Cutaneous hemophagocytosis: Clinicopathologic features of 21 cases

Francesca Boggio, MD,[a,b] Viviana Lora, MD,[c] Carlo Cota, MD,[c] Amanda Pereira, MD,[a,d] Robert Müllegger, MD,[e] Lucia Prieto-Torres, MD,[a,f] and Lorenzo Cerroni, MD[a]

Graz and Wiener Neustadt, Austria; Milan and Rome, Italy; Florianópolis, Brazil; and Zaragoza, Spain

Background: Hemophagocytosis is well known in cytotoxic cutaneous T-cell lymphomas (CTCLs), in which it may represent a sign of hemophagocytic lymphohistiocytosis syndrome (HLHS), and is also typical of cutaneous Rosai-Dorfman disease (cRDD) (without prognostic relevance). Only rarely, has cutaneous hemophagocytosis (CH) been described in other skin conditions.

Objective: To characterize the clinicopathologic features of CH in skin biopsy specimens from patients with conditions other than CTCL or cRDD.

Methods: Case series analyzing clinicopathologic features and follow-up data on patients presenting with histopathologic signs of CH.

Results: Biopsy specimens from 21 patients were included. None of the patients had HLHS. The majority (n = 11) presented with leukocytoclastic vasculitis. Other associated diseases were lupus erythematous (n = 2), arthropod bite reaction (n = 2), erysipelas (n = 1), acne conglobata (n = 1), and Sweet syndrome (n = 1). Three patients had a nonspecific rash concomitant with *Chlamydia* pneumonia, middle ear infection, and pharyngitis, respectively.

Limitations: This was a single-center, retrospective study.

Conclusion: Isolated CH in conditions other than CTCL and cRDD is a histopathologic finding related mostly to leukocytoclastic vasculitis. Extensive investigations should be performed only if patients have other signs or symptoms of HLHS. (J Am Acad Dermatol 2018;78:377-82.)

Key Words: arthropod bite reaction; cutaneous hemophagocytosis; cutaneous lupus erythematosus; erysipelas; hemophagocytic syndrome; leukocytoclastic vasculitis.

Macrophagic cytophagocytosis (hemophagocytosis) refers to the engulfment of blood cells by nonmalignant macrophages (sometimes referred to as "bean bag" cells) and is characterized histopathologically by the presence of erythrocytes, platelets, or leukocytes (or fragments of these cells) within the cytoplasm of macrophages. In the context of a characteristic clinical presentation, it represents a diagnostic clue

Abbreviations used:

CH:	cutaneous hemophagocytosis
cLE:	Cutaneous lupus erythematosus
cRDD:	cutaneous Rosai-Dorfman disease
CTCL:	cutaneous T-cell lymphoma
HLHS:	hemophagocytic lymphohistiocytosis syndrome
LV:	leukocytoclastic vasculitis
RDD:	Rosai-Dorfman disease

From the Research Unit Dermatopathology, Department of Dermatology, Medical University of Graz[a]; School of Pathology, University of Milan, Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Milan[b]; Dermopathology Unit, San Gallicano Dermatologic Institute, Rome[c]; Anatomic Pathology Unit, Hospital Universitário Polydoro Ernani de São Thiago, Universidade Federal de Santa Catarina, Florianópolis[d]; Department of Dermatology, General Hospital of Wiener Neustadt[e]; and Hospital Clínico Universitario Lozano Blesa, Zaragoza.[f]

Funding sources: None.

Conflicts of interest: None declared.

Accepted for publication August 22, 2017.

Reprints not available from the authors.

Correspondence to: Lorenzo Cerroni, MD, Department of Dermatology, Medical University of Graz, Auenbruggerplatz 8, A-8036 Graz, Austria. E-mail: lorenzo.cerroni@medunigraz.at.

