Sweet’s Syndrome as a Possible Consequence of Azacitidine Subcutaneous Administration in IPSS Intermediate-2 Myelodysplastic Syndrome

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Abstract

Sweet’s Syndrome (SS) is also called “acute febrile neutrophilic dermatoses”. The salient features are pyrexia, elevated neutrophil count, painful red skin lesions and a dense and diffuse dermal infiltrate consisting predominantly of mature neutrophils. We describe the clinical course of an 69-year-old women with myelodysplastic syndrome who received rapidly ulcerative skin lesion on whole right arm. Skin biopsy confirmed the diagnosis of Sweet syndrome. It is a peculiar case because the patient received azacitidine and developed Sweet’s Syndrome. The optimal treatment has not been defined. Systemic corticosteroids are the “gold standard” therapy for SS. Other first-line systemic treatments for SS are potassium iodide and colchicines. The lesion presented advanced dressings and was targed as having a hith degree of difficulty to cure. The use of Hyaff, an ester of hyaluronic acid, has proven to be a valid and advanced topical tool for the treatment of such cases. Following unsuccessful treatment with standard therapeutic strategies, we needed to move through more advanced treatments. We report that Sweet’s Syndrome is a possible complication of azacitidine administration and suggest paying maximum attention to cases in which skin lesions are probably related to the drug.

Keywords: Sweet's syndrome; Azacitidine; Hyaluronic acid; Advanced dressing

Introduction

Sweet’s Syndrome (SS), also called “acute febrile neutrophilic dermatoses”, was first described by Dr. Robert Douglas Sweet [1,2]. The salient features of Sweet’s Syndrome are pyrexia, elevated neutrophil count, painful red skin lesions, and a dense and diffuse dermal infiltrate consisting predominantly of mature neutrophils. The pathogenesis of SS is poorly understood. The optimal treatment has not yet been defined. We hereby describe a peculiar case of a myelodysplastic syndrome (MDS) patient who received azacitidine and developed Sweet’s Syndrome.

Case Report

A 68-year-old female was referred to the Hematology Unit in November 2009, for severe anemia (Hb 7.4 gr/dl), leukocytosis (12 × 10⁹/l) and thrombocytopenia (74 × 10⁹/l). Peripheral blood examination showed 4% of blast cells. A bone marrow examination revealed 10% of type I and II blast cells and trilineal dysplasia; a diagnosis of refractory anemia with an excess of blast type II cells, according to WHO (World Health Organization) classification, was made. Cytogenetic analysis detected a trisomy 8 in all analyzed metaphases. The patient was classified as intermediate-2 risk, according to IPSS (International Prognostic Scoring System) stratification. In December 2009, she received the first cycle of azacitidine, which was administered subcutaneously at the standard dose of 75 mg/m² with a 5+2+2 schedule (5 days on, 2 days off, 2 days on). After the second cycle, she developed an ulcerative skin lesion at the biceps of her right arm at the site of azacitidine injection. The lesion was 10 x 10 cm in diameter, nodular, inflammatory, diffuse, extensive, edematous, beefy, spontaneously painful and surrounded by an inflammatory peripheral area (Figure 1). An Echo-color Doppler of the right arm vessels was performed to exclude thrombosis. Blood and skin cultures at presentation were negative. A skin biopsy was performed.

Histological analysis showed edema of the dermal papillae and papillary dermis, leukocytoclastic vasculitis and the presence of a dense and diffuse distribution of neutrophils, eosinophils and also lympho-histiocytic cells in the upper dermis, in the dermal-epidermal junction and in the epidermidis (Figure 2).

Diagnosis for acute febrile neutrophilic dermatosis was made, due to the evidence of both major criteria and all minor criteria for Sweet’s Syndrome.

The lesion evolution was rapid and progressive. Erythema and edema affected the entire limb and the perilesional areas (Figure 3). The general condition was poor. The patient appeared dramatically ill, with high fever (40°C), shivers and weakness. She presented diffuse pain and poor compliance to the treatment. The patient was then treated with supportive care specific to her disease, intensive antibiotic therapy (piperacilline/tazobactam and ciprofloxacin) and intensive surgical local wound care. Surgical wound care was performed every 3-5 days, through non-traumatic cleansing, and disinfection with Amukine 0.05% and a saline solution. The wound was covered with hyaluronic acid 0.2% and silver sulfadiazine 1% gauzes, sterile laparotomic gauzes, and finally, with a moderately compressive
bandage. After surgical medication and systemic therapy, edema, erythema, and exuberant granulomatous tissue on the wound bed were significantly reduced.

