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CASE REPORT

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Sweet Syndrome in a Patient with Acute Leukemia on Azacitidine and Venetoclax Treatment

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ABSTRACT

Introduction: Sweet syndrome, also called acute febrile neutrophilic dermatosis, is a rare disorder characterized by skin lesions accompanied by high fever and elevated inflammatory markers. **Case Presentation:** In January 2023, a 73-year-old Caucasian male was diagnosed with acute myeloblastic leukemia and subsequently chemotherapy with azacitidine and venetoclax was initiated. One week after the second round of chemotherapy with azacitidine, the patient developed a fever of 39°C. Physical examination revealed purple plaques on the skin of the head, neck, and arms associated with pain but not itching. Initially, the plaques appeared at the site of the subcutaneous azacitidine injection (left upper extremity) and then began to spread. The infectious diseases consultation established the diagnosis of multiple abscesses. Antibiotic therapy was initiated with meropenemum and linezolidum, and later colistin was associated, but the skin lesions and the patient's condition worsened. A dermatology consultation was performed, which established the diagnosis of Sweet syndrome, and subsequently corticosteroid therapy was started. The skin lesions started to improve after 3 days. **Conclusions:** Sweet syndrome is a rare condition that is difficult to diagnose because of the wide spectrum of differential diagnoses.

Keywords: Sweet syndrome, acute febrile neutrophilic dermatosis, acute myeloblastic leukemia, azacitidine

INTRODUCTION

Sweet syndrome, also called acute febrile neutrophilic dermatosis, is a rare disorder affecting the skin and mucosae. It is characterized by skin lesions accompanied by high fever and elevated inflammatory markers.[1]

The etiology of Sweet syndrome may be idiopathic or secondary to an underlying condition such as infection, autoimmune disease, or malignancy. In addition, Sweet syndrome may be induced by medication such as contraceptive drugs, chemotherapy, granulocyte colony-stimulating factor (G-CSF) or

TABLE 1. Laboratory investigations

	Initial laboratory examination	Laboratory investigations after the second round of azacitidine	Laboratory investigations at the onset of Sweet syndrome
White blood cells, /mm^3	1,360	1,070	1,290
Neutrophiles, /mm^3	530	340	1,010
Lymphocytes, /mm^3	740	700	250
Monocytes, /mm^3	90	20	30
Basophils, /mm^3	0	0	0
Eosinophils, /mm^3	0	1	0
Hgb, g/dL	6	8.2	5.7
Htc, %	17.3	23.2	16.5
Platelets, /mm^3	31,000	21,000	123,000
Erythrocyte sedimentation rate, mm/h	40	30	87

granulocyte-macrophage colony-stimulating factor (GM-CSF), non-steroidal anti-inflammatory drugs (NSAIDs), or vaccination.[2]

We hereby report a case of a patient who was diagnosed with acute myeloblastic leukemia (AML) in January 2023, started treatment with azacytidine and venetoclax, and developed Sweet syndrome.

CASE PRESENTATION

In January 2023, a 73-year-old Caucasian male, diagnosed with myelodysplastic syndrome in 2022, presented to the emergency department for severe asthenia and fatigue. The initial laboratory examination revealed severe pancytopenia (Table 1), therefore the patient was admitted to the Hematology Department of the Emergency County Clinical Hospital of Târgu Mureș, Romania.

Blood smear revealed 2% blasts, anisocytosis, macrocytes, ovalocytes, and a low platelet count. Bone marrow aspiration revealed 52% blasts with an immunophenotype consisting of AML with aberrant CD4 and CD22 markers and negative myeloperoxidase.

Because the patient was not a candidate for intensive induction therapy, chemotherapy with azacitidine and venetoclax was initiated according to international protocols.3 After the first round of chemotherapy, venetoclax was discontinued due to severe pancytopenia. One week after the second round of chemotherapy with azacitidine, the patient developed a fever of 39°C at home and was admitted to the hematology department on an emergency basis. Physical examination revealed tender, swollen violaceous plaques and nodules on the skin of the head, neck, and arms associated with pain but not itching (Figures 1, 2, and 3). Initially, the plaques appeared at the site of the subcutaneous azacitidine injection (left upper limb) and then began to spread (Figure 1). Laboratory examination revealed leukopenia, anemia, and severe systemic inflammation (Table 1).

