Kikuchi Disease-Like Inflammatory Pattern in Cutaneous Inflammatory Infiltrates Without Lymph Node Involvement

A New Clue for the Diagnosis of Lupus?

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Abstract: Kikuchi–Fujimoto disease (KFD) is a rare and benign disorder that usually occurs in young adults with enlarged lymph nodes containing infiltrate of cytotoxic T cells and nuclear debris. It can be a manifestation of systemic lupus erythematosus (SLE) although the strength of this association has varied among studies. Although specific KFD cutaneous lesions are well described, pure cutaneous lesions have never been reported. We studied a series of patients prospectively entered into a database between 2007 and 2014 with skin biopsies showing diffuse or localized inflammatory infiltrates reminiscent of cutaneous KFD, without lymph-node-related KFD. We called these skin lesions “Kikuchi disease-like inflammatory pattern” (KLIP). Twenty-nine patients, whose median age was 49 years at the time of skin biopsy, were selected and retrospectively analyzed using standardized clinical and histology charts. In skin biopsies, KLIP was localized to restricted areas within the inflammatory infiltrate (17%) or diffuse (83%), and was the only histological finding (45%) or accompanied interface dermatitis with or without dermal mucinosis (55%). Clinical dermatological findings varied widely. A definite diagnosis could be established for 24 patients: 75% had connective tissue diseases or vasculitis, mainly cutaneous lupus erythematosus (CLE) (n = 16, 67%), including 5 SLE with satisfying American College of Rheumatology criteria; 3 of the remaining patients had malignant hemopathies. CLE patients were mostly young females with acute (n = 5), subacute (n = 4), or chronic CLE (n = 6) or lupus tumidus (n = 1). Two were classified as having anti-tumor necrosis factor-alpha–induced lupus. Because two-thirds of these patients were finally diagnosed with CLE, we think that KLIP may represent a new histopathological clue for the diagnosis of lupus based on skin biopsy, requiring clinical-immunological comparison to make the correct diagnosis. KLIP should not be considered a variant of classical KFD, but rather as an elementary pattern of cutaneous inflammation, that might be the expression of the same cytotoxic process within skin infiltrates as that involved in KFD. This lesion might reflect a particular T-cell-mediated autoimmune process directed against mononuclear cells within cutaneous lupus infiltrates.

INTRODUCTION

Kikuchi–Fujimoto disease (KFD), or histiocytic necrotizing lymphadenitis, is a rare and benign disorder that mainly affects women under 40 years old. This clinical-pathological entity, first described in 1972, is characterized by fever and painful regional, predominantly cervical, lymphadenopathy. Histologically, involved lymph nodes exhibited paracortical areas of apoptotic necrosis with abundant nuclear debris and a proliferation of histiocytes, plasmacytoid dendritic cell, SCLE = subacute cutaneous lupus erythematosus, LKD = systemic lupus erythematosus, TNF = tumor necrosis factor.

Although its etiology is unknown, autoimmune mechanisms or abnormal responses to viruses were proposed. In that large study on 244 patients, KFD was associated with systemic lupus erythematosus (SLE) in 13% of them, notably 28% of Asian subjects, with other noninfectious inflammatory diseases and viral infections diagnosed in 10% and 7% of KFD, respectively.

Cutaneous manifestations have been observed in 16% to 40% of KFD patients. First reported by Kuo, the description of the histopathological findings of skin lesions was subsequently limited to single case reports or small case series. Summarized in a 2008 literature review by Atwater et al. In 2010, Kim et al described the largest series of 16 KFD cases with skin involvement. The cutaneous lesions varied clinically but all skin biopsies showed lymphohistiocytic infiltration with nonneutrophilic karyorrhexis, similar to that seen in the involved lymph nodes, and 75% had interface dermatitis. Etiologies were mainly inflammatory dermatoses, 25% of which were SLE.

