Overlap Between Systemic Lupus Erythematosus and Kikuchi Fujimoto Disease

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CPC: overlap between systemic lupus erythematosus and kikuchi fujimoto disease

Case presentation

A 33-year-old African-Caribbean man with a history of possible Kikuchi Fujimoto disease (KFD) versus systemic lupus erythematosus (SLE) was evaluated for 3 weeks of fevers to 38.9°C and cough accompanied by fatigue, anorexia, weight loss, diffuse rash, lymphadenopathy, and oral and nasal ulcers.

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Each author certifies that his or her institution has approved the reporting of this case, that all investigations were conducted in conformity with ethical principles of research.

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His past medical history was significant for a hospitalization for febrile neutropenia 2 years prior to this evaluation. At that time, he presented with 2 weeks of fever, shaking chills, malaise, arthralgia, and myalgia. This had been preceded by 2 months of fatigue, 10-lb weight loss, and the development of scarring alopecia. He was noted at this time to have had diffuse lymphadenopathy, including the occipital, anterior, and posterior cervical regions. He also was found to have malar erythema, oral ulcers, and a rash on his scalp, ears, face, chest, arms, and legs. The rash was characterized by erythematous, hyperpigmented papules, and plaques with scale, follicular plugging, and areas of scarring. He was treated empirically with intravenous (i.v.) piperacillin/tazobactam as his work-up ensued. His treating physicians were specifically concerned for an underlying malignancy, an autoimmune process, or an infectious process. His laboratory tests from his initial presentation showed anemia, leucopenia, an elevated erythrocyte sedimentation rate, and a twice normal level of lactate dehydrogenase (LDH; Table 1). Posteroanterior and lateral radiographs of the chest were normal. Blood cultures, urine cultures, and serologic work-up for a viral infection were negative (Table 2). Positive serologies for autoimmune disease included an anti-nuclear antibody (ANA) in a speckled pattern, Smith, ribonucleoprotein (RNP), and Ro, and a low C3 level (Table 2). Biopsies of the skin and one cervical lymph node were consistent with KFD. The patient was discharged from the hospital and followed by his internist with the putative diagnosis of KFD versus SLE. The internist recommended rheumatologic consultation, but the patient was not able to follow through. The patient was treated with hydroxychloroquine 200 mg daily as prescribed by his internist and felt generally well up until the time of his second hospitalization. He reported that if he missed his hydroxychloroquine for a few days, he would develop arthralgias and malaise.

At the time of his second admission, 2 years later, the patient complained of a mildly productive cough with dyspnea, fevers, malaise, increased rash, and increased lymphadenopathy. He described a preceding upper respira-

tory infection for which he was prescribed amoxicillin/clavulanate. He also noted oral and nasal ulcers, arthralgia, and myalgia. He denied sick contacts. His review of systems was negative for photosensitivity, sicca symptoms, Raynaud's phenomenon, pleurisy, gastrointestinal, neurologic, genitourinary, or other complaints. His medications at the time of presentation consisted of the amoxicillin/clavulanate 875/125 mg twice daily and hydroxychloroquine 200 mg daily. He had no known drug allergies, and his family history was noncontributory. He was a school bus mechanic and was married with two young children. He did not smoke, drink alcohol, or use illegal drugs.

The physical examination was significant for a temperature of 38.7°C, oral and nasal ulcers, malar erythema, discoid rash of face, scalp, ears, chest, back, arms, and legs, and diffuse cervical lymphadenopathy. The cardiopulmonary, abdominal, musculoskeletal, and neurologic examinations were normal. Laboratory values at that time are revealed anemia, leukopenia, elevated ESR, and serologies as shown (Tables 1 and 2). Rheumatologic consultation was obtained. Computerized axial tomography scan imaging was performed at this time, and the biopsies from the first admission were reviewed. The patient was treated with broad-spectrum antibiotics (piperacillin/tazobactam, 3.375 g i.v. every 6 h and levofloxacin 500 mg i.v. every 24 h) and prednisone 1 mg/kg. The hydroxychloroquine was increased to 400 mg daily. After 1 week, he became afebrile, and his white blood cell count normalized. He was discharged with a diagnosis of SLE with features of Kikuchi's disease and was treated with hydroxychloroquine 400 mg p.o. daily and a prednisone taper over 2 months. He has been seen in our clinic for 2 years following this episode and has been without flare of his disease.

