The Spectrum of Histopathologic Findings in Cutaneous Lesions in Patients With Still Disease

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Key Words: Still disease; Juvenile rheumatoid arthritis; Histologic spectrum

ABSTRACT

Objectives: Still disease is a rare disorder characterized by seronegative arthralgias/arthritis, spiking fever, and either an evanescent salmon-colored rash or persistent papules and plaques.

Methods: We describe the clinical and biopsy findings in 10 patients with the evanescent rash of Still disease.

Results: Fourteen biopsy specimens were studied from seven women and three men with a mean age of 44.4 years. The skin lesions were typically erythematous macules, papules, or plaques with a median duration of 3 weeks. All patients had systemic symptoms, including fever and arthralgias. The infiltrate was predominantly lymphocytic in six biopsy specimens, approximately equal lymphocytic and neutrophilic in four biopsy specimens, and predominantly (although never exclusively) neutrophilic in four biopsy specimens. Other findings included focal vacuolar interface changes, neutrophilic eccrine hidradenitis, epidermal neutrophils, dermal mucin, and acanthosis associated with numerous upper epidermal dyskeratotic cells.

Conclusions: It is important to be aware of the broad histologic spectrum that may be encountered in Still disease and to consider Still disease in the differential diagnosis of neutrophil-rich, lymphocyte-rich, and mixed inflammatory dermatoses. While the histologic findings seen in biopsy specimens of the evanescent rash are nonspecific, a distinctive variant also exists characterized by prominent epidermal apoptosis, especially involving the upper layers.

In 1897, George Frederick Still1 described a series of children with a form of arthritis that he believed was distinct from rheumatoid arthritis. In this landmark account of the disease that is now named after Still, there is no mention of the cutaneous findings in his patients. This is curious since the evanescent rash is one of the most common and characteristic findings in Still disease. In fact, a triad of joint pain, fever, and rash characterizes the disease, and the rash is considered a major criterion for diagnosis. While Still details the bony pathology, drawing distinction with rheumatoid arthritis, there is no mention of cutaneous pathology. Since Still’s original description, there have been only a handful of publications focusing on the cutaneous pathology in the initial rash of Still disease. More recently, features of the more chronic rash associated with Still disease, so-called persistent papules and plaques, have been better characterized histologically, including upper keratinocyte dyskeratosis and scattered superficial dermal
Table II
Yamaguchi et al\(^8\) Criteria for Still Disease\(^a\)

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Minor Criteria</th>
<th>Exclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature of 39°C or higher, lasting 1 week or longer</td>
<td>Sore throat</td>
<td>Infections</td>
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<tr>
<td>Arthralgia lasting 2 weeks or longer</td>
<td>Lymphadenopathy and/or splenomegaly</td>
<td>Malignancies</td>
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<tr>
<td>Macular or papular nonpruritic salmon-pink rash appearing during fever</td>
<td>Liver dysfunction (elevated transaminases or LDH)</td>
<td>Rheumatic diseases</td>
</tr>
<tr>
<td>Leukocytosis (&gt;10,000/µL), including 80% or more granulocytes</td>
<td>Negative RF and negative ANA</td>
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*ANNA, antinuclear antibody; LDH, lactate dehydrogenase; RF, rheumatoid factor.

\(^a\) Diagnosis requires at least five criteria with at least two being major criteria.

Our own experience examining skin biopsy specimens from patients with the evanescent rash of Still disease suggested to us that there is a broader spectrum of pathologic changes than many published sources promote. We undertook this study to examine the spectrum of histologic findings in cutaneous eruptions seen in patients with the evanescent eruption of Still disease. Herein we describe our experience.

Materials and Methods

This study was conducted with approval from the Brigham and Women’s Hospital institutional review board. The files of our hospital were searched for biopsies performed between 1990 and 2013 from patients with a confirmed clinical diagnosis of adult Still disease. For all patients, the medical records were reviewed to ensure that patients met the Yamaguchi et al\(^8\) criteria for the disease. H&E-stained sections of the biopsy specimens identified by our search were reviewed. The patients’ medical records were reviewed to obtain relevant clinical information.

