Kikuchi-Fujimoto disease preceded by lupus erythematosus panniculitis: do these findings together herald the onset of systemic lupus erythematosus?

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Abstract

Kikuchi-Fujimoto disease (KFD), also known as histiocytic necrotizing lymphadenitis, is a rare disorder that must be distinguished from systemic lupus erythematosus (SLE). Although a minority of patients with KFD develop SLE, most patients have a self-limited disease. Importantly, KFD can have skin manifestations resembling cutaneous lupus. Therefore, the diagnosis of SLE should be predicated on a complete rheumatologic workup and not on the constellation of skin disease and lymphadenitis. Nonetheless, as our exceedingly rare case illustrates, patients who do not initially meet diagnostic criteria for SLE require dermatologic follow-up. We present a young adult woman who had a remote history of KFD and later presented with combined features of discoid lupus and lupus erythematosus panniculitis (LEP). On subsequent rheumatologic workup, she fulfilled criteria for SLE. We discuss the differential diagnosis of both KFD and LEP and emphasize how strong communication among dermatologists and other healthcare providers is essential in the management of patients with KFD.

Keywords: Kikuchi-Fujimoto disease, systemic lupus erythematosus, lupus erythematosus panniculitis, lupus profundus

Introduction

Kikuchi-Fujimoto Disease (KFD), also known as histiocytic necrotizing lymphadenitis, is a rare disorder that must be distinguished from systemic lupus erythematosus (SLE). It is characterized by painful cervical lymphadenopathy, leukopenia, and systemic symptoms including fever and malaise [1,2]. The etiology of KFD is unknown, but infectious and autoimmune etiologies have been postulated [2]. A correlation between KFD and SLE is well-documented, with reports of SLE diagnoses established before, during, and after KFD diagnoses [3]. Furthermore, the histologic features of KFD are often indistinguishable from lupus lymphadenitis, which supports the prevailing opinion that findings of KFD in the lymph node of a patient with SLE should be interpreted as a manifestation of lupus and not KFD. The distinction between KFD and lupus lymphadenitis would be most important when patients develop KFD without additional criteria to establish a diagnosis of SLE. This is important because KFD is considered a benign and self-limited disorder. In contrast, SLE can be life-threatening, requiring coordination of care among a multidisciplinary network of healthcare providers [4]. Therefore, the diagnosis of KFD should be made with the caveat that histologic findings can be indistinguishable from those of lupus and patients should be monitored for the dermatologic and

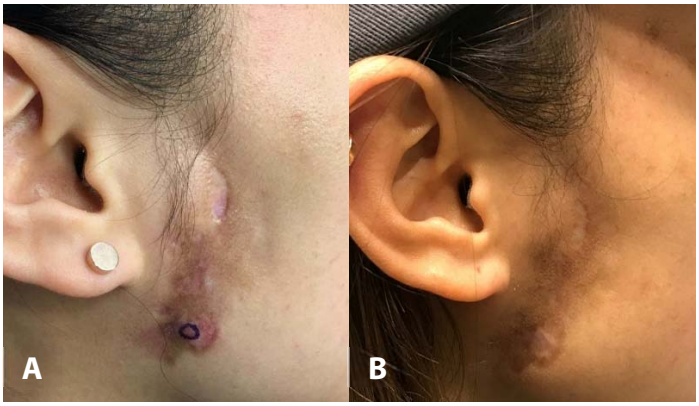

Figure 1. *Discoid lupus overlying lupus erythematosus panniculitis.* ***A)*** *An atrophic hyperpigmented plaque with sclerotic foci, erythema, and an underlying lipodystrophy.* ***B)*** *Follow-up photograph at six months with hydroxychloroquine, methotrexate, and topical tacrolimus therapy.*

extracutaneous manifestations of both diseases [5,6]. We present an exceedingly rare and illustrative case of KFD-lupus overlap, review the pertinent literature on how KFD and SLE can be distinguished, and discuss the implications for practicing dermatologists and dermatopathologists.

