Original Study

Characteristics of Sweet Syndrome in Patients With Acute Myeloid Leukemia

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Abstract

Sweet syndrome (SS) is a dermatologic disorder observed in various benign or malignant conditions including acute myeloid leukemia (AML). We reviewed 2178 AML patients treated from 2000 to 2011 and identified 21 patients who developed SS. SS occurred more frequently in the setting of AML with myelodysplasia-related features, −5/del(5q) cytogenetics, and FMS-related tyrosine kinase 3 genetic aberrations.

Introduction: Sweet syndrome (SS) is associated with hematologic malignancies including acute myeloid leukemia (AML). **Patients and Methods:** Records of patients with AML treated at our institution were reviewed to identify those with SS. Patient characteristics, laboratory values, and cytogenetic and molecular abnormalities were retrospectively reviewed. **Results:** We identified 21 of 2178 (1%) AML patients who demonstrated clinical signs and symptoms, and histological features consistent with SS. Eleven patients (52%) were classified as AML with myelodysplasia-related features and 3 patients had therapy-related AML. Three patients had received treatment with granulocyte colony stimulation factor, 1 patient liposomal all-*trans*-retinoic acid, and 2 patients received hypomethylating agents before development of SS. Cytogenetic analysis revealed diploid karyotype in 7 patients (33%); −5/del(5q) in 8 patients (38%): 3 patients had −5/del(5q) as the sole abnormality and 5 patients had −5/del(5q) as part of complex cytogenetics; and complex cytogenetics in 5 patients (24%). Gene mutations in FMS-related tyrosine kinase-3 (*FLT3*) gene were identified in 7 of 18 evaluable patients (39%), including *FLT3*−internal tandem duplication in 4 patients and *FLT3*−D835 tyrosine kinase domain mutation in 3 patients. **Conclusion:** SS occurs in 1% of AML patients; −5/del(5q) karyotype, *FLT3* mutations, and AML with myelodysplasia-related features were more frequent among patients with SS.

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Introduction

Sweet syndrome (SS), or acute febrile neutrophilic dermatosis, is characterized by recurrent fever and presence of a dense papillary or upper reticular dermal infiltrate of normal-appearing mature polymorphonuclear cells (PMNs).[1,2] SS was originally reported by Robert Douglas Sweet in 1964, when he described a case series of 8 women between the ages of 32 and 55 years, who presented with fever, tender erythematous cutaneous plaques, neutrophilia, and a dense neutrophilic infiltrate in the upper dermis on histology. All 8 patients responded promptly to glucocorticoid therapy.[3] Generally, the cutaneous lesions in SS manifest as erythematous plaques and nodules of variable size that mostly involve the extremities or head and neck and less frequently trunk, back, and mucosal surfaces.[4] SS can occasionally cause an intense systemic response

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involving the lungs, liver, and musculoskeletal system, sometimes resulting in shock, multiple organ failure, and death. However, in most instances the manifestations of SS might be reversible with rapid initiation of glucocorticoid therapy.[5-7]

Sweet syndrome is frequently idiopathic; however, in a minority of cases a possible etiologic association can be identified with infections, autoimmune disorders, medications (drug-associated SS; DA-SS) or malignancies (also called malignancy-associated SS; MA-SS). Von den Driesch in 1994 proposed the currently used diagnostic criteria for SS, in turn a modification of diagnostic criteria for SS previously proposed by Su and Liu. These criteria consist of major and minor criteria (see Patients and Methods). Major and at least 2 minor criteria must be fulfilled to confirm a diagnosis of SS.[4,8] Fever, neutrophilia, and increased erythrocyte sedimentation rate (ESR) level remain part of the diagnostic criteria for idiopathic SS and MA-SS, however, these findings can occasionally be absent in MA-SS.[9] For DA-SS, the diagnosis requires establishment of a temporal association between development of SS rash, initiation of therapy with the responsible drug, and improvement when the drug is withheld.[10]