To the best of our knowledge, histological findings similar to KFD strictly limited to the skin have never been described. Herein, we report on patients with cutaneous lesions...
histologically similar to KFD, but without lymph-node involvement. In these patients, we called the histological appearance “Kikuchi disease-like inflammatory pattern” (KLIP), observed alone or with other features, evaluated the histological spectrum of this pattern, and established the etiological context in which it developed.

**METHODS**

**Study Population**

We prospectively entered into a dedicated database all patients with histological inflammatory cutaneous infiltrates suggestive of KLIP in skin biopsies assessed in the Department of Pathology of Henri-Mondor Hospital between April 2007 and April 2014. Skin biopsies were either obtained from the hospital's Dermatology or Internal Medicine Departments or sent from external Pathology Laboratories for a second opinion.

This study was conducted in accordance with Declaration of Helsinki and was approved by the Saint-Louis Hospital Institutional Review Board (No. 00003835).

**KLIP Definition**

Formalin-fixed, paraffin-embedded skin biopsies were studied. Three-micrometer-thick sections were stained with hematoxylin–eosin–saffron (HES) and pH 2.5 Alcian blue stain, and immunohistochemical analyses used monoclonal antibodies to CD3, CD4, CD8, CD20, CD68, CD123, granzyme B, and myeloperoxidase (MPO) (Dako, France). We used a standard avidin–biotin–peroxidase method with diaminobenzidine (DAB) chromogen, and the BOND-III Autostainer (Leica Microsystems, Newcastle-upon-Tyne, UK), after antigen retrieval by heating in the appropriate buffer. All skin biopsies were examined and interpreted by the same pathologist (NO).

KLIP was defined as a dermal infiltrate, or foci within dermal infiltrates, composed of mononuclear cells and nuclear debris, without neutrophils. Immunohistochemically labeled mononuclear cells were CD163\(^+\) macrophages, some of which were MPO\(^+\) cells, CD8\(^+\) lymphocytes, including cytotoxic (granzyme B\(^+\)) cells, and CD123\(^+\) PDC (Fig. 1A–D).

**Retrospective Clinical Data Analysis**

The clinical data of the patients from Henri-Mondor Hospital were retrospectively obtained from medical charts. For the assessment of patients from other institutions, medical records were obtained from dermatologists or hospitals managing them. The following information was collected using a standardized form: clinical, biological, immunological, histological and radiological findings, diagnosis, treatment and management of patients.

**FIGURE 1.** Histological appearance of the Kikuchi disease-like inflammatory pattern (KLIP). A, KLIP associated with a mononuclear cell infiltrate containing nuclear debris (arrows, hematoxylin–eosin–saffron staining, \(\times 400\)). B, Many CD3\(^+\) T cells are seen. C, Cytotoxic granzyme B\(^+\) T cells are present. D, The infiltrate also comprises many CD68\(^+\) histiocytes. E, Many histiocytes express the myeloperoxidase. F, Plasmacytoid dendritic cells are identified using CD123 immunostaining. (B–F, immunohistochemistry revealed by diaminobenzidine, \(\times 400\)).
outcome from the time of the skin biopsy and throughout follow-up. SLE diagnosis was defined according to ACR criteria and we based on international classification to precise subtypes of cutaneous lupus.\textsuperscript{17,18} We excluded patients with histologically proven KFD in lymph-node biopsies, and those not further investigated at the time of KLIP diagnosis and thus without follow-up.

**Retrospective Histopathological Data Analysis**

The dedicated skin-biopsy database was retrospectively reviewed to evaluate the KLIP-histological spectrum. Indeed, we prospectively evaluated in all skin biopsies the following parameters: epidermal inflammatory lesions: eczematous pattern, psoriasiform hyperplasia, lichenoid interface dermatitis; topography of dermal infiltrates; subepidermal band-like, perivascular, perinodal; infiltration depth: superficial dermis, mid-dermis, deep dermis or hypodermis; cellular composition of the infiltrates: lymphocytes, plasma cells, mature neutrophils, mature eosinophils; Alcian blue stain-detected dermal mucinosis; and leukocytoclastic or lymphocytic vasculitis of dermal vessels. In all cases, we determined whether KLIP was diffuse or localized in a part of the inflammatory infiltrate (extensive versus localized KLIP).