Radiology discussion

In a computed tomography (CT) of the neck from the second admission multiple, multilevel cervical, supraclavicular, and prevascular superior mediastinal lymph nodes are seen, which are slightly larger than 1 cm. The largest lymph node in this region is 1.8×2.1 cm. Of note, 1 cm is the upper limit of normal in the neck. A 1.8-cm lymph node was measured in the anterior mediastinum (upper limit of normal in this region is 1.5 cm.) There were also enlarged subpectoral lymph nodes bilaterally (Fig. 1a, b). In the CT of the abdomen and pelvis, there are mildly enlarged lymph nodes in the paraaortic and inguinal regions. No evidence of necrosis is seen in any of the lymph node groups. In general, these are nonspecific findings, which may reflect reactive or neoplastic etiology.

Pathology discussion

Light microscopic findings

A left occipital lymph node biopsy showed a distorted nodal architecture with extensive areas of cortical and paracortical necrosis. The necrotic zones contained abundant nuclear debris surrounded by many histiocytes with crescent-shaped nuclei. Peripheral to the zones of necrosis were prominent lymphoid hyperplasia with transformed lymphocytes and immunoblasts along with a few admixed plasma cells and histiocytes. Neither hematoxylin bodies nor prominent neutrophilic infiltrate were observed (Fig. 2a, b). CD-123 staining demonstrated the presence of plasmacytoid dendritic cells (PDCs; Fig. 2c). In this example, there was some staining of endothelium as well. The pathologic impression of the lymph node was that of histiocytic lymphadenitis consistent with KFD but not exclusive of SLE.

Table 1 Basic laboratory tests

Value	Admission 1	Admission 2	Reference range
White blood cell	1.6	1.4	4.0–10.0×10 ⁹ /μL
Differential	N (55%), L (25%), M (9%), B (10%)	N (56%), L (33%), M (10%)	N (40–74%), L (19–48%), M (3.4–9%), B (0–1.5%)
Hemoglobin	11.3	11.0	12–16 g/dl
Platelet	183	177	150–350×10 ⁹ /μl
Sodium	131	141	135–145 mEq/l
Potassium	3.8	4.2	3.5–5.1 mEq/l
Chloride	96	115	98–106 mEq/l
Carbon dioxide	25	23	22–29 mEq/l
Urea nitrogen	12	5	7–19 mg/dl
Creatinine	0.9	0.8	0.6–1.2 mg/dl
Glucose	91	91	70–105 mg/dl
Total protein	8.5	5.9	6.0–8.3 g/dl
Albumin	3.8	2.6	3.7–5.1 g/dl
Total bilirubin	0.4	0.6	0.2–1.5 g/dl
Aspartate aminotransferase	107	85	3–50 U/l
Alanine aminotransferase	51	63	3–60 U/l
Alkaline phosphatase	68	51	20–125 U/l
Lactate dehydrogenase	890	356	105–333 U/l
International normalized ratio	1.07	1.07	0.8–1.2
Protime	12.0	10.7	11–13 s
Partial thromboplastin time	32.7	34.6	25–35 s
Sedimentation rate	65	22	0–15 mm/h
C-reactive protein	Not done	0.21	0–1 mg/dl