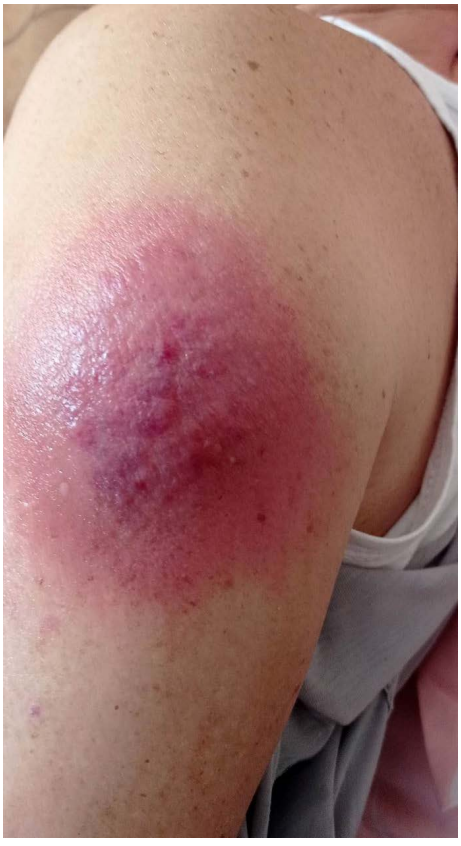

FIGURE 1. Left upper limb: tender, swollen violaceous plaque the site of the subcutaneous azacitidine injection

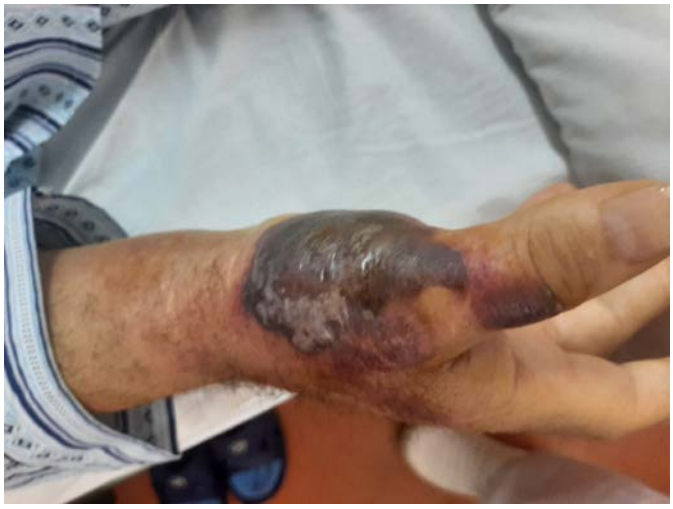

FIGURE 2. Tender, swollen violaceous plaques on the left hand

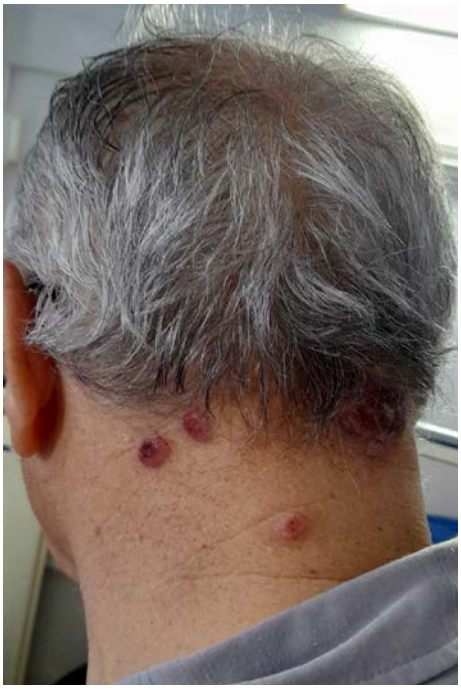

FIGURE 3. Tender, swollen violaceous nodules with hematic crust on the back of the neck

An infectious diseases consultation was performed, which established the diagnosis of multiple abscesses and recommended hemocultures and bacteriological examination of secretions from the abscesses, as well as antibiotic therapy with meropenemum and linezolidum. After three days, another infectious diseases consultation was required because the skin lesions worsened and widened, and inflammatory markers increased. It was recommended to continue treatment with meropenemum and linezolidum and to add colistin to the therapeutic regimen. The results of hemocultures and bacteriological examination of secretions from the abscesses were negative. The patient's condition deteriorated visibly with persistent fever, further extension of the skin lesions, and a further increase in in-