Case Synopsis

A 25-year-old woman of east Asian ancestry presented to the dermatology clinic for cosmetic laser treatment of a brown, atrophic, sclerotic, and indurated plaque on her right preauricular region (**Figure 1A)**. This plaque was believed to be the sequela of a two-year history of parotitis that was refractory to systemic antibiotics and topical corticosteroids. On questioning, the patient endorsed a history of photosensitivity, complex oral aphthae, fatigue, and arthralgia. Physical examination revealed no additional discoid lesions, evidence of scarring alopecia, or dermatitis. A punch biopsy of the plaque showed combined features of discoid lupus and lupus erythematosus panniculitis (LEP) including brisk lichenoid interface, perivascular, periadnexal, and subcutaneous lymphocytic inflammation with hyaline lipomembranous fat necrosis (**Figure 2**). The patient's complete blood count (CBC), complete metabolic panel (CMP), and lipid panel were within normal limits. An antinuclear antibody (ANA) titer was 1:320 with a speckled pattern. Extractable nuclear antigens (ENA) and anti-double-stranded DNA (anti-dsDNA) were negative, no antibodies against cardiolipin or beta2-glycoprotein-I were identified, and C3 level was within normal limits. Altogether, the clinical, histologic, and serologic findings supported the diagnosis of SLE.

The patient's past medical history was also notable for lymphadenitis at age 16. An excisional biopsy of a tender left cervical lymph node had revealed non-infectious necrotizing lymphadenitis with a paucity of neutrophils, which suggested a differential diagnosis of KFD versus lupus lymphadenitis (**Figure 3**). Neither hematoxylin bodies nor Azzopardi phenomenon were present to favor lupus and a battery of special stains, immunohistochemical stains, and *in situ* hybridization study, including Epstein-Barr encoding region, human herpes virus 8, acid-fast bacillus, Gömöri methenamine silver, and periodic acid–Schiff helped to exclude an infectious etiology. Given her young age, ethnicity, isolated lymphadenitis, and absence of additional clinical findings at the time, a presumptive diagnosis of KFD

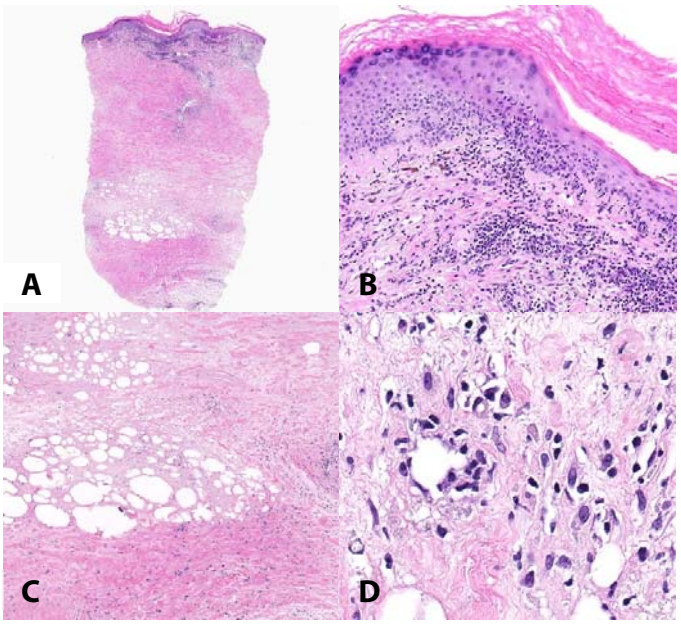

Figure 2. *Lupus erythematosus panniculitis and discoid lupus.* ***A)*** *Interface, perivascular, and subcutaneous inflammation is present. H&E, 2x.* ***B)*** *Florid interface dermatitis with basement membrane alterations, pigment incontinence, epidermal atrophy, and scale. H&E, 100x.* ***C)*** *Hyaline lipomembranous fat necrosis in an area of resolving lobular panniculitis. H&E, 100x.* ***D)*** *Inflammation with histiocytes, lymphocytes, and plasma cells. Some lymphocytes encircle adipocytes. H&E, 400x.*

had been established. Curiously, at the time KFD was diagnosed, her ANA titer was 1:2560 with a speckled pattern. However, an elevated titer in isolation does not warrant a diagnosis of SLE by the American College of Rheumatology or the Systemic Lupus International Collaborating Clinics criteria [7,8]. The patient was lost to dermatologic follow-up for almost a decade before presenting with the preauricular plaque.