0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2017.08.041

for the hemophagocytic lymphohistiocytosis syndrome (HLHS), which is an aggressive and life-threatening condition caused by excessive immune system activation. HLHS may occur as a primary (familial) or secondary (reactive) disorder triggered by a variety of conditions such as infections or malignancies.[1-3] Besides HLHS, the presence of intact leukocytes within the cytoplasm of macrophages (emperipolesis) is a characteristic histopathologic finding of Rosai-Dorfman disease (RDD).[4] In the skin, histopathologic signs of hemophagocytosis are well described in cases of cutaneous T-cell lymphoma (CTCL) with a cytotoxic phenotype,[5-9] particularly those involving the subcutaneous tissue, and in cutaneous RDD (cRDD),[10] but they have been reported only rarely in biopsy specimens taken from patients with conditions other than CTCL or cRDD, mostly in the setting of leukocytoclastic vasculitis (LV).[11-17] The implications of this potentially significant histopathologic finding have yet to be clearly elucidated, as only a few case reports have been published so far.

We collected data from 21 patients presenting with histopathologic features of cutaneous hemophagocytosis (CH) not associated with CTCL or cRDD to better characterize the clinicopathologic background related to this unusual histopathologic finding.

CAPSULE SUMMARY

- Cutaneous signs of hemophagocytosis may be present in T-cell lymphomas and Rosai-Dorfman disease.
- Rarely, signs of hemophagocytosis can also be observed in skin biopsy specimens from patients with other conditions.
- In the absence of specific signs and symptoms, extensive investigations are not necessary in patients with histopathologic signs of hemophagocytosis.

MATERIAL AND METHODS

Histopathologic reports mentioning CH were collected from the database of the Research Unit Dermatopathology, Department of Dermatology, Medical University of Graz, Austria, during the period from 2003 to 2017. Three of the cases had been sent in consultation to 1 of us (L.C.). Patients with a concomitant or pre-existing diagnosis of CTCL or cRDD were excluded. The study was approved by the ethic committee of the Medical University of Graz (21-080 ex 09/10).

The histologic features of the hemophagocytic cells were analyzed for distribution (interstitial and/or perivascular), extent (described as mild, moderate, or severe and indicated as +, ++, and +++, respectively), and location in the skin specimen (papillary and/or reticular dermis). Histopathologic features of concomitant skin diseases, if present, were noted as well.

RESULTS

A total of 22 formalin-fixed skin biopsy specimens from 21 patients were included in the study (male-to-female ratio, 15:6; mean age, 56,4 years; median age, 63 years; and range, 4-87 years). Clinical and histopathologic findings for all patients are listed in Table I.

Clinically, the majority of patients (n = 11) presented with features of LV (Fig 1) located mostly on the lower extremities. Cutaneous lupus erythematosus (cLE) was observed in 2 patients (both with a known history of cLE) (Fig 2), arthropod bite reaction was noted in 2 (Fig 3), and erysipelas (on the breast after mastectomy for a breast carcinoma) and acne conglobata (bilateral on the axillae and groin) were seen in 1 each. The specimen from the patient with acne conglobata was obtained in the context of surgical treatment of the condition. One patient (case 20) had recurrent, asymptomatic plaques on the extremities for approximately 1 year that responded to short courses of systemic steroids and was classified as Sweet syndrome. In the remaining 3 cases, at the time of the skin biopsy no clear-cut associated dermatologic condition could be found (Fig 4). These 3 patients experienced mild systemic symptoms (fever and malaise) with a nondescript rash. In 1 of them (case 17) a concomitant *Chlamydia* pneumonia was diagnosed; the second patient (case 18) had a middle-ear infection, and the third (case 19) had a viral pharyngitis.

Skin biopsy specimens in all cases revealed inflammatory infiltrates with variable degrees of hemophagocytosis (Fig 5). The features of hemophagocytosis were found mostly in the papillary and mid dermis (22 biopsy specimens), with concomitant involvement of the reticular dermis in 10 cases (in these cases too, a top-heavy arrangement of the hemophagocytic cells was observed). The subcutaneous fat was not involved (other than at the cutaneous-subcutaneous junction in cases with involvement of the reticular dermis). Other histopathologic features differed in the various groups, corresponding to the background conditions. Eleven cases revealed features consistent