**RESULTS**

Among the 34 skin biopsies with a KLIP recorded between April 2007 and April 2014, 2 were associated with nodal KFD and thus considered to be skin manifestations of classical KFD and excluded, and 3 others were excluded because patients were not fully investigated and lost-to-follow-up. Finally, 29 cases were retained for analysis, 21 from Henri-Mondor Hospital and 8 from other institutions.

**Clinical and Immunological Features, and Final Diagnoses**

Patients with KLIP were mainly females (21, 72%), whose median age at the time of skin biopsy was 49 (range, 14–83) years. Most were Caucasian (n = 18, 62%), while the others were Asian (n = 4, 14%), Afro-Caribbean (n = 3, 10%), North African (n = 2, 7%), or sub-Saharan (n = 2, 7%).

Dermatological findings were extremely heterogeneous, comprising papules/erythematous papules (n = 15), erythema (n = 4), nonspecific infiltrated lesions (n = 3), chilblain (n = 3), atrophic lesions (n = 2), nodules (n = 2), papulovesicles (n = 2), annular erythema (n = 1), lichenoid lesion (n = 1), ulcerative lesion (n = 1), desquamative lesion (n = 1), folliculitis and pseudo-folliculitis (n = 1). Lesions were mainly localized on the face, arms, and trunk (Table 1 and Fig. 2A–D).

Extracutaneous manifestations, present in 12 of 29 (41%) patients, included: general symptoms (asthenia, anorexia, and/or weight loss) (n = 3), fever (n = 2), pulmonary symptoms (dysnea n = 1, pneumonia n = 1, pleurisy n = 1), digestive symptoms (n = 1), renal symptoms (proteinuria) (n = 1), enlarged axillary and/or cervical lymph nodes (n = 1), arthralgias (n = 2), myalgias (n = 1), and/or Raynaud's phenomenon (n = 1).

For the 3 patients with lymphadenopathy, lymph-node biopsies revealed angioimmunoblastic T-cell lymphoma (n = 1), follicular hyperplasia (n = 1), or a necrotic polymorphous inflammation with no classical KFD features (n = 1).

Immunological tests revealed that 18 of 26 (69%) patients were antinuclear antibody (ANA)-positive (3 patients were not assessed immunologically); 6 of 18 ANA-positive patients had anti-double-stranded DNA (dsDNA) antibody, 3 of them had also decreased complement levels and were anti-Sm–positive, 2 were anti-Ro–positive, and 1 was also anticardiolipin (ACL) IgG–positive. Dermatomyositis-specific anti-melanoma differentiation-associated gene 5 (MDA5) antibodies were detected in 1 patient and anti-smooth muscle antibody in another one.

A diagnosis could be established with certainty for 24 of 29 (83%) patients (Table 1). Most had a connective tissue disease or vasculitis (18/24, 75%), including mainly cutaneous lupus erythematosus (CLE) (16/24, 67%), while the 2 other patients had dermatomyositis or Behcet’s disease. Three had malignant hemopathies: 1 angioimmunoblastic T-cell lymphoma, 1 cutaneous T-cell lymphoma, and 1 acute myeloid leukemia. The other diagnoses comprised: drug reaction with eosinophilia and systemic symptoms (DRESS), atopic dermatitis or acute viral infection. A connective tissue disease or vasculitis was diagnosed in 83% of ANA-positive patients, as shown in Figure 3.

Diagnosis preceded the onset of cutaneous manifestations leading to histological characterization of KLIP in 9 patients (7 lupus, 1 dermatomyositis, 1 Behcet’s disease), and was concomitant for 14 patients. Diagnosis of cutaneous T-cell lymphoma was established several months later, based on a repeat skin biopsy. Finally, 5 patients had no definitive diagnoses; 4 resolved (3 spontaneously, 1 with systemic corticosteroids) and 1 was still under investigation at the time of this analysis.