Table 2 Additional laboratory tests

Value	Admission 1	Admission 2	Normal Value
Anti-nuclear antibody	1:80, speckled pattern	1:320, speckled pattern	Negative
Anti-dsDNA	Negative	Negative	Negative
Anti-Smith	2.17	3.75	<1.00
Anti-RNP	>6.0	3.75	<1.00
Anti-SSA	3.0	2.6	<1.00
Anti-SSB	<1.00	<1.00	<1.00
C3	72	40.6	85–193
C4	16.5	19	12–36
Anticardiolipin	IgG, IgA, IgM <10	Negative IgG/M/A	<Negative IgG/M/A
Dilute Russel viper venom test	Normal	Normal	Normal
Anti B2 glycoprotein 1 antibody,	N/A	Negative IgG/M/A	Negative IgG/M/A
Myeloperoxidase antibody	0	0	<2 EU/ml
Proteinase 3 antibody	1	4	<6 EU/ml
Serum immune electrophoresis	IgA 447, IgG 1960, IgM 86, interpretation polyclonal hypergammaglobulinemia	IgA 386, IgG 1990, IgM 83, interpretation polyclonal hypergammaglobulinemia	IgA 70–312 mg/dl IgG 639–1,349 mg/dl IgM 56–352 mg/dl 9–67 U/l
Angiotensin converting enzyme	67	N/A	Negative
HIV antibody	Negative	N/A	<400 copies/ml
HIV viral load	<400	N/A	0.00–0.89
Parvovirus IgG/IgM	Ig G=2.1/IgM=0.4	N/A	IgG <10, IgM <20
HHV 6	IgG=10, IgM=<20	N/A	Nonreactive
HTLV	Nonreactive	N/A	0.00–0.90 ISR
EBV VCA IgM, VCA IgG, nuclear ag IgG	VCA IgM=0.32, VCA IgG >5.0, nuclear ag IgG 4.98, suggestive of past EBV infection.	N/A	
CMV IgM	Negative	N/A	Negative
Heterophile antibody	Negative	N/A	Negative
RPR	Nonreactive	N/A	Nonreactive
Antistreptolysin O titer	92	N/A	0–125 IU/ml
Hepatitis B sag	Negative	Negative	Negative
Hepatitis B core Ab	Negative	Negative	Negative
IgG and IgM			
Hepatitis B surface Ab IgG	Negative	Negative	Negative
Hepatitis C antibody	Negative	Negative	Negative

The bone marrow was approximately normocellular for the age of the patient. The myeloid to erythroid ratio was increased due to a relative increase in the myeloid series and a relative decrease in the erythroid series. Maturation was seen in both cell lines but is mildly left-shifted in the myeloid series. Megakaryocytes were increased in number. Plasma cells were seen in increased number, sometimes forming small collections. Immunostaining showed the plasma cells to be polytypic and with a normal kappa/lambda ratio of 2:1 to 3:1 (Fig. 3).

A 4-mm erythematous papule from the left forearm was biopsied and showed a cell-poor vacuolar interface dermatitis. There was a concomitant superficial perivascular lymphocytic and histiocytic infiltrate. A striking feature of the biopsy was prominent leukocytoclasia with engulfment of nuclear debris by histiocytes. The histiocytes had an almost bean bag morphology due to the extent of phagocytosis of apoptotic debris. In

addition, there were histiocytic forms with serpentine twisted nuclear contours and discernible eosinophilic cytoplasm without intracytoplasmic nuclear debris. Focal mural and fibrin deposition within vessels was noted (Fig. 4a, b). The scalp biopsy showed the same fundamental process but with more epidermal atrophy. There was also an interface change involving the follicle. Attendant hyperkeratosis and follicular plugging was noted, and the extent of mononuclear cell infiltration and degree of apoptosis and macrophage infiltration were more extensive (Fig. 5a, b).

Direct immunofluorescent and phenotypic studies

Direct immunofluorescent studies showed prominent deposits of immunoglobulin G (IgG), IgM, and IgA along the dermal epidermal junction, which defines a positive lupus

band test (not pictured). Phenotypic studies showed many lysozyme positive histiocytes. There was a dominance of CD8-positive lymphocytes over those of the CD4 subset, as demonstrated by granzyme and TIA-1 positivity. There were many CD123-positive PDCs. The MXA [which is a protein expressed in response to type I interferons (IFNs)] stain shows striking staining amidst perivascular inflammatory cells and showed epithelial staining primarily in an intercellular array and cytoplasmic array confined to the lower third of the epidermis (Fig. 6).