Results

Clinical Features

Our search identified 10 patients with Still disease who had skin biopsies performed. Relevant clinical data, including age, site and appearance of skin lesions, systemic symptoms, and results of serologic studies, are summarized in Table II. Seven patients were women and three were men. Ages ranged from 29 to 64 years (mean age, 44.4 years). Only one patient carried an established diagnosis of Still disease at the time of biopsy. Another had a “presumed” diagnosis based on clinical findings at the time of biopsy, but a definitive diagnosis was not yet established. While all of our patients were diagnosed in adulthood and would qualify as having adult-onset Still disease, of note, one patient (patient 2) had a history of skin lesions since age 10 years and was diagnosed with Still disease at age 50 years.

The skin lesions were typically erythematous macules, papules, or plaques. The duration of the current cutaneous eruption ranged from 2 to 8 weeks (median duration, 3.7 weeks). In three patients, the lesions were described as urticarial. The extremities were involved in nine patients. The trunk was involved in six patients, and the face was involved in one. In all but one patient, Still disease was raised in the clinical differential diagnosis. The clinical differential diagnosis included lupus erythematosus and dermatomyositis in one patient for whom Still disease was not considered at the time of biopsy. Other clinical differential diagnoses considered at the time of biopsy included drug eruption, urticaria, urticarial vasculitis, vasculitis, viral exanthem, connective tissue disease, parovirus, hypersensitivity reaction, serum sickness, sarcoidosis, familial Mediterranean fever, and cutaneous tuberculosis. All patients had systemic symptoms, including fever and arthralgias. Three patients had lymphadenopathy, and three complained of sore throat. All patients had negative rheumatoid factor, and all but one had negative antinuclear antibody (ANA) testing.

Possible alternative diagnoses that were considered included lupus for patient 4, who had a known positive ANA and a family history of lupus. However, the combination of her classic evanescence rash, associated symptoms, and laboratory work (Table 2) was felt to better fit with a diagnosis of Still disease. Patient 9 was diagnosed with and treated for a streptococcal throat infection 8 days prior to undergoing a skin biopsy. The persistence of her symptoms, including sore throat, fever, elevated WBC count, and arthralgias, prompted a reevaluation of her symptoms, which led to a diagnosis of Still disease. Of note, patient 10 carried a concurrent diagnosis of sarcoidosis and, therefore, had a second reason to have lymphadenopathy.

Clinical follow-up data were available for nine of the patients, ranging from 6 months to 27 years in duration. In the most recent clinical notes, four patients still had ongoing flares of disease. Patients 1 and 4 were diagnosed with macrophage activation syndrome 6 months and 3 years after their initial Still disease diagnosis, respectively. Other hematologic complications included thrombocytopenia (patient 7) and disseminated intravascular coagulation (patient 8). None of the 10 patients were diagnosed with lupus or other connective tissue diseases during the follow-up period.

