CASE REPORT

Histiocytoid Variant of Sweet Syndrome Associated with Azacitidine and Recurrence upon Rechallenge

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NTRODUCTION

Sweet syndrome was first described in 1964, at which time it was termed acute febrile neutrophilic dermatosis.[1] Up to 20% of patients with Sweet syndrome have an associated malignancy, of whom about 85% have a hematologic disorder.[2] The hallmark of Sweet syndrome is a nodular and diffuse dermal infiltrate of neutrophils identified on biopsy.[3] The mechanism of the syndrome is not completely understood, but it is known to be mediated by neutrophils.[4] More than three-quarters of patients have systemic findings, with fever in 50%–80% of patients.[3] Many medications have been reported to induce the syndrome; granulocyte colony-stimulating factor, antibiotics, and vaccines are most frequently observed.[2,5]

Although it is predominantly mature neutrophils that infiltrate the dermis, abnormal or immature myeloid cells have also been observed.[2] In patients with hematologic disorders, both abnormal neutrophils (leukemia cutis) and mature neutrophils may constitute the dermal infiltrate.[2] A pathologic histiocytoid variant of Sweet syndrome has been described, characterized by an infiltrate of immature myeloid cells.[6]

Azacitidine is an antineoplastic agent that is administered for 7 consecutive days every 28 days to treat adult patients with myelodysplastic syndrome or acute myeloid leukemia (AML) who are not eligible for hematopoietic stem cell transplant.[7] Two case reports of azacitidine-associated Sweet syndrome[8,9] and one case of histiocytoid Sweet syndrome associated with azacitidine[10] were retrieved from a literature search of PubMed, Embase, and MEDLINE. The case described here is notable because the patient experienced 2 episodes of Sweet syndrome while receiving azacitidine, with the recurrent episode (after rechallenge with azacitidine) appearing to be the histiocytoid variant.

CASE REPORT

A 66-year-old man with type 2 diabetes mellitus, dyslipidemia, and hypertension received a diagnosis of chronic myelomonocytic leukemia which transformed to AML.* He had no known drug allergies. At admission, his medications were irbesartan, atorvastatin, gliclazide, and metformin–sitagliptin. Azacitidine therapy was prescribed for the AML, with each 28-day cycle consisting of 7 days of azacitidine therapy followed by 21 days of no therapy. Twelve days into the second cycle, painful red plaques developed on the back of the patient's neck and left arm, with fever commencing 3 days later. Erythematous, indurated, and raised plaques were present over the back of the neck and left upper arm, and biopsy demonstrated early Sweet syndrome. He had a leukocyte count of 1.2×10^9/L (normal range 4.0 to 11.0×10^9/L), hemoglobin of 96 g/L (normal range 137–180 g/L), absolute neutrophil count of 1.0×10^9/L (normal range 2.8 to 8.0×10^9/L), and platelet count of 217×10^9/L (normal range 150 to 400×10^9/L). As such, he had leukopenia, anemia, and mild neutropenia, with a normal platelet count.

The results of repeated blood culture (8 sets of samples) were negative, and the patient continued to exhibit fever, with periodic episodes of hypotension that eventually led to admission to the intensive care unit. He was treated empirically with filgrastim, meropenem, vancomycin, and micafungin. However, another edematous erythematous plaque developed on the left groin, his temperature remained elevated, despite the antibiotic therapy, and other diagnoses were therefore considered. A second skin biopsy of the left upper thigh yielded findings characteristic of

*The patient provided informed consent for publication of this report.

Sweet syndrome, with pathologic examination demonstrating diffuse neutrophilic infiltrate extending through the dermis and subcuticular fat. Prednisone (1 mg/kg per day) was started, the lesions gradually improved, and the patient became hemodynamically stable.

The patient was rechallenged with azacitidine, as others have tolerated rechallenge,[8] and he continued with the monthly courses. However, about 2 days after completion of his seventh cycle (i.e., 7 months since initiation of azacitidine), he noticed a painful lesion on his left shin. He was admitted with signs of sepsis, and increasing size and pain of the leg ulceration. The plastic surgery team found what appeared to be full skin thickness necrosis. Additional medications prescribed since the previous episode of Sweet syndrome were insulin, several cycles of antifungals, ranitidine, zopiclone, ondansetron, and prednisone 1 mg/kg per day (for treatment of the initial episode). Microbiology cultures were negative for bacteria and fungi. The surgical tissue sample contained a nodular and diffuse infiltrate of immature neutrophils that were strongly positive for CD15 and myeloperoxidase. Additionally, these cells had a histiocytic appearance, widespread spongiotic vesiculation of the overlying epidermis, and some pustule formation. There was no evidence of dermal or subcuticular necrosis or vasculitis. These pathologic findings led to a probable diagnosis of a histiocytoid variant of Sweet syndrome. The same dermatopathologist reviewed slides from both the first and second episodes and concluded that the findings in samples from the 2 episodes were similar. The patient's condition improved with debridement, skin grafting, and prednisone. At the time of writing, he had not received any more cycles of azacitidine.