Clinical discussion

This is a case of a 33-year-old male patient with fevers, malar and discoid rashes, oral and nasal ulcers, lymphadenopathy, leukopenia, and positive ANA, anti-Smith, anti-RNP, and anti-Ro antibodies. He meets 5/11 American College of Rheumatology diagnostic criteria for SLE, which is more than the four required for definitive diagnosis; however, his prominent lymphadenopathy, leukopenia, and the histopathologic changes discussed above are reminiscent of KFD.

When the patient first presented, the differential diagnosis also included non-Hodgkin's lymphoma and Hodgkin lymphoma, sarcoidosis, human immunodeficiency virus, Epstein–Barr virus (EBV), bacterial infection, multicentric

Fig. 1. **a, b** CT scan of neck and chest showing diffuse lymph node enlargement without areas of necrosis (arrows)

Fig. 2. **a** Lymph node biopsy showing extensive necrosis surrounded by hyperplastic paracortex. **b** At higher magnification the necrosis is seen in association with transformed lymphoid cells, plasmacytoid dendritic cells, and histiocytes. **c** CD-123 staining highlighting plasmacytoid dendritic cells

Castleman's disease, tuberculosis, toxoplasmosis, cat-scratch disease, and metastatic carcinoma, all of which can present with lymphadenitis. Based on the patient's age, gender, and his systemic symptoms, Hodgkin lymphoma was an especially important consideration. These conditions, however, were all ruled out during his evaluation.

KFD, also known as histiocytic necrotizing lymphadenitis, was first described in 1972. It is classically seen in young Asian women. There is a 2:1 female/male predominance with a mean age of 25 years at presentation. Lymph node involvement is predominantly in the cervical chain (70–90%). KFD can be asymptomatic or it can present as a fever of unknown origin, with neutropenia, myalgias, and rash. Major presenting features of KFD are lymphadenop-

Fig. 3. Bone marrow biopsy is approximately normocellular for the age. Collections of plasma cells are indicated with the ovals. Immunostaining shows the plasma cells to be polytypic and with a normal kappa/lambda ratio of 2:1 to 3:1

athy (100%), fever (35%), and rash (10%). Fatigue, arthralgia, arthritis, myalgia, weight loss, hepatosplenomegaly, and oral ulcers are seen in less than 10%. Laboratory findings include leukopenia (18%), elevated erythrocyte sedimentation rate (16%), anemia, transaminitis, positive ANA, increased LDH, positive viral serologies (including EBV, cytomegalovirus, and others), thrombocytopenia, and leukocytosis, all seen in less than 10% of cases. The diagnosis of KFD is based on pathology as detailed above. However, there is a significant morphologic overlap between KFD and SLE, and the distinction between these two entities may not be possible based on the pathologic findings alone. Although the presence of more numerous plasma cells, hematoxylin bodies, deposition of DNA on vessel walls, and prominent neutrophilic infiltrate favor SLE, the absence of these features neither excludes SLE nor is diagnostic of KFD. The differential diagnosis of KFD includes SLE, other connective tissue disease, viral disease, hemophagocytic syndrome, lymphoma, and tuberculosis. An important clinical feature of KFD is its self-limited nature. Sixty-four to 80% of cases resolve within 1–4 months without therapy, and there is only a 1–3% relapse rate [1]. Patients with severe or persistent disease may benefit from treatment with glucocorticoids [1], and there is one case report of a patient with recurrent disease treated successfully with hydroxychloroquine [2].

SLE is a chronic inflammatory disease of unknown etiology, which can affect the skin, joints, blood, kidneys, nervous system, cardiopulmonary system, and other organ systems of the body. Autoantibody production is a characteristic of SLE. Immunologic abnormalities associated with SLE include a positive ANA, low complement levels, antibodies to

extractable nuclear antigens, and anti-phospholipid antibodies. SLE has a variable clinical course and may be characterized by flares and periods of remission. Approximately 51 per 100,000 persons in the USA are diagnosed with SLE [3]. The female/male ratio is 9:1. African-Americans and Hispanics have SLE more commonly than Caucasians and have a higher degree of disease morbidity [4]. The therapy of SLE depends on disease activity and organ involvement and its severity; corticosteroids, non-steroidal anti-inflammatory drugs, antimalarials, and immunosuppressive agents, including methotrexate, azathioprine, mycophenolate mofetil, and cyclophosphamide are all used in the management of SLE patients.