On 6-month follow-up, her symptoms have responded well to hydroxychloroquine, methotrexate, and intramuscular triamcinolone. Scarring, mild lipoatrophy, and pigmentary alterations are evident at the right preauricular region despite treatment with systemic, topical, and intralesional corticosteroids. However, the plaque has not increased in diameter (**Figure 1B)**.

Case Discussion

Kikuchi-Fujimoto disease was described almost simultaneously by Kikuchi and Fujimoto in 1972 [9,10]. Although it has been documented in patients of various racial and ethnicities, there is a noted prevalence among women of east Asian ancestry with a typical disease onset in the early twenties to mid-thirties [4]. Kikuchi-Fujimoto disease most frequently involves the cervical lymph nodes, although generalized lymphadenopathy and involvement of retroperitoneal, peritoneal, mediastinal, inguinal, axillary, supraclavicular, and intraparotid nodes has been described [4,11-14]. Hepatosplenomegaly has also been reported [13]. Patients usually describe low-grade fever, malaise, and night sweats [4]. Laboratory abnormalities are nonspecific and can include anemia, leukopenia,

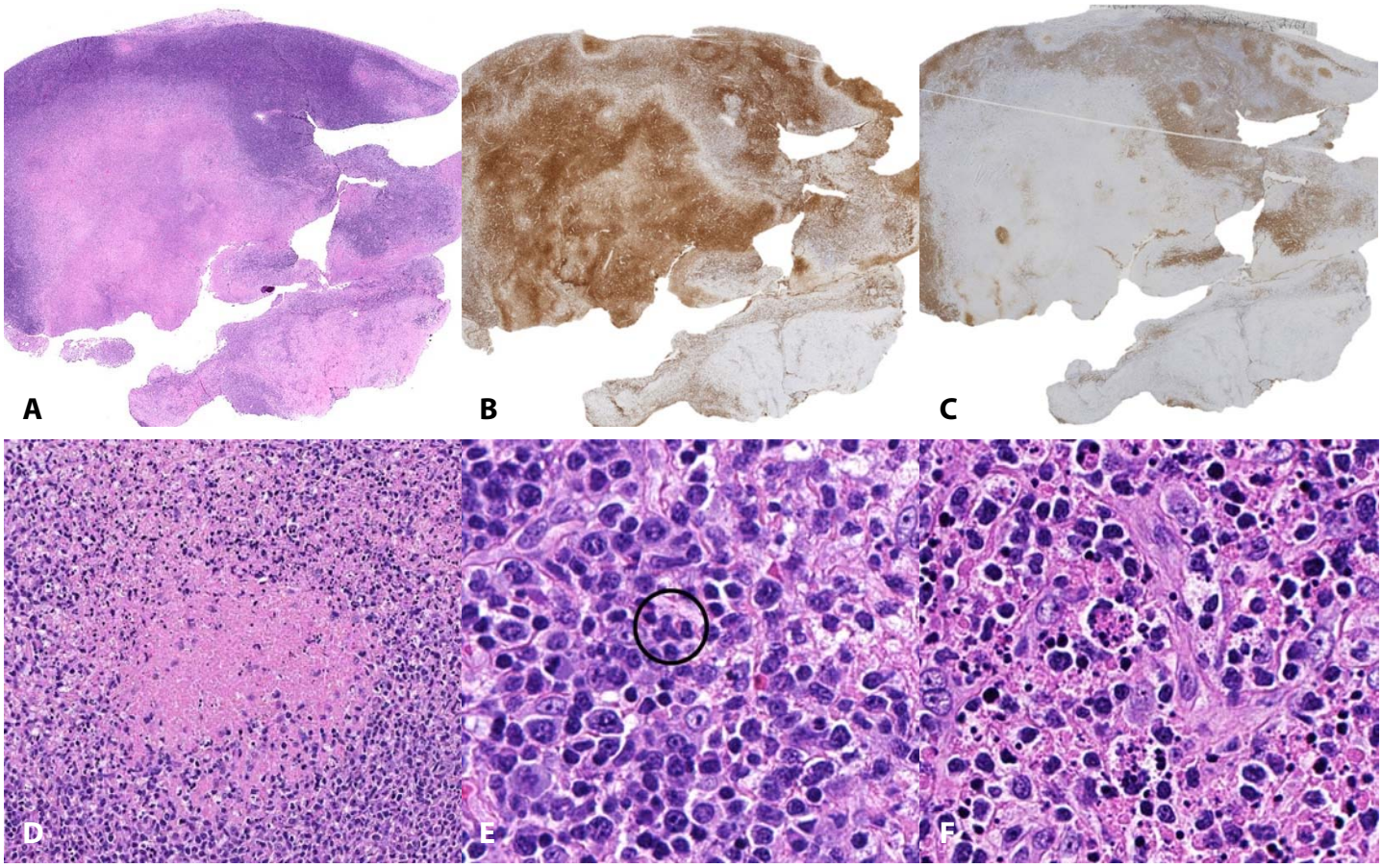

Figure 3. *Necrotizing lymphadenitis.* ***A)*** *A large portion of lymph node architecture is effaced by necrosis. Some smaller, clearly demarcated zones of necrosis are visible at the node periphery. H&E, 2x.* ***B)*** *CD3 immunostain highlights a preponderance of T-cells in areas with necrosis. CD3, 2x.* ***C)*** *CD20 highlights relatively sparse B-cells in these areas. CD20, 2x.* ***D)*** *A roughly circumscribed, demarcated focus of necrosis expanding the paracortex in the most preserved portion of the lymph node is surrounded by histiocytes. H&E, 100x.* ***E)*** *Crescentic histiocytes (circled) adjacent to the necrosis are accompanied by immunoblasts, foamy histiocytes, and plasmacytoid cells. H&E, 40x.* ***F)*** *Macrophages ingesting nuclear debris are present at the center of the necrosis. Neutrophils and eosinophils were not identified. H&E, 40x.*