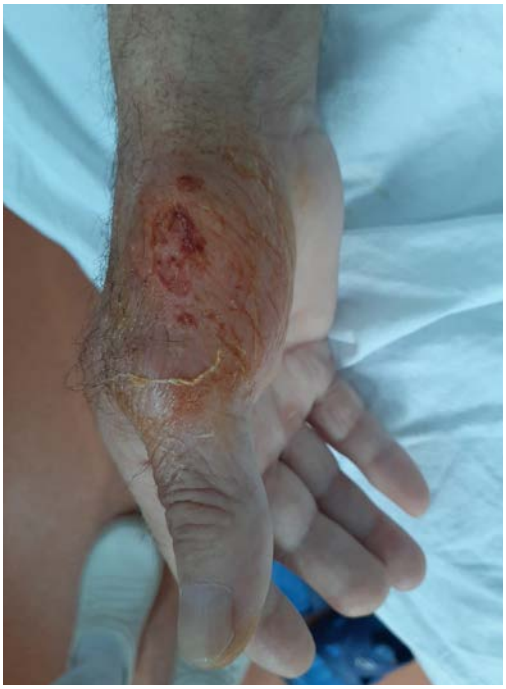

FIGURE 4. The left hand after 3 days of corticosteroid therapy. The violaceous plaque disappeared, being replaced by an ulcerative lesion

FIGURE 5. The left hand after 3 days of corticosteroid therapy. The violaceous plaque disappeared, being replaced by an ulcerative lesion

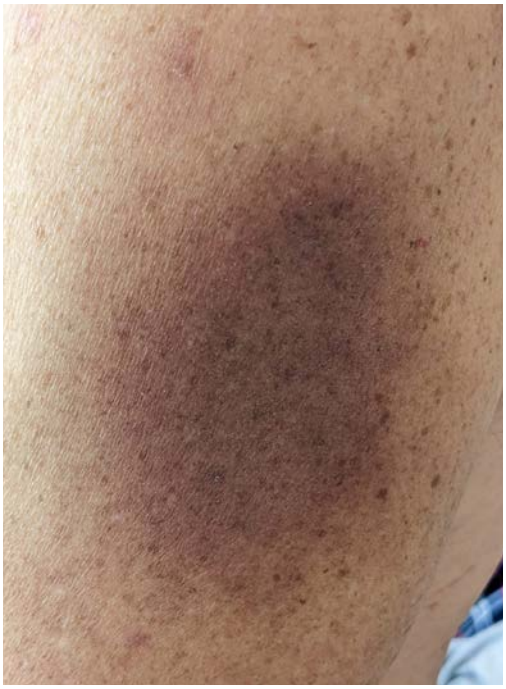

FIGURE 6. The site of the subcutaneous azacitidine injection on the left upper limb after 3 weeks, showing the complete resolution of the plaque, which was replaced by a brown cicatrice.

flammatory markers, prompting another infectious diseases consultation, which this time suggested the diagnosis of pyoderma gangrenosum and recommended consultation with a dermatologist. The dermatology consultation established the diagnosis of Sweet syndrome and recommended a biopsy and intravenous corticosteroid therapy. The patient refused the biopsy. Corticosteroid therapy was started with intravenous methylprednisolonum 0.5 mg/kg in gradually decreasing doses in association with antibiotics and antifungal therapy. After three days, the skin lesions began to improve (Figure 4), and laboratory testing prior to discharge revealed an erythrocyte sedimentation rate of 23 mm/h. For the following rounds of chemotherapy, azacitidine was replaced with decitabine, which was well tolerated. Figure 5 and Figure 6 show the lesions almost 3 weeks after the diagnosis of Sweet syndrome has been established.

The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of the Emergency County Clinical Hospital of Târgu Mureș (12357/19.05.2023). The patient signed an informed consent on admission regarding anonymous data collection for scientific purposes.

DISCUSSION

Sweet syndrome was first described in 1964 by Dr. Robert Douglas Sweet in England as 'acute febrile neutrophilic dermatosis' in eight patients, all women, with the same constellation of pathologic signs and symptoms: "fever, neutrophil polymorphonuclear leukocytosis of the blood, raised painful plaques on the limbs, face, and neck, and histologically a dense dermal infiltration with mature neutrophil polymorphs".[4]

The pathophysiology of Sweet syndrome is unknown. There are many theories, the most reliable is related to type III hypersensitivity reaction, but also to overproduction and inadequate regulation of inflammatory cytokines such as G-CSF, GM-CSF, interleukin (IL)-1, IL-3, IL-6, and IL-8.[5,6] Classically, Sweet syndrome is characterized by fever, leukocytosis, and tender erythematous skin lesions (papules, nodules, and plaques) that usually respond rapidly to corticosteroid therapy.[7]

Drug-induced Sweet syndrome can be triggered by many drugs, but the most common cases were reported in association with G-CSF, retinoids, azathioprine, and sulfamethoxazole and trimethoprim.[7,8] The temporal relationship between azacitidine administration and the appearance of the Sweet syndrome lesions, as well as the absence of relapse after discontinuation of the drug suggest a drug-related etiology.