SLE and KD associations have been previously reported [1, 5, 6], and differentiating between the two entities may not always be possible at the time of initial presentation. Necrotizing lymphadenitis can be a clinical manifestation of SLE seen either as a presenting symptom or in a patient with preexisting SLE [7]. It has been suggested that patients presenting with KFD receive periodic follow-up for several years to detect possible evolution to SLE. The distinction between SLE and KFD can be a challenge for the clinician, and as in our case, the two syndromes may have overlapping features or may coexist.

Immunologic discussion—pathology perspective

When one considers the phenotypic profile of SLE, it is understandable that a cytokine milieu could be generated that could produce a morphologic and phenotypic profile indistinguishable from idiopathic or virally triggered KFD. There are unique features of KFD that parallel known pathogenetic mechanisms in SLE. Perhaps, one could use the phenotypic

Fig. 4. **a** Low power view showing prominent interstitial mucin and leukocytoclasia. **b** High power focus of a perivascular lymphohistiocytic infiltrate with prominent karyorrhexis. **c** CD8 immunostain highlighting cytotoxic T cells

profile that defines KFD as the more extreme expression of the distinctive phenotypic profile typical of SLE. A unique aspect of KFD is one of extensive CD8 T cell and PDC infiltration along with enhanced leukocyte apoptosis and engulfment of nuclear debris by scavenger histiocytes. It has been suggested that apoptosis-associated genes, especially caspases, are upregulated, while apoptosis inhibitory genes, including *bcl-2* by immunohistochemistry, are downregulated in KFD [8]. As with TEN/SJS, where excessive soluble Fas ligand–Fas interaction at the level of the keratinocyte is associated with extensive and progressive apoptosis, the serum soluble Fas ligand is also markedly elevated in patients with KFD [9].

In a recent study examining the phenotypic profile of biopsies procured from patients with dermatomyositis, SLE, or discoid lupus erythematosus, it was found that biopsies of SLE patients were characterized by a dominance of CD8 lymphocytes in the dermis and within the epidermis with numerous CD123 PDCs concentrated around vessels and at sites of interface dermatitis with MXA (Magro CM, unpublished data), the signature protein indicative of an IFN alpha-rich microenvironment, being significantly expressed in the epidermis and amidst inflammatory cells. Hence, one can view KFD in the setting of SLE as at the polar end of the normal phenotypic profile of SLE. It is possible that, in patients with KFD, the apoptotic response is unusually marked and serves as a substrate to trigger the induction and growth of IFN elaborating PDCs. The role of Fas ligand gene polymorphisms has not been explored in KFD, although it is known to occur in patients with SLE. In addition, an additional gene polymorphism controlling IFN production may also play some role in the pathogenesis of KFD. Patients with SLE demonstrate an IFN gene expression “signature” characterized by strong overexpression of IFN-responsive genes in leukocytes and target tissues. One of the key genes of the IFN-alpha pathway, *IRF5*, was found to be strongly associated with SLE. Various functional single nucleotide gene polymorphisms lead to upregulation of IFN regulatory 5 expression, the sequelae of which would be one of excessive IFN alpha

Fig. 5. **a** Low power view of scalp lesion shows follicular plugging and interface dermatitis involving the epidermis and adnexal structures. **b** High power view of interface dermatitis