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<tr>
<th>Case</th>
<th>Sex/Age, y</th>
<th>History of Still Disease Comorbidities</th>
<th>Skin Lesions</th>
<th>Distribution</th>
<th>Time Since Onset of First Rash; Duration of Current Lesions</th>
<th>Clinical Differential at the Time of Biopsy</th>
<th>Associated Symptoms</th>
<th>Laboratory Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/42</td>
<td>No</td>
<td>Erythematous and urticarial plaques</td>
<td>Extremities</td>
<td>3 wk; 3 wk</td>
<td>Still disease, familial Mediterranean fever, urticaria, urticarial vasculitis, drug eruption</td>
<td>Fever, arthralgias, sore throat</td>
<td>Neg, ferritin, 4,169 ng/mL; AST, 56 IU/L; ALT, 70 IU/L; Alk phos, 239 IU/L; WBC, 14.7 x 10^3/µL</td>
</tr>
<tr>
<td>2</td>
<td>M/50</td>
<td>“Presumed” Still disease at the time of biopsy; hypertension, hyperlipidemia, coronary artery disease, gout, reflex</td>
<td>Salmon-colored macules and papules</td>
<td>Chest</td>
<td>40 y; 2 wk</td>
<td>Still disease</td>
<td>Fever, arthralgias, sore throat, nausea/vomiting</td>
<td>Neg, ferritin, 134 ng/mL; AST, 19 IU/L; ALT, 20 IU/L; Alk phos, 52 IU/L; WBC, 20.1 x 10^9/µL</td>
</tr>
<tr>
<td>3</td>
<td>M/53</td>
<td>Yes</td>
<td>Erythema and erythematous papules; erythematous urticarial lesions</td>
<td>Chest, extremity</td>
<td>3 mo; 3 wk</td>
<td>SCLE, dermatomyositis</td>
<td>Fever, arthralgias, fatigue, anorexia, liver damage found on biopsy specimen</td>
<td>Neg, ferritin, 1,487 ng/mL; AST, 20 IU/L; ALT, 38 IU/L; Alk phos, 76 IU/L; WBC, 26 x 10^9/µL</td>
</tr>
<tr>
<td>4</td>
<td>F/29</td>
<td>No</td>
<td>Maculopapular eruption</td>
<td>Upper and lower extremities, chest</td>
<td>6 wk; 6 wk</td>
<td>Still disease</td>
<td>Fever, lymphadenopathy, splenomegaly, headache, arthralgias, joint swelling</td>
<td>Pos, ferritin, 17,460 ng/mL; AST, 141 IU/L; ALT, 131 IU/L; Alk phos, 115 IU/L; WBC, 9.4 x 10^9/µL</td>
</tr>
<tr>
<td>5</td>
<td>F/29</td>
<td>No</td>
<td>Macular erythema; erythematous macules, papules, and patches</td>
<td>Face; trunk and extremities diffusely</td>
<td>9 y; 3 wk</td>
<td>Still disease</td>
<td>Fever, arthralgias, myalgias</td>
<td>Neg, ferritin, 1,533 ng/mL; AST, 14 IU/L; ALT, 17 IU/L; Alk phos, 100 IU/L; WBC, 18.3 x 10^9/µL</td>
</tr>
<tr>
<td>6</td>
<td>F/64</td>
<td>No; hypertension, hyperlipidemia</td>
<td>Erythematous macules</td>
<td>Trunk, extremities</td>
<td>4 wk; 4 wk</td>
<td>Still disease, viral exanthem, drug eruption, sepsis, connective tissue disease</td>
<td>Fever, arthralgias, lymphadenopathy, hepatomegaly</td>
<td>Neg, ferritin, 1,470 ng/mL; AST, 20 IU/L; ALT, 38 IU/L; Alk phos, 76 IU/L; WBC, 26 x 10^9/µL</td>
</tr>
<tr>
<td>7</td>
<td>M/29</td>
<td>No</td>
<td>Macules and papules</td>
<td>Extremities</td>
<td>2 wk; 2 wk</td>
<td>Still disease, parvovirus, vasculitis</td>
<td>Fever, arthralgias</td>
<td>Neg, ferritin, 104 IU/L; AST, 20 IU/L; WBC, 20 x 10^9/µL</td>
</tr>
<tr>
<td>8</td>
<td>F/35</td>
<td>No</td>
<td>Erythematous macules</td>
<td>Extremities</td>
<td>8 wk; 8 wk</td>
<td>Still disease, dermato myositis</td>
<td>Fever, arthralgias, malaise</td>
<td>Neg, ferritin, 4,708 ng/mL; AST, 37 IU/L; ALT, 18 IU/L; Alk phos, 155 IU/L; WBC, 22.6 x 10^9/µL</td>
</tr>
<tr>
<td>9</td>
<td>F/57</td>
<td>No; diagnosed with and treated for strep throat 8 days prior</td>
<td>Macular erythema with few erythematous and edematous plaques</td>
<td>Trunk and extremities</td>
<td>2 wk; 2 wk</td>
<td>Urticaria, urticarial vasculitis, hypersensitivity reaction, serum sickness, Still disease</td>
<td>Sore throat, fever, arthralgias and joint swelling</td>
<td>Neg, ferritin, 4,562 ng/mL; AST, 24 IU/L; ALT, 24 IU/L; Alk phos, 126 IU/L; WBC, 23.8 x 10^9/µL</td>
</tr>
<tr>
<td>10</td>
<td>F/46</td>
<td>No; hypothyroidism, sarcoidosis</td>
<td>Erythematous plaques and urticarial wheals</td>
<td>Extremities</td>
<td>6 mo; 4 wk</td>
<td>Still disease, sarcoidosis, cutaneous tuberculosis</td>
<td>Fever, cough, arthralgias, lymphadenopathy</td>
<td>Neg, ferritin, 31 IU/L; ALT, 32 IU/L; Alk phos, 131 IU/L; WBC, 6.9 x 10^9/µL</td>
</tr>
</tbody>
</table>