**Histological Description of KLIP**

Histologically, KLIP appeared to be restricted to areas of the skin biopsies (n = 5, 17%) (Fig. 4), sometimes subtle localized foci, or diffuse (n = 24, 83%) (Fig. 5). It was either the sole inflammatory pattern (n = 13, 45%), or associated with other features (n = 16, 55%), especially lichenoid interface dermatitis, as seen in Figure 5A and B showing notable interface dermatitis lesions. Interface dermatitis was isolated (n = 10) or associated with cutaneous mucinosis (n = 6), but no other findings were associated. Among the 29 patients, a final diagnosis could be established for 9 of 13 with isolated KLIP and 15 of 16 with KLIP and interface dermatitis, which corresponded to CLE for 7 and 9 patients, respectively.

**Treatments and Outcomes**

Treatment consisted of corticosteroids (topical n = 10, systemic n = 11) associated, for some patients, with a background therapy depending on the underlying disease. Hydroxychloroquine was prescribed for 14 of 16 (88%) patients for whom the lupus diagnosis was retained. Among 3 patients who received no treatment, 2 had no diagnosis.

After a median 10-month follow-up (range, 1–72 months), 25 patients’ diseases responded to treatment or resolved spontaneously, except for 3 who died (DRESS, angioimmunoblastic T-cell lymphoma, or SLE). No disease had recurred at the time of follow-up.

Epidemiological, clinical, biological, histological features, treatments, and outcomes are detailed and compared according to the underlying diseases in Table 1.

**Characteristics of Lupus Patients**

Notably, 14 of 16 lupus patients were female (male/female ratio: 1/8) with a median age of 40.5 (range, 14–70) years at the time of skin biopsy. According to ACR criteria for SLE diagnosis,\textsuperscript{19} and based on the international classification of CLE,\textsuperscript{18} 4 different CLE categories were established, including 5

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| Characteristics                                      | Lupus (n = 16) | Other Diagnoses (n = 8) | No Diagnosis (n = 5) |
|------------------------------------------------------|----------------|------------------------|---------------------|
| **Demographical**                                    |                |                        |                     |
| Median age at KLIP diagnosis, years (range)          | 40.5 (14–70)  | 49.5 (35–83)           | 52 (29–77)          |
| Male/female, n (%)                                   | 2/14 (12/88)  | 3/5 (37/63)            | 3/2 (60/40)         |
| **Clinical**                                         |                |                        |                     |
| Dermatological findings                              |                |                        |                     |
| Lesions                                              | Papules, erythema, lichenoid lesions, annular lesions, desquamative lesions, ulcerative lesions, chilblain | Papules, erythema, papulovesicles, folliculitis, pseudo-folliculitis, nodules, infiltrative patches | Papules, erythema, papulovesicles, papulonodules, infiltrative patches |
| Distribution                                         | Scalp, face, arms, trunk in a photodistributed pattern, fingers | Arms, trunk, leg   | Arms, trunk, leg    |
| Photosensitivity, n                                  | 8              | 0                      | 0                   |
| Extracutaneous symptoms, n (%)                       | 4 (25)         | 6 (75)                 | 2 (40)              |
| General symptoms (asthenia, anorexia, weight loss)   | 0              | 2                      | 1                   |
| Fever (>38°C)                                        | 0              | 2                      | 0                   |
| Adenopathy                                           | 0              | 1                      | 2                   |
| Arthralgias                                          | 1              | 1                      | 0                   |
| Myalgias                                             | 0              | 1                      | 0                   |
| Renal                                                | 1              | 0                      | 0                   |
| Digestive                                            | 0              | 1                      | 0                   |
| Pulmonary                                             | 1              | 3                      | 0                   |
| Raynaud’s phenomenon                                 | 1              | 0                      | 0                   |
| **Biological, n**                                    |                |                        |                     |
| Inflammatory syndrome                                | 1              | 2                      | 1                   |
| (CRP >10 mg/L, ESR >20 mm)                           |                |                        |                     |
| Lymphopenia (< 1500/mm³)                             | 1              | 2                      | 0                   |
| Neutropenia (<1500/mm³)                              | 1              | 0                      | 0                   |
| Thrombocytopenia (<100,000/mm³)                      | 1              | 0                      | 0                   |
| Elevated LDH (>2N)                                   | 1              | 3                      | 1                   |
| EBV test                                             | 0              | 1/2 PCR +              | 2/2 serologic tests + (chronic non active infection) |
| HHV6 test                                            | 0              | 2/2 PCR –              | 1/1 serologic test-, 1/1 PCR- |
| ANA, n (not done, n)                                 | 13 (0)         | 3 (2)                  | 2 (1)               |
| Anti-dsDNA                                           | 6              | 0                      | 0                   |
| **Histological, n (%)**                              |                |                        |                     |
| Cutaneous KLIP                                       |                |                        |                     |
| Localized/extensive KLIP infiltrate, n (%)           | 2/14 (12/88)   | 3/5 (37/63)            | 0/5 (0/100)         |
| Isolated KLIP infiltrate, n (%)                      | 7 (44)         | 2 (25)                 | 4 (80)              |
| KLIP infiltrate + lichenoid dermatitis, n (%)        | 5 (31)         | 4 (50)                 | 1 (20)              |
| Characteristics                          | Lupus (n = 16) | Other Diagnoses (n = 8) | No Diagnosis (n = 5) |
|-----------------------------------------|---------------|------------------------|---------------------|
| KLIP infiltrate + lichenoid dermatitis + |               |                        |                     |
| cutaneous mucinosis, n (%)              | 4 (25)        | 2 (25)                 | 0 (0)               |
| Direct immunofluorescence, n            | 4/5+          | 1/1–                   | 0                   |
| EBER in situ hybridization               | 0             | 2/2 –                  | 0                   |
| Others                                  | 0             |                        |                     |