Fig. 6. Demonstration of the distinctive phenotypic profile of KFD as characterized by a CD8 dominant T cell infiltrate with numerous lysozyme positive histiocytes. The apoptotic debris is highlighted by these two phenotypic markers indicating the origin of the apoptotic fragments. There are numerous CD123-positive plasmacytoid dendritic cells with strong expression of MXA in the epidermis and amidst inflammatory cells. This phenotypic profile is essentially an exaggeration of that observed in SLE

production [10, 11]. A specific IFN gene polymorphism has been identified, which could be operational in some cases of KD. IRF5 encodes an IFN-induced transcription factor. Polymorphism at SNP rs2004640 creates a novel splice site in exon B allowing the expression of a novel IRF5 isoform [10]. A second mutation rs10954213 creates a functional polyadenylation site and hence a shorter and more stable gene transcript [12]. Type I IFNs are typically produced in response to infection. Large amounts are produced by PDCs stimulated by viral RNA and DNA through toll receptors 7 and 9 [13]. In SLE, it may also be triggered in response to nucleic acid antigens released from apoptotic cells [14]. Type I IFNs exert many downstream effects on the immune system: stimulating maturation and antigen presenting function of monocytes, increasing survival of activated T cells and stimulating differentiation and class switching of B cells [13].

Therefore, in summarizing the events leading to KFD, an antibody response directed at epithelial antigen typical of any cutaneous SLE reaction may be the inciting trigger. The CD8 cells could be responding to antigen or could represent secondary effector cells via the mechanism of antibody-dependent cellular immunity. The soluble Fas ligand produced by these sensitized CD8 T cells would then bind in a nonspecific manner to any cell expressing Fas which in the context of skin would include not only keratinocytes but lymphocytes and histiocytes leading to upregulation of caspases and cell death via the apoptotic pathway.

Immunologic discussion—rheumatology perspective

This case of an overlap between KFD and SLE begs the question of whether there are similar pathophysiologic processes underway in the two disorders. In both disorders the lymph node pathology can show histiocytic necrotizing lymphadenitis, and in both, the plasmacytoid histiocyte or PDC plays a role. In the lymph node, PDCs are localized to the “T zone,” which is centered around the high endothelial venules [15], where they also present antigen [16]. The pathology in KFD often centers around T zone of the lymph node [17], although in this case, the lymph node architecture was not preserved and the T zone was not clearly seen.

Plasmacytoid dendritic cells are a link between the innate and adaptive immune systems. In response to stimuli, they produce large quantities of type I IFNs, which can both directly inhibit the viral life cycle and activate the adaptive immune system to kill targeted cells. Plasmacytoid dendritic cells are thought to have a role in autoimmunity as well. Animal models support a pathologic role for type 1 IFN in lupus [18–23]. In patients with lupus, there is an association between disease activity and type I IFN levels in the peripheral blood [24–27]. Not all lupus patients have measurably increased levels of type 1 IFN, but they may have increased type 1 IFN-responsive gene expression “signatures” in blood mononuclear cells [16, 18]. This suggests that these cells have been exposed to high levels of type 1 IFN elsewhere (e.g., in the tissues). Consistent with

this is the finding that there is an accumulation of PDCs in cutaneous SLE lesions [28, 29]. Also consistent with this is the finding of the accumulation of PDC in the lymph nodes of lupus patients [6] or in mouse models of lupus. [30] Thus, the lymphocytes that circulate in the body circulate to the lymph node, see the PDC, and, when they are later sampled from the blood, have a high type 1 IFN “signature.”

A question that arises is, “Could the accumulation of PDCs in KFD and in SLE play a similar pathophysiologic role?” It is possible that local PDC accumulation and type I IFN production explain the lymphadenopathy and the necrotizing lymphadenitis seen in both of these diseases.