Alk phos, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; Neg, negative; plt, platelets; Pos, positive; RF, rheumatoid factor; SCLE, subacute cutaneous lupus erythematosus.
Histopathologic Features

Fourteen biopsy specimens taken from 10 patients were examined. The histologic findings are summarized in Table 3. The biopsy specimens showed a spectrum of inflammation, both in terms of density of inflammation as well as composition of the infiltrate. Neutrophils comprised less than 10% of inflammatory cells in six biopsy specimens. These biopsy specimens were characterized by a predominantly lymphocytic infiltrate that was nearly exclusively perivascular in distribution. The lymphocytic infiltrate was mild or sparse in three biopsy specimens and moderately dense with a “cuffed” pattern resembling a gyrate erythema in three cases. An approximately equal lymphocytic and neutrophilic component was seen in four biopsy specimens. The neutrophilic component was perivascular and interstitially distributed, as well as sparse or mild in density, in these four biopsy specimens. The lymphocytic component was predominantly perivascular. In three biopsy specimens, approximately 75% of the inflammatory infiltrate was composed of interstitial and perivascular neutrophils with the remainder comprising perivascular lymphocytes. The neutrophilic infiltrate was sparse in one biopsy specimen and moderately dense in two biopsy specimens taken from patient 10. The two biopsy specimens from patient 9 were noted to have associated neutrophilic eccrine hidradenitis. In two biopsy specimens, neutrophils were seen within the epidermis. Dermal mucin was seen in two biopsy specimens and was abundant in one. Focal vacuolar interface changes were seen in seven biopsy specimens.

Two biopsy specimens from one patient (patient 3) with 3 weeks of erythematous papules showed striking histologic findings unlike that seen in any of the other nine patients. The biopsy specimens showed vacuolar interface changes, often associated with numerous apoptotic keratinocytes at all layers of the epidermis, with many in the upper layers of the epidermis. The inflammatory component in these two biopsy specimens was composed of lymphocytes.

Two samples had immunofluorescence studies performed (patients 6 and 3). Both showed nonspecific immunoreactivity.
Still disease is a rare disorder of uncertain pathogenesis characterized by arthritis or arthralgias, fever, leukocytosis with neutrophilia, and a highly characteristic salmon-colored evanescent cutaneous eruption that tends to accompany episodes of fever. Other characteristic features seen in some of our patients include sore throat, elevated ferritin levels, lymphadenopathy, and splenomegaly. Rheumatoid factor and ANA tests are negative.

A review of the major dermatopathology textbooks reveals that most make no mention of the pathology of the eruption associated with Still disease. In addition, a survey of those that do discuss Still disease reveals a puzzling finding—there seems to be little agreement on the histopathologic features. One textbook tells the reader that in adult Still disease, “there are no associated lymphocytes” and the “presence of neutrophils in the dermis is another characteristic feature.” UpToDate, a reference used by many of our clinical colleagues, states the rash associated with adult Still disease “reveals dermal edema and mild perivascular inflammation in the superficial dermis, consisting primarily of lymphocytes and histiocytes.” Only rare textbooks hint that a spectrum of inflammatory changes, ranging from chronic to acute inflammation, may be encountered.

