the presence of CD68 and myeloperoxidase with an absence of esterase and CD34). (In contrast to the final minor criterion—a predominance of CD8+ cytotoxic vs CD4+ lymphocytes—our index patient's biopsy showed a ratio of 6:1 of CD4+ to CD8+ lymphocytes.) Interestingly, these findings have also been reported in lymph node biopsies of patients with KFD [16, 17, 22]. In another series reported by Kim et al., 5 of 16 KFD patients harbored mucin in their skin biopsies [15], a feature shared by our patient's biopsy. Thus, although we were not able to obtain an informative lymph node biopsy from our index patient, the histologic features of his skin biopsy unequivocally supported a KFD, rather than an isolated AOSD diagnosis [23].

The co-occurrence of KFD/AOSD in the same patient may offer a window into the potential pathophysiologic mechanisms they share. A number of inflammatory mediators have been associated with KFD or AOSD individually, including IL-6, IL-18, and IFN-γ [24, 25]. Although IL-1β has been

shown to play a role in apoptosis, and apoptosis has been shown to be a key finding noted in the lymph nodes of patients with KFD [26, 27], the role of IL-1β in KFD has not yet been established. Given that both the KFD and AOSD aspects of our index patient's disease resolved rapidly upon IL-1β inhibition, we hypothesize that KFD pathogenesis may involve IL-1β dysregulation and that KFD alone might also respond to anti-IL-1β-targeted strategies.

**Disclosures** None.

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