Malignancy-associated SS, constituting only 15% to 20% of cases of SS, has been reported in association with hematological and visceral malignancies, with acute myeloid leukemia (AML) being the most common malignancy associated with MA-SS.[11-14] SS might also occur as a paraneoplastic condition in other hematological conditions such as myelodysplastic syndrome (MDS), B and T cell non-Hodgkin lymphoma, chronic lymphocytic leukemia, multiple myeloma, myeloproliferative neoplasms (MPN), or in the setting of visceral malignancies such as genitourinary, breast, or colorectal cancer. In MA-SS, the cutaneous manifestations of SS can occur before, during, or after the diagnosis of the malignancy and thus its onset might herald the diagnosis of malignancy in individuals with no previous malignancy or might indicate a recurrence in patients with a previous history of cancer.[2,15] In SS associated with hematological diseases such as AML, MDS, and MPN, the PMNs in the dermal infiltrate might be clonally derived from either the malignant or nonmalignant cells.[16-18] Occasionally, malignant cells can be found among the PMNs (representing concurrent leukemia cutis).[18] Similarly, medications used in management of hematological malignancies such as granulocyte colony stimulation factor (G-CSF), granulocyte-macrophage colony stimulating factor, all-*trans*-retinoic acid (ATRA), and hypomethylating agents such as azacytidine and decitabine have been associated with SS, supporting the role of cytokines, maturation defects, and epigenetic changes in the pathogenesis of SS.[15,19-24]

Although AML is the most common hematological malignancy associated with SS, the exact incidence and molecular characteristics of AML patients who develop SS remains undefined. In this study, we sought to identify specific disease features and cytogenetic or molecular aberrations that occur in patients with AML and SS.

Patients and Methods

The charts of all patients with AML who had been diagnosed, received treatment, and had follow-up at M.D. Anderson Cancer Center between January 2000 and December 2011 were retrospectively reviewed after receiving approval from our institutional review board (IRB; protocol PA11-0878). Patients who had a skin biopsy during the management of AML were identified and only patients with skin biopsy consistent with neutrophilic dermatosis (SS) were included. To identify the patients who met von den Driesch-modified Su and Liu diagnostic criteria for SS, the clinical characteristics were reviewed. This diagnostic criteria consists of major criteria (ie, abrupt onset of tender erythematous papules and nodules, and dense neutrophilic infiltrate in the dermis without leukocytoclastic vasculitis) and minor criteria including presence of fever $\geq 38^{\circ}C$, at least 2 of 4 abnormal laboratory values (White blood cell count [WBC] > 8000, neutrophils $> 70\%$, ESR > 20 mm/h and positive C-reactive protein), a disease condition associated with SS (eg, infection, malignancy, inflammatory disorder, etc) and an excellent response to treatment with glucocorticoids. To diagnose SS, both major criteria and at least 2 minor criteria had to be fulfilled. Patients who fulfilled the von den Driesch diagnostic criteria were included in our analysis. Patients were excluded from this analysis if the clinical signs and symptoms were consistent with skin infection, abscess, or if infectious organisms were isolated from skin culture. Similarly, patients were excluded if the signs and symptoms or skin biopsy were more consistent with other causes of neutrophilic dermatosis (such as pyoderma gangrenosum) or if there was histological evidence of vasculitis. In addition, patient characteristics, and AML characteristics at initial diagnosis and at the time of diagnosis of SS were reviewed. The latter included cytogenetics and molecular aberrations by banding karyotype, fluorescence in situ hybridization (FISH) analysis, and reverse transcriptase polymerase chain reaction (RT-PCR).

Additionally, after obtaining separate IRB protocol approval from our institution (PA13-0840), FMS-related tyrosine kinase-3 (*FLT3*) mutational analysis (codon 835 and internal tandem duplication [ITD]) was performed on DNA extracted from formalin-fixed paraffin embedded (FFPE) tissue sections of the skin lesions from patients who were found to have *FLT3* mutations, using previously described methods.[25]

Descriptive statistics including median and range for continuous variables such as age and laboratory measurements, and time to improvement of SS signs and symptoms are provided. Frequency counts and percentages for categorical variables such as sex, classification of AML, and cytogenetic and genetic mutations expression are also described. The Kaplan–Meier method was used for analysis of overall survival from diagnosis of AML and reported as median months with a 95% confidence interval. Statistical software IBM SPSS Statistics 19.0 (IBM Corp, Armonk, NY) was used for the statistical analyses.

Results

A total of 2178 patients with newly diagnosed AML underwent induction chemotherapy and had follow-up at our institution between the years 2000 and 2011. Six hundred ninety-seven patients (32%) had documented skin biopsies during the course of their AML therapy or during follow-up during this time period. Twenty-nine of these patients received a histological diagnosis of neutrophilic dermatosis. Of these, 8 patients did not meet the von den Driesch modified criteria for diagnosis of SS (3 patients were considered to have skin infections as the underlying etiology, 4 patients had neutrophilic dermatosis but not SS based on histological assessment by a pathologist, and 1 patient was diagnosed with vasculitis). Thus, 21 patients met the von den Driesch