Review of the primary literature is also revealing, perhaps accounting for the presence of seemingly contradictory information encountered in textbooks. One author informs...
The more recent literature seems to have moved on from the conflicting histologic characterization of the evanescent rash of Still disease to focus on more unusual variants, particularly persistent papules and plaques.\cite{2,3,6,7} The histologic findings seen in patient 3 are characteristic of those described in these cases but, interestingly, the lesions in our patient were described as evanescent. The presence of significant acanthosis and mounds of parakeratosis seems incompatible with an evanescent lesion, so we must question the accuracy of the clinical history. Some authors have noted that, in some patients, the persistent rash may follow the typical evanescent lesion, and it is possible our case represents a transitional morphologic stage between the classic and rheumatoid-type arthritis beginning before age 16 years, and rheumatoid arthritis. It is difficult to discern whether the patients they are referring to in the discussion of histopathology in fact have Still disease or if their rash is a manifestation of rheumatoid arthritis; however, the study and tables indicate that most of the patients with rash also had fever and lymphadenopathy, and many had splenomegaly. Although it was published in 1956, this study is often referenced and may have contributed to some extent to the confusing literature. One of its authors performed a follow-up study—this time focusing exclusively on the rash in adults with Still disease—including four patients from his previous study.\cite{14} In this follow-up study, the author states the biopsy specimens showed “in cases 1, 2, and 10 polymorphs beneath the epidermis quite similar to the juvenile cases.” Of the 14 cases, how many were biopsied? Are cases 1, 2, and 10 the cases included in the previous study? If any other cases were biopsied, what did those biopsy specimens show? The study does not answer these questions. More recently, one group of investigators in an article published in 2005 cites the study by Yamaguchi et al\cite{8} as stating “the histology of the typical evanescent rash is characterized by a relatively sparse perivascular mixed inflammatory infiltrate containing some neutrophils.”\cite{2} Again, in 2012, the same authors make a similar statement.\cite{5} Yet, the study by Yamaguchi et al makes no mention of the skin pathology in patients with Still disease other than the unusual statement that “this disease almost lacks specific clinical, laboratory, and histologic features” in the Introduction.\cite{8}

So, how can we make sense of the contradicting statements regarding the histopathology of Still disease? We believe that, given the rarity of the disorder and the broad spectrum of histologic findings encountered, it is not surprising that different pathologists and clinical centers would have different experiences due to sampling bias. We believe our cases are likely fairly representative of the spectrum of changes seen in cutaneous Still disease. Given that we and others have described biopsy specimens exhibiting a spectrum ranging from lymphocytic-rich to neutrophil-rich infiltrates as well as interface changes, which can be either vacuolar or lichenoid, the differential diagnosis almost seems impossibly large and includes broad categories such as gyrate erythemas and connective tissue disease. An important differential diagnostic consideration that is nearly impossible to distinguish on histology is systemic lupus erythematosus–associated neutrophilic dermatosis.\cite{15} What, then, is the role of the biopsy in suspected Still disease? Clearly, the clinical context is important. It may be that biopsy of a salmon-colored evanescent rash in a patient that clearly meets criteria for Still disease is unnecessary. In other patients, who are more difficult to classify, biopsy may be helpful, if only to exclude other possibilities. For example, the presence of numerous eosinophils was not seen in any of our cases, and we are unaware of this as a feature of Still disease. The presence of numerous eosinophils, which may be seen in some entities considered in the differential diagnosis (ie, drug eruption) with Still disease, could be very helpful in arriving at the correct diagnosis.

The histo...
evanescent lesion and persistent lesions. Another possibility, given that the patient was taking steroids at the time of biopsy, is that the treatment may have altered the clinical and/or pathologic appearance of the lesions. In contrast to the evanescent lesions, some authors consider the combination of clinical findings and histopathology of the persistent lesions to be distinctive. The presence of apoptotic keratinocytes preferentially distributed in the upper half of the epidermis would be unusual for most lichenoid or vacuolar interface tissue reactions such as drug eruption, lichen planus, or other forms of connective tissue disease (ie, lupus erythematosus, dermatomyositis) that may be considered in the differential diagnosis. The lack of significant numbers of eosinophils may be helpful in the distinction with drug eruption. Recognition of the persistent form of the disease may be particularly important since some authors have suggested it is associated with a worse prognosis, at least in adults. The experience of some authors suggests that the persistent lesions are more common than may be appreciated, implying that despite the relatively distinctive histologic appearance, this cutaneous manifestation is probably underrecognized.

In summary, the histologic findings in the evanescent rash of Still disease are broad and nonspecific. Biopsy of the evanescent rash may be more useful to rule out other disorders rather than to rule in a diagnosis of Still disease. In contrast, a second variant of rash in patients with Still disease, persistent pruritic papules and plaques, has unusual and characteristic histologic features that are likely to be readily recognizable to the pathologist who is aware of this manifestation. As more cases are studied, we expect the clinicopathologic spectrum of Still disease may continue to be expanded and refined. We hope that increased awareness of the broad spectrum of cutaneous pathologic findings in Still disease will raise this disease as a diagnostic consideration more frequently in patients with fever, arthralgias, and rash and thus lead to improved patient care.

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References