| Diagnoses, n                           |               |                        |                     |
|                                        | SLE, 5; SCLE, 4; CCLE, 6; lupus tumidus, 1 | Dermatomyositis, 1; Behet’s disease, 1; angioimmunoblastic T-cell lymphoma, 1; cutaneous T-cell lymphoma, 1; acute myeloid leukemia, 1; DRESS, 1; atopic dermatitis, 1; acute viral infection, 1 | 0                     |

| Treatment, n                           |               |                        |                     |
|                                       | Topical corticosteroids | Systemic corticosteroids | Hydroxychloroquine |
|                                       | 5             | 5                      | 14                  |
|                                       | 3             | 4                      | 0                   |
|                                       | 0             | 0                      | 0                   |
| Others                                 | MMF, 1; CYC, 1; leflunomide, 1 | MTX, 1; colchicine, 1; chemotherapy, 3; local tacrolimus, 1; ganciclovir, 1 | Anti-histamine, 2; colchicine, 1 |

| Outcome, n                             |               |                        |                     |
|                                       | Complete response | Partial response | No response | Death | Not available |
|                                       | 14            | 1                      | 0           | 1     | 0             |
|                                       | 4             | 2                      | 0           |       | 0             |
|                                       | 0             | 2                      | 0           |       | 1             |

ANA = antinuclear antibody; CCLE = chronic cutaneous lupus erythematosus; CRP = C-reactive protein; CYC = cyclophosphamide; DRESS = drug reaction with eosinophilia and systemic symptoms; dsDNA = double-stranded DNA antibody; EBER = Epstein-Barr virus-encoded RNA; EBV = Epstein-Barr virus; ESR = erythrocyte sedimentation rate; HHV6 = human herpes virus 6; KLIP = Kikuchi disease-like inflammatory pattern; LDH = lactate dehydrogenase; MMF = mycophenolate mofetil; MTX = methotrexate; PCR = polymerase chain reaction; SCLE = subacute cutaneous lupus erythematosus; SLE = systemic lupus erythematosus.
acute (ACLE), 4 subacute (SCLE), 6 chronic (CCLE) including 3 chilblain lupus, and 1 intermittent (ICLE) or lupus tumidus. Two of them were classified as anti-TNF-alpha-induced lupus with SCLE or CCLE-like lesions, respectively. Thus, KLIP appeared to be associated with various dermatological lesions, including CLE-specific (annular erythema, atrophic lesions, chilblain) or nonspecific manifestations (erythema in a photodistributed pattern).