Ester of hyaluronic acid (Jaloskin®, distributed by Fidia Advanced Biopolymers srl) was applied between the branches of healthy skin. The re-grown skin appeared thin and frail. Jaloskin® was applied in a single layer in intimate contact with the wound base and was made to adhere by gentle pressure, with attention given that no air bubbles remained trapped below. The dressing was then protected with sterile dry gauzes held in place with surgical tape or a bandage when appropriate. No adhesive plasters were used on the films. Removal and dressing change were done when necessary, based on clinical judgment.

At each of the open areas, we assisted at a slow but progressive reduction of the ulcerated area. After two months, the wound was almost entirely re-epithelialized (80%). Three months after the first application of Jaloskin®, the wound healed. The area was skin-colored, shiny, wet and well-hydrated (Figure 4). The newly formed tissue resulted thinner than the surrounding skin and thicker and more resistant than the initial one. In the first months blood tests were performed every 2-3 days and once a week in the remaining period. We noticed a correspondence in the improvement of skin lesion, blood cell count and general clinical condition of the patient, who permanently discontinued the treatment with azacitidine.

Figure 1: Preoperative appearance of the ulcerative skin lesion at the biceps of her right arm at the site of azacitidine injection.

Figure 2: Histological analysis of the lesion which shows the presence of leukocytoclastic vasculitis and an inflammatory infiltrate compatible with Sweet’s Syndrome diagnosis (Hematoxiline Eosine stain 40X).

Figure 3: Rapid and progressive evolution of the lesion: edema and erythema affected the entire limb and the perilesional areas.

Figure 4: Complete re-epithelialization of the wound after four months: the area was skin-colored, shiny, wet and well-hydrated.

Discussion

SS is particularly common in MDS [3]. SS can be classified into three different variants: classic SS, malignancy-associated SS and drug-induced SS. The first class is the most common, and it may be associated with infection, inflammatory bowel disease or pregnancy [4]. The malignancy-associated SS is most commonly related to hematological malignancies [5] but is also associated with solid tumors that have been reported so far [4]. The third subtype is associated with the administration of several drugs, especially G-CSF [6] and other such commonly used drugs as trimethoprim-sulphamethoxazole, all-trans-retinoic acid, hydralazine, carbamazepine, diazepam and diclofenac [4].

Diagnostic criteria for SS include a diffuse infiltrate of mature neutrophils. In addition to the dense polymorphonuclear infiltrated cells that are in the upper dermis, edema is characteristically present. Skin lesions of SS are typically tender; they can appear as red or purple-red papules, nodules or pustular dermatosis that are painful [7]. Larger lesions may develop into plaques. The eruption is often distributed asymmetrically; the most frequent sites are the upper extremities, the face and neck [1-8].

Its pathogenesis is poorly understood, but it has been hypothesized that it is a deregulated secretion of cytokines as a response to several
trigger causes [9,10]. Skin lesions of SS may also occur at skin trauma sites as an expression of skin hypersensitivity or cutaneous pathergy [9].

Systemic corticosteroids are the "gold standard" of therapy for SS. Other first-line systemic treatments for SS are potassium iodide and colchicine. Topical or intralesional corticosteroids can be used to treat patients who have a small number of localized lesions as either monotherapy or concurrently with another therapy. Second-line agents for treating SS have been used as monotherapy, either in the initial management of the patient or after first-line therapies have failed. They include indomethacin, doxazosin, cyclosporin, and dapsone [4]. To the best of our knowledge, this is the first case reported of SS associated with azacitidine subcutaneous administration. Azacitidine has been approved in the USA and Europe for the treatment of higher-risk MDS and AML (Acute Myeloid Leukemia) with 20-30% of bone marrow blast cells. The drug is able to induce an overall 50-60% response, including a 10-20% complete remission. It is known that the drug injection in subcutaneous tissues may cause a high local production of IL-4 and IL-6 [11], developing a hypersensitive skin reaction, which is then maintained and amplified by a high level of local and systemic neutrophilic cells. We cannot exclude that our case was related to the drug; in fact, the erythematous plaque that initially infiltrated the drug injection site, extended to cover the whole region of the right arm biceps as an ulcerated blood lesion with erythematous peri-lesional areas.

According to our experience, we suggest the utility of a multi-disciplinary treatment that involves continuous hematological supportive care as well as local plastic surgical treatment. In cases of poor compliance, patients are initially treated in an operating room, and then treated as outpatients.

In conclusion, the use of Hyaff, an ester of hyaluronic acid, has proven to be a valid and advanced topical tool for the treatment of such cases [12-15]. We report that SS is a possible complication of azacitidine administration and suggest paying maximum attention to cases in which skin lesions are probably related to the drug.

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