Lymph node enlargement occurs by the following possible processes: increased cellular entry, decreased exit, and cell proliferation. Cell proliferation probably plays some role in cases of necrotizing lymphadenitis because PDCs can stimulate the proliferation of T cells, especially cytotoxic T cells [31]. Type I IFN may also stimulate lymphocyte entry from the blood into lymph nodes and induce retention of these cells in lymph nodes. Exit from lymph nodes is mediated by a sphingosine-1-phosphate (S1P) receptor on lymphocytes. Lymphocytes are thought to follow a gradient of S1P from the lymph node to the efferent lymphatics via one of the receptors for S1P. Type I IFN actually induces a down-regulation of this receptor via the T-cell activation marker CD69. Therefore, if there is increased type I IFN, there will be greater retention of lymphocytes within the node. Type I IFN-induced lymphocyte retention in lymph nodes is associated with peripheral blood lymphopenia [32]. It is possible that this trapping of cells in lymphoid organs account for the lymphopenia seen in SLE and sometimes in KFD.

This case of a patient with SLE, with features of KFD, brings up the question of whether PDCs and type I IFNs play a similar role in both conditions, accounting for the similarities between the two diseases. Further study needs to be done to investigate this. One approach would be to examine IFN gene expression signatures in KFD. Since KFD is self-limited while SLE is chronic, future investigation could also include examining whether there is clearance or dormancy of the immune stimulus in Kikuchi's but an ongoing stimulus in SLE.

Conclusion

This case provides important perspective on the overlap and/or coexistence of SLE and KFD and brings up the question of whether they are part of the same spectrum. The patient discussed here was initially thought to have KFD based on his initial clinical presentation and biopsy findings. Based on his chronic disease course, additional clinical and serologic findings consistent with SLE, and demographic features, a diagnosis of SLE better explained this patient's syndrome. For the clinician caring for patients with features of SLE and Kikuchi's, determining the exact diagnosis and prognosis can be challenging. Although there are immunological similarities, the prognosis is different—

SLE is a chronic disease, and KFD is generally a self-limited entity. In some cases, the answers to diagnosis may only be seen with time. Further investigation into the differences and similarities between SLE and KFD may yield important insights.

References

1. Jang YJ, Park KH, Seok HJ (2000) Management of Kikuchi's disease using glucocorticoid. *J. Laryngol. Otol.* 114:709–11
2. Rezaei K, Kuchipudi S, Chundi V (2004) Kikuchi–Fujimoto disease: hydroxychloroquine as a treatment. *Clin. Infect. Dis* 39: e124–e126
3. Lawrence RC, Helmick CG, Arnett FC (1998) Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum.* 41:778–799
4. Jimenez S, Cervera R, Font J (2003) The epidemiology of systemic lupus erythematosus. *Clin. Rev. Allergy Immunol.* 25:3–12
5. El-Ramahi KM, Karrar A, Ali MA (1994) Kikuchi disease and its association with systemic lupus erythematosus. *Lupus* 3:409–11
6. Goldblatt F, Andrews J, Russell A, Isenberg D (2008) Association of Kikuchi–Fujimoto's disease with SLE. *Rheumatology* 47:554–555
7. Eisner MD, Amory J, Mullaney B (1996) Necrotizing lymphadenitis associated with systemic lupus erythematosus. *Semin. Arthritis Rheum.* 26:1–6
8. Ohshima K, Karube K, Hamasaki M (2004) Apoptosis- and cell cycle-associated gene expression profiling of histiocytic necrotizing lymphadenitis. *Eur. J. Haematol.* 72:322–9
9. Kato K, Ohshima K, Anzai K (2001) Elevated serum-soluble Fas ligand in histiocytic necrotizing lymphadenitis. *Int. J. Hematol.* 73:84–6
10. Kozyrev SV, Lewén S, Reddy PM (2007) Structural insertion/deletion variation in IRF5 is associated with a risk haplotype and defines the precise IRF5 isoforms expressed in systemic lupus erythematosus. *Arthritis Rheum* 56:1234–41
11. Niewold TB, Kelly JA, Flesch MH (2008) Association of the IRF5 risk haplotype with high serum interferon-alpha activity in systemic lupus erythematosus patients. *Arthritis Rheum.* 58:2481–7
12. Graham RR, Kyogoku C, Sigurdsson S, et al. (2007) Three functional variants of IFN regulatory factor 5 (IRF5) define risk and protective haplotypes for human lupus. *Proc Natl Acad Sci U S A.* 104:6758–6763
13. Kirou KA, Mavragani CP, Crow MK (2007) Activation of type I interferon in systemic lupus erythematosus. *Expert Rev. Clin. Immunol.* 3:579–588
14. Barrat FJ, Meeker T, Gregorio J, et al. (2005) Nucleic acids of mammalian origin can act as endogenous ligands for Toll-like receptors and may promote systemic lupus erythematosus. *J. Exp. Med.* 202:1131–1139
15. Cella M, Jarrossay D, Facchetti F (1999) Plasmacytoid monocytes migrate to inflamed lymph nodes and produce large amounts of type I interferon. *Nat. Med.* 5:919–923
16. Qu C, Moran TM, Randolph GJ (2003) Autocrine type I IFN and contact with endothelium promote the presentation of influenza A virus by monocyte-derived APC. *J. Immunol* 170:1010–1018
17. Tsang WY, Chan JK, Ng CS (1994) Kikuchi's lymphadenitis. A morphologic analysis of 75 cases with special reference to unusual features. *Am. J. Surg. Pathol.* 18:219–231
18. Heremans H, Billiau A, Colombatti A (1978) Interferon treatment of NZB mice: accelerated progression of autoimmune disease. *Infect. Immun.* 21:925–930
19. Braun D, Geraldes P, Demengeot J (2003) Type I interferon controls the onset and severity of autoimmune manifestations in lpr mice. *J. Autoimmun.* 20:15–25