Interestingly, only 9 of 16 (56%) lupus patients had histopathological clues for a CLE (lichenoid interface dermatitis, alone n = 5 or associated with a dermal mucinosis n = 4). KLIP was the sole histopathological finding in 7 of 16 lupus patients. Moreover, 4 of 5 investigated lupus patients had positive lupus-band tests on direct immunofluorescence. We did not find any relationship between the presence of a lupus-specific histological finding and a clinical CLE subtype.

Clinical, histological, and immunological data of the 16 lupus patients are detailed in the Supplemental table.

**DISCUSSION**

To our knowledge, cutaneous KLIP has not yet been described. This histological appearance may be considered a new inflammatory pattern with a broad spectrum of expression, ranging from pure lesions, sometimes seen as subtle localized lesional foci, to more diffuse or polymorphous presentations, comprising other features suggestive of CLE. Most of the patients had inflammatory dermatoses, especially various CLE subtypes.

![FIGURE 2](image1.png)

**FIGURE 2.** Clinical appearances of dermatoses associated with KLIP. A, Erythematous papules in a photodistributed pattern in a patient with systemic lupus erythematosus. B, Annular lesion of a patient with subacute cutaneous lupus erythematosus. C, Chilblain lupus erythematosus. D, Erythematous infiltrated lesions on the leg of a patient with angioimmunoblastic T-cell lymphoma.

![FIGURE 3](image2.png)

**FIGURE 3.** Distribution of diagnoses according to the detection of antinuclear antibodies (ANA) on immunological tests. ND = not done.
be noted that lupus patients were younger (median age, 40.5 years) and more often females than patients with other or no diagnoses, in agreement with the known predominance of young females with lupus.

Cutaneous manifestations histologically associated with KLIP were variable, as are the dermatological signs of KFD. In agreement with that statement, Kim et al described rash, erythematous macules, papules, or patches as the most frequent cutaneous lesions, whereas erosions, nodules, and bullae were also seen but less frequently. In our study, erythema and papules were also the most common cutaneous lesions in lupus and nonlupus patients, whereas infiltrative lesions and nodules were only reported in nonlupus patients, differing 2 with malignant hemopathies. Thus, such rare cutaneous KLIP manifestations plead for investigation of an underlying malignant hemopathy.

Kucukardali et al reported that 7% of KFD patients were ANA-positive, ranging from 3% in the European to 23% in the Asian population, whereas Dumas et al reported 45% ANA positivity among Caucasian patients. Nearly 70% of our patients were ANA-positive and most (83%) were diagnosed with connective tissue diseases or vasculitis. All SLE patients were ANA-positive and had specific lupus-autoantibodies. The patients with pure cutaneous lupus were exclusively ANA-positive, except 3 CCLE who were ANA-negative, in accordance with the literature.

Thus, cutaneous KLIP appeared to be frequently associated with connective tissue diseases, which represented 75% of final diagnoses. SLE is known to be associated with KFD, especially when cutaneous manifestations are present. In a meta-analysis of KFD skin manifestations, Paradel et al tended to confirm that observation because 9 of 27 (33%) patients with skin manifestations had potentially lupus whereas Dumas et al confirmed a statistically significant association between cutaneous KFD and SLE. Herein, 16 of 29 (55%) of our KLIP patients had CLE. Interestingly, unlike KFD-associated lupus, all cutaneous lupus subtypes were represented, including SLE (25%), SCLE (31%), CCLE (38%), and ICLE (6%). Thus, cutaneous KLIP appeared to be a clue orienting the histopathological diagnosis toward CLE, while not being specifically associated with any disease subtype. Three of our patients had malignant hemopathies, whereas, to the best of our knowledge, KFD has never been reported in association with lymphoma. Therefore, although KLIP and cutaneous KFD share strong similarities, they should not be considered variants of the same disease.