Approximately 20% of Sweet syndrome cases are associated with malignancies and up to 80% with hematologic disorders,[9] the most common of which are AML and myelodysplastic syndrome (MDS).[10] Studies suggest that the association of Sweet syndrome and MDS has a poor outcome.[9] In 2015, Kazmi *et al.* conducted a retrospective study demonstrating that 1% of patients with AML develop Sweet syndrome.[11]

The differential diagnosis of Sweet syndrome includes various diseases (Table 2).[12,13] Because of the similarity between Sweet syndrome and necrotizing infections, diagnosis may be difficult and may delay the initiation of corticosteroid treatment,[14] as demonstrated by our case in which the diagnosis and treatment were postponed due to a misdiagnosis of multiple abscesses, and treatment was started with antibiotics that the patient did not respond to. As it can be observed in the pictures, the patient responded very quickly to corticosteroid therapy and the lesions began to heal the very next day.

Sweet syndrome can also represent a rarely reported side effect of azacitidine treatment. According to the literature, the time frame between azacitidine administration and the appearance of Sweet syndrome varies from 5 days to 9 months.[15] Studies also suggest that patients in whom Sweet syndrome occurred in association with azacitidine treatment had leukopenia.[6,16] Although Sweet syndrome is classically associated with leukocytosis,

TABLE 2. Differential diagnosis of Sweet Syndrome[12,13]

Clinical	Cellulitis Erysipelas Allergic contact dermatitis Herpes simplex Leprosy
Neutrophilic dermatosis	Pyoderma gangrenosum Behcet's disease Bowel associated dermatitis arthritis syndrome
Cutaneous vasculitis	Erythema elevatum diutinum Cutaneous polyarteritis nodosa granuloma faciale Cockade purpura
Reactive erythemas	Annular urticaria Erythema multiforme
Panniculitis	Lupoid panniculitis Erythema nodosum
Granulomatous disorders	Sarcoidosis Inflammatory granuloma annulare Palisaded neutrophilic granulomatous dermatitis
Histopathological	Leukemia cutis Neutrophilic eccrine hidradenitis Leukocytoclastic vasculitis
Others	Eosinophilic cellulitis (Wells syndrome)

most patients are known to develop leukopenia after chemotherapy.[17]

In 2012, Trikett *et al.* reported two cases of azacitidine-related Sweet syndrome and claimed that by that time, only three other cases of azacitidine-related Sweet syndrome had been reported in the United States.[18] In 2015, Troccola *et al.* reported the case of a 68-year-old female patient who was diagnosed with MDS in 2009 and subsequently started therapy with azacitidine who, similarly to our case, developed lesions on the upper limb at the administration site.[19] Doodnauth *et al.* also reported a case of a 76-year-old male patient diagnosed with MDS who developed Sweet syndrome after 7 days of azacitidine administration. Similarly to our case, the patient had neutropenia and the lesions appeared first at the site of azacitidine administration.[20]

Although our patient refused the biopsy, the diagnosis was supported by the lesions that appeared first at the site of azacitidine administration, which did not respond to antibiotic therapy but responded promptly to corticosteroid therapy.

Although rare, Sweet syndrome may also have extracutaneous manifestations affecting the central nervous system, lungs, kidneys, bones, muscles, eyes, spleen, and even intestines.[10] As far as treatment options are concerned, as mentioned above, corticosteroid therapy is the best first-line option. When corticosteroids are contraindicated, colchicine and dapsone are indicated as second-line therapy.[14]

CONCLUSIONS

Sweet syndrome is a rare condition that is difficult to diagnose because of the wide spectrum of differential diagnoses. We present the case of a patient in whom the diagnosis of Sweet syndrome and the initiation of corticosteroid therapy were delayed and resulted in worsening of the symptoms. Azacitidine administration is a rare cause of drug-induced Sweet syndrome. Perhaps the strongest evidence for the etiology of drug-induced Sweet syndrome is the temporal relationship between azacitidine administration and the appearance of Sweet syndrome lesions.

CONFLICT OF INTEREST

Nothing to declare.

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