20. Adam C, Thoua Y, Ronco P (1980) The effect of exogenous interferon: acceleration of autoimmune and renal diseases in (NZB/W) F1 mice. *Clin. Exp. Immunol.* 40:373–382
21. Mathian A, Weinberg A, Gallegos M (2005) IFN- α induces early lethal lupus in preautoimmune (New Zealand Black $\times$ New Zealand White) F1 but Not in BALB/c Mice. *J. Immunol.* 174:2499–2506
22. Santiago-Raber ML, Baccala R, Haraldsson KM (2003) Type-I Interferon Receptor Deficiency Reduces Lupus-like Disease in NZB Mice. *J. Exp. Med.* 197:777–788
23. Hron JD, Peng SL (2004) Type I IFN protects against murine lupus. *J. Immunol.* 173:2134–2142
24. Baechler EC, Batliwalla FM, Karypis G (2003) Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. *Proc Natl Acad Sci USA* 100:2610–2615
25. Crow MK, Kirou KA, Wohlgemuth J (2003) Microarray analysis of interferon-regulated genes in SLE. *Autoimmunity* 36:481–490
26. Bennett L, Palucka AK, Arce E (2003) Interferon and granulopoiesis signatures in systemic lupus erythematosus blood. *J. Exp. Med.* 197:711–723
27. Kirou KA, Lee C, George S (2004) Coordinate overexpression of interferon-alpha-induced genes in systemic lupus erythematosus. *Arthritis Rheum.* 50:3958–3967
28. Farkas L, Beiske K, Lund-Johansen F (2001) Plasmacytoid dendritic cells (natural interferon- α/β -producing cells) accumulate in cutaneous lupus erythematosus lesions. *Am. J. Pathol.* 159:237–243
29. Blomberg S, Eloranta ML, Cederblad B (2001) Presence of cutaneous interferon-alpha producing cells in patients with systemic lupus erythematosus. *Lupus* 10:484–490
30. Nakano H, Yanagita M, Gunn MD (2001) CD11c(+)B220(+)Gr-1(+) cells in mouse lymph nodes and spleen display characteristics of plasmacytoid dendritic cells. *J. Exp. Med.* 194:1171–1178
31. Yoneyama H, Matsuno K, Toda E (2005) Plasmacytoid DCs help lymph node DCs to induce anti-HSV CTLs. *J. Exp. Med.* 202:425–435
32. Shiow LR, Rosen DB, Brdickova N, et al., CD69 acts downstream of interferon- α/β to inhibit S1P1 and lymphocyte egress from lymphoid organs. *Nature* 2006; 440: 540–544.