We think that KLIP and KFD may however involve a common pathogenic process, limited to the skin for KLIP, as opposed to systemic expression in KFD. As discussed above, KFD seems to be mostly associated with systemic forms of lupus. Therefore, an analogy may be made with another cytotoxic process, that is, the cytophagic panniculitis that is observed in hemophagocytic syndrome, a life-threatening systemic disease, but also in subcutaneous panniculitis-like T-cell lymphoma without systemic macrophage-activation syndrome. KFD pathogenesis is not well known but it is thought to involve the activation of cytotoxic cells from the nonadaptive and adaptive immune systems, including PDC, MPO+ macrophages and cytotoxic CD8+ T cells. The nature of the target cells releasing nuclear debris is not known, but they may be the lymphoid and/or myeloid cells of the infiltrates themselves. Hence, the process may be an expression of autoimmunity, whether or not it is associated with lupus. Another potential mechanism that could explain KFD development is an abnormal
response to viral infection, especially to herpesviridae, but this association remains controversial. Moreover, latent viral infection with herpesviridae (e.g., human herpes virus 6 and Epstein-Barr virus) is suspected to play a role in the drug hypersensitivity syndrome. Interestingly, Carlson et al reported 2 cases of antibiotic-induced eruption potentially related to chronic active Epstein-Barr virus infection with cutaneous pathologic findings reminiscent of KFD. In our series, none of the 29 patients received antibiotics before developing skin lesions nor had a chronic active viral infection due to herpesviridae when tested, especially human herpes virus 6 (n = 4) or Epstein-Barr virus (n = 5), except one patient diagnosed with an angioimmunoblastic T-cell lymphoma. He had an active infection related to Epstein-Barr virus detected in peripheral blood, but no evidence of the virus in cutaneous lesions.

In the skin, the identification of nuclear debris is common in the neutrophilic infiltrates of leukocytoclastic vasculitis, infections, or neutrophilic dermatoses. Neutrophilic variants of lupus, not to be confused with KLIP, have been described. They often show urticarial lesions and have been integrated into the recently described group of so-called “neutrophilic urticarial dermatoses.” Particular cellular debris had previously been reported in lupus lesions. In synovial fluid, they were termed LE cells or Hargrave’s cells and considered to represent neutrophilic debris phagocytosed by neutrophils or macrophages. In the kidney, cellular debris can be observed in interstitial nephropathies (Gross’ hematoxylin bodies), considered to be pathognomonic of lupus. Whether these lesions are pathogenically linked to KLIP variants is an intriguing question.

Taken together, these results suggest that KLIP may be considered a new histopathological inflammatory pattern, strongly associated with autoimmune disease, especially lupus. Although this pattern may have relatively good specificity for diagnosis, it is probably rare. During the same time period, we diagnosed cutaneous lupus based on skin biopsies in 499 patients. Thus, KLIP was observed in 5.8% of those biopsies, with 3.2% being confirmed lupus. Therefore, the sensitivity of KLIP for lupus diagnosis may not exceed 5%, although it is difficult to assess using such retrospective data.

Finding KLIP in skin biopsies should lead to additional adequate laboratory investigations. In light of our observations, we propose an algorithm that may help obtain a diagnosis and therapeutic strategy detailed in Figure 6 when inflammatory dermatosis with a KLIP is seen in skin biopsies. Briefly, for ANA-positive females with erythema or papules in a
photodistributed pattern or specific CLE manifestations, a CLE diagnosis can be retained with high confidence, and these features may lead to prescribing hydroxychloroquine. On the other hand, patients over 50 years old with atypical eruptions, for example, infiltrative lesions or nodules, with general symptoms and negative autoantibody status, should be investigated more, especially to search for a malignant hemophaty. Hydroxychloroquine has been reported to be effective against KFD, even when it is not associated with lupus or another autoimmune disease. In light of that finding, hydroxychloroquine may serve as a therapeutic test in patients with KLIP in skin biopsies but without a definite diagnosis.

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