Histiocytoid Sweet syndrome may indicate leukemia cutis: A novel application of fluorescence in situ hybridization

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Background: In patients with malignancy-associated Sweet syndrome, a thorough evaluation for leukemia cutis should be considered.

Objective: We sought to describe the clinicopathologic characteristics of histiocytoid Sweet syndrome.

Methods: We retrospectively identified patients with histiocytoid Sweet syndrome at our institution from January 1992 through December 2010. We evaluated the underlying cutaneous infiltrate using immunohistochemistry and fluorescence in situ hybridization.

Results: We re-evaluated all 22 patients with hematologic malignancy–associated Sweet syndrome. Six patients had a monocytoid infiltrate that was consistent with histiocytoid Sweet syndrome; subsequent evaluation of these patients demonstrated cytogenetic abnormalities on prior bone-marrow biopsy specimens. Fluorescence in situ hybridization analysis was feasible in cutaneous specimens from 5 of the 6 patients and demonstrated the same cytogenetic abnormalities that were identified on prior bone-marrow biopsy specimens in 4 patients. Therefore, these 4 patients may have had a form of leukemia cutis.

Limitations: This was a retrospective study.

Conclusion: For patients with histiocytoid Sweet syndrome, an underlying hematologic malignancy, and a monocytoid infiltrate on biopsy specimen, fluorescence in situ hybridization of the cutaneous infiltrate may be beneficial to identify cytogenetic abnormalities that may indicate leukemia cutis. (J Am Acad Dermatol 2014;70:1021-7.)

Key words: cytogenetic abnormalities; fluorescence in situ hybridization analysis; histiocytoid Sweet syndrome; leukemia cutis; malignancy-associated Sweet syndrome; Sweet syndrome.

In 1964, Sweet syndrome, also known as acute febrile neutrophilic dermatosis, was initially described by Robert Douglas Sweet.[1] Since then, Sweet syndrome has become part of a larger group of dermatologic diseases with an underlying neutrophilic infiltrate.[2] The diagnostic criteria of Sweet syndrome were delineated by Su and Liu,[3] and one of the major criteria required for diagnosis is histopathologic evidence of a neutrophilic infiltrate, typically in the absence of leukocytoclastic vasculitis.[2,4,5] Sweet syndrome can be associated with an underlying hematologic myeloid disorder, solid tumor malignancies, inflammatory bowel disease, and gastrointestinal tract and upper respiratory tract infections.[6-10] A number of medications are also known to cause Sweet syndrome.[11,12]

Abbreviations used:

FISH: fluorescence in situ hybridization
MLL: mixed lineage leukemia gene

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More recently, Requena et al[13] described a variant of Sweet syndrome, histiocytoid Sweet syndrome, in which a predominantly histiocytoid-appearing infiltrate was identified on histopathologic evaluation. The mononuclear cells were immunoreactive for CD15, CD43, CD45, CD68, MAC-386, HAM56, myeloperoxidase, and lysozyme, consistent with histiocytoid-appearing immature myeloid cells.[13] In a subset of the cases, fluorescence in situ hybridization (FISH) studies to determine the presence of BCR/ABL gene fusion was performed and was negative in all the cases tested in their study.[13] The BCR/ABL FISH analysis was used in an effort to exclude leukemia cutis, but only from chronic myelogenous leukemia, which was not a confirmed diagnosis in the majority of patients in that study. The observations by Requena et al[13] have also been reported by other investigators.[14-17]

CAPSULE SUMMARY

- Histiocytoid Sweet syndrome is characterized by a predominance of mononuclear cells on histopathologic evaluation.
- Patients given the diagnosis of histiocytoid Sweet syndrome may have leukemia cutis.
- When a diagnosis of histiocytoid Sweet syndrome is being considered, additional histopathologic investigations may be needed to evaluate for leukemia cutis, because these mononuclear cells may harbor corresponding cytogenetic abnormalities.

These findings have prompted both clinicians and pathologists to consider a broader definition of Sweet syndrome in cases where the traditional diagnostic criteria[3] are not fully met. Using FISH analysis in 5 cases, we demonstrated that the cytogenetic abnormalities identified on prior bone-marrow biopsy specimens were also present in skin biopsy specimens. In this study, we demonstrate the importance of evaluating patients with histiocytoid Sweet syndrome for leukemia cutis.

METHODS

After Mayo Clinic Institutional Review Board approval, we identified patients with a diagnosis of Sweet syndrome at Mayo Clinic, Rochester, MN, between January 1, 1992, and December 31, 2010. Patients who denied research authorization for review of their medical records were not included in this study. We identified 21 patients with an underlying hematologic malignancy and concomitant diagnosis of Sweet syndrome. One patient who was not identified in our initial search was added to the 21 identified patients. All cases selected were evaluated by 2 reviewers to confirm the diagnostic criteria for Sweet syndrome[3] were met. For the 22 patients, the following clinical data were abstracted from the medical records using the institutional patient database: age; sex; location, description, and duration of the lesion; underlying hematologic malignancy; duration of disease; bone-marrow biopsy specimen abnormalities; and treatment and response to treatment.

In 6 patients, a chromosomal abnormality was noted in the bone-marrow biopsy specimen. In 5 patients, FISH analysis was performed to evaluate for the presence of a chromosomal abnormality in the cutaneous infiltrate of their initial biopsy specimen. In 1 patient, it was not possible to design a FISH strategy to specifically evaluate the cutaneous infiltrate for the chromosomal abnormality identified in the bone marrow.

Briefly, formalin-fixed, paraffin-embedded sections were prepared for FISH analysis as described previously.[18] Probes used in this study were centromere 8 and cMYC (8q24.1), DEK (6p23) and CAN (9q34), ABL (9q34) and BCR (22q11.2), centromere 9 and CTD-244M18 (9q21), 7q (D7S486), and MLL (11q).

RESULTS

Clinical data

Clinical characteristics and appropriate laboratory data for each patient are listed in Table I. Eight female patients ranged in age from 40 to 76 years (median, 64 years), and 14 male patients ranged in age from 51 to 80 years (median, 72 years). The most common cutaneous presentation was erythematous plaques (Fig 1), with underlying tenderness, fever, arthralgia, and fatigue. Eighteen patients were treated with systemic corticosteroids, usually followed by resolution of their skin lesion. In 1 patient, topical corticosteroids were used; in 3 patients, the treatments were not described. Three patients did not respond to treatment with systemic corticosteroids and were subsequently treated with colchicine.

The most common hematologic malignancies were myelodysplastic syndrome in 10 patients and acute myelogenous leukemia in 3 patients. Myeloproliferative disorder, multiple myeloma, and chronic lymphocytic leukemia occurred in 2 patients each. Non-Hodgkin lymphoma, refractory anemia with excess blasts, and chronic myelogenous leukemia each occurred in 1 patient. In 6 patients, bone-marrow biopsy specimens demonstrated a