DISCUSSION

The diagnosis of Sweet syndrome involves fulfillment of the 2 major criteria and at least 2 of the 4 minor criteria proposed by Su and Liu in 1986.[11] The patient described here met both of the major diagnostic criteria: abrupt onset of painful erythematous plaques or nodules and histopathologic evidence of a dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis. In addition, he met 3 of the 4 minor criteria: temperature above 38°C, association with an underlying malignancy, and good response to glucocorticoid therapy. The fourth minor criterion is abnormal laboratory values at presentation (erythrocyte sedimentation rate > 20 mm/h, positive result for C-reactive protein, leukocyte count > 8.0×10^9/L, and/or > 70% neutrophils).[11] This patient's second episode resembled necrotizing Sweet syndrome, as he presented with the signs and symptoms of necrotizing fasciitis (edema, erythema, inflammation rapidly extending horizontally and vertically).[12] There was gross appearance of necrosis during debridement; however, no microscopic evidence of necrosis was found in the tissue, and pathologic examination showed cells with a histiocytic appearance. These features led to a probable diagnosis of a histiocytoid variant of Sweet syndrome. The histopathology samples from the first episode were described (at the time of initial examination) as consistent with Sweet syndrome and, upon retrospective review by the same pathologist, were deemed consistent with the same pathophysiologic process as in the second episode. Therefore, we feel confident in concluding that this case represents a recurrent phenomenon secondary to rechallenge with azacitidine.

The findings for this patient met not only the criteria for Sweet syndrome as outlined by Su and Liu,[11] but also the 5 criteria for drug-induced Sweet syndrome suggested by Walker and Cohen.[13] Specifically, this case met the 3 descriptive criteria (abrupt onset of painful erythematous plaques or nodules, histiopathologic evidence, and temperature > 38°C), the criterion for a temporal relationship between administration of azacitidine and development of the syndrome, and the criterion for resolution of symptoms when corticosteroids were given and azacitidine was withheld. To further assess the causality of Sweet syndrome in relation to azacitidine, the algorithm of Naranjo and others[14] was applied with the suggested modification of Thompson and others[15] for drug-induced Sweet syndrome. A specific time element was not added to this scale, as the timing has been extremely variable in the cases reported. According to the expanded scale,[15] the adverse drug reaction score in this case was 5, which indicated a probable association (defined as any score between 5 and 8) between azacitidine and Sweet syndrome.

Sweet syndrome may be idiopathic, malignancy-associated, or drug-induced. Potential causes of the idiopathic form are infection (fungal or bacterial), inflammatory bowel disease, or pregnancy. The patient described here might have had an infection, as he presented with mild neutropenia (1.0×10^9/L), fevers, chills, rigours, and several episodes of loose watery stools. However, no organism was cultured. Fittingly, malignancy-associated Sweet syndrome is most often associated with AML. About one-third of patients with Sweet syndrome, and up to half of those in whom an underlying malignancy is the trigger, experience recurrence.[2]

The patient described here had AML, but drug-related causes must also be considered. A search was performed for reports of Sweet syndrome associated with each of the patient's medications. Filgrastim and azacitidine are the 2 drugs most likely to be associated with this condition.[2,15] Filgrastim was excluded as a potential cause in this case, because the patient was not receiving filgrastim when the first episode occurred. The product monograph for azacitidine states that Sweet syndrome was identified in postmarket adverse drug reactions (in more than one patient), and the drug is associated with a high rate of dermatologic adverse events.[2] Alencar and others[9] reported 3 cases of Sweet syndrome associated with the use of azacitidine–decitabine in combination with histone deacetylase inhibitors in

patients with myelodysplastic syndrome. In each case, the syndrome developed at a different point in the therapy (after the second dose or after relapse of myelodysplastic syndrome following 7 cycles).[9] Tricket and others[8] reported one case of a severe, erythematous, painful leg rash that developed on the third day of the patient's initial cycle of azacitidine and a second case in which a skin rash, chills, and fever developed after the fifth drug dose. For both patients, biopsy showed Sweet syndrome, and all symptoms resolved after discontinuation of azacitidine. Both of these patients tolerated reinitiation of azacitidine.[8] Tintle and others[16] described a patient in whom Sweet syndrome developed 3 days after his first azacitidine cycle, who was able to continue azacitidine with concurrent corticosteroids.

Only one case report of azacitidine associated with a histiocytoid variant of Sweet syndrome has been published. Pang and others[10] described a 41-year-old woman in whom biopsy-confirmed histiocytoid Sweet syndrome developed about 1 week after receipt of azacitidine and vorinostat as part of a clinical trial for natural killer/T-cell lymphoma. This was her second histiocytoid episode, with the first one being attributed to her lymphoma. The lesions resolved with discontinuation of treatment and administration of oral steroids; they recurred upon rechallenge and resolved again with steroids. The patient continued to receive cycles of azacitidine and had no further episodes of Sweet syndrome.

CONCLUSIONS

Sweet syndrome may be idiopathic, malignancy-induced, or drug-induced, and it is therefore difficult to identify the true cause. The patient described here had AML, but both of his episodes of Sweet syndrome fit all 5 of the criteria for drug-induced Sweet syndrome. Azacitidine is the only drug the patient was taking that fits with the timeline of development of Sweet syndrome (3–5 days after administration, which is similar to the timeline reported for other cases). Clinicians using azacitidine should be alert to the possibility of this adverse effect, which is characterized by a clinical presentation similar to that of necrotizing fasciitis. In our experience and that of others, corticosteroids have been therapeutically useful for Sweet syndrome and its histiocytoid variant.

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