presence of atypical lymphocytes on peripheral blood smear, elevated liver function tests, elevated lactate dehydrogenase, and elevated erythrocyte sedimentation rate [15]. Anti-nuclear antibodies have been described in patients with KFD. In one investigation, however, 23 of 33 patients with KFD and a positive ANA titer had or developed SLE. Overall, 13-25% of patients with KFD-like disease will have a prior, concomitant, or subsequent diagnosis of SLE [16-18]. Nonetheless, most patients with KFD never meet criteria for SLE. Therefore, it is unclear whether KFD represents a *forme fruste* of SLE or an etiologically distinct lymphadenopathy with both clinical and histologic overlap [2]. The concomitant occurrence of KFD in autoimmune diseases distinct from SLE [13,19,20] offers equivocal evidence to support the latter postulate; however, SLE is the most commonly reported autoimmune disease association [12,13]. Nonetheless, a clinical work-up is required to exclude SLE in any patient receiving a diagnosis of KFD regardless of their antecedent medical history.

In KFD, lymph nodes show paracortical expansion by demarcated histiocytic infiltrates with central necrosis. Karyorrhectic debris, histiocytes (sometimes with crescentic nuclei), and enlarged lymphoid cells resembling plasmacytoid dendritic cells and immunoblasts are often present [15,16]. In cases with little necrosis, these infiltrates are sometimes confused with lymphoma [12]. Conspicuously absent from KFD are neutrophils, which are sometimes present in lupus lymphadenitis. Lupus lymphadenitis and KFD share the remainder of these histologic findings. However, the presence of neutrophils, hematoxylin bodies, and the Azzopardi phenomenon would favor lupus [4]. Yet, many cases of lupus lymphadenitis, including the present example, are devoid of these distinguishing features [3,21,22]. Extensive effacement of nodal architecture, which was identified in the present case and contrasts with the patchy, delineated foci of paracortical necrosis often seen in KFD, is also more common in lupus [4]. However, the amount and localization of necrosis can vary widely in KFD [12].

The combination of discoid lupus and LEP is an uncommon finding in cutaneous lupus erythematosus, identified in only 2% of patients [23]. It has a female-to-male ratio of 4:1 [24]. Approximately one third of patients with LEP will have discoid lupus and only 10%-24% of patients with LEP meet criteria for SLE [24-26]. The differential diagnosis includes other autoimmune disease-associated panniculitides [27] and subcutaneous panniculitis-like T-cell lymphoma (SPTCL), which can be distinguished by lymphoid cytologic atypia, a preponderance of cytotoxic CD8-positive cells surrounding adipocytes, Ki-67 hotspots, and T-cell clonality [28,29]. In rare circumstances, KFD can also have skin manifestations that mimic lupus replete with panniculitis. Of great importance to dermatologists, some investigations have reported skin findings in 33% to 40% of patients with KFD, with a majority of biopsies revealing interface dermatitis [5]. Notably, Kim et al. presented a series of 16 patients with cutaneous KFD after excluding from the study patients with concomitant or previous diagnoses of SLE [6]. In their case series, vacuolar interface changes, necrotic keratinocytes, superficial and deep lymphohistiocytic infiltrate, dermal mucin, and less frequent panniculitis were identified. In these exceedingly rare cases, a complete rheumatologic workup and follow-up is required to distinguish KFD with cutaneous manifestations from SLE.

Interestingly, Notaro et al. reported a case of SPTCL in a patient with KFD [30]. SPTCL is conventionally understood to be an indolent cytotoxic T-cell lymphoma comprised of CD8-positive lymphocytes that rim adipocyte lobules. Although we now understand that a proportion of cases are hereditary, owing to an underpinning mutation in *HAVCR2* [31,32], the etiology of many cases remains elusive. SPTCL occasionally shows striking histologic overlap with lupus panniculitis [33] and some patients, including those with wild type *HAVCR2*, have underlying autoimmune diatheses including SLE [34]. Although there is excellent overall survival, the low SPTCL mortality rate is almost invariably attributable to concomitant hemophagocytic lymphohistiocytosis (HLH), which can occur albeit

with a much lower frequency in the settings of SLE, KFD, and SLE/KFD overlap [13,35,36]. Therefore, patients presenting with KFD or LEP should also be monitored for the development of HLH and efforts, including T-cell clonality testing, can be considered in select cases to help exclude SPTCL. T-cell clonality testing was not ordered in our case as the clinical and histomorphologic findings argued against SPTCL. In particular, the presence of interface changes, localization on the face, and lipoatrophy were more in keeping with LEP. Although the patient described by Notaro et al. had developed HLH as a sequela of his concomitant SPTCL and KFD, he did not meet criteria for SLE.

Conclusion

Although a correlation between KFD and SLE has been established in the hematology literature, it is important for dermatologists, particularly those who specialize in the care of patients with rheumatologic illnesses, to be familiar with KFD and consider it in the differential diagnosis of SLE when patients present with rash and lymphadenitis. Our patient fulfilled clinical criteria for SLE years following the onset of a lymphadenitis that was clinically and histologically indistinguishable from KFD. The development of cutaneous lupus erythematosus in a patient with concomitant or pre-existing KFD should prompt a workup for SLE. However, care should be taken to avoid an over-diagnosis of SLE since skin manifestations are common in KFD and the disease is often self-limited. Exceedingly rare cases, such as ours, underscore how it is important for patients with a KFD diagnosis to be followed closely since there is presently no method of determining which patients will develop SLE. Nonetheless, ANA testing is indicated. Furthermore, when there is extensive involvement of the subcutaneous fibroadipose tissue, SPTCL should be excluded since SPTCL is associated with a much greater risk of HLH than what is generally reported in SLE, KFD, and LEP. It is incumbent on dermatologists and dermatopathologists to be familiar with KFD and ensure that KFD patients presenting with skin findings receive the appropriate management.

Potential conflicts of interest

The authors declare no conflicts of interests.

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