SHORT COMMUNICATION

VM VIA MEDICA

Myelodysplasia-associated Sweet's syndrome: clinical and laboratory presentation and response to thalidomide

Bartlomiej Wawrzycki[1*], Dariusz Jawniak[2], Aldona Pietrzak[1], Justyna Szumilo[3], Dorota Krasowska[1]

[1]Chair and Department of Dermatology, Venereology and Pediatric Dermatology, Medical University of Lublin, Lublin, Poland
[2]Department of Hemato-Oncology and Bone Marrow Transplantation, Medical University of Lublin, Lublin, Poland
[3]Chair and Department of Clinical Pathomorphology, Medical University of Lublin, Lublin, Poland

Introduction

Sweet's syndrome (SS) is an uncommon disease of not entirely understood pathophysiology. Depending on the clinical context, it can be classified into classic SS, malignancy-associated SS (MASS) and drug-induced SS (DISS) [1]. The classic variant is the most frequent, accounting for more than 50% of cases. On average, 20% of SS patients have an underlying malignancy, and 10% belong to the drug-induced subtype (DISS) [1]. Since prognosis depends on comorbid conditions, it is essential to establish a proper diagnosis.

Case report

A 73-year-old patient was referred to our clinic because of an almost 3-year history of recurrent bouts of tender papulo-nodules and plaques. Two skin biopsies performed earlier (2014) had described lymphocytic perivascular infiltrates. He was diagnosed as having cutaneous lupus erythematosus and was treated with methylprednisolone at daily doses ranging from 16 to 32 mg. Initially, there was a prompt clinical response and long-lasting remission. Unfortunately, over time the disease became increasingly severe with multiple relapses and reduced symptom-free intervals. He received hydroxychloroquine at a dose of 200 mg per day but with no improvement. On admission, the patient presented with widespread nodules and plaques with targetoid-appearance (Figure 1). There were also aphthous-like ulcers on the oral mucosa (Figure 2).

Figure 1. Widespread nodules and plaques with targetoid-appearance

Figure 2. Aphthous-like ulcers on the oral mucosa

*Address for correspondence: Bartlomiej Wawrzycki, Department of Dermatology, Venereology and Pediatric Dermatology, Medical University of Lublin, Staszica 11H, 20–081, Lublin, Poland, e-mail: bartekwawrzycki@gmail.com

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Table I. Patient's blood morphology during the curse of the disease

Date	2014	10.2016	08.2017	10.2017	11.2017	03.2018	05.2018	01.2019	06.2019	09.2019
Course of disease, investigations, and treatment	Onset of Sweet's syndrome	Diagnostic workup (i.e. skin biopsy, exclusion of solid tumors, IBD, autoimmune conditions and infections). Corticosteroid/dapsone regimen*		Bone marrow aspirate and trephine biopsy MDS-MLD	Resolution of skin symptoms. Tapering of prednisone*					
Thalidomide	–	–	–	–	100 mg/d	50 mg/d	25 mg/d	50 mg/d	25 mg/d	25 mg/d
Hb [dL]		10.7	10.8		13.6	13.2	12.6	12.8	13.7	13.3
WBC [G/L]		3.63	7.77		7.97	5.71	6.46	4.96	5.45	4.88
ANC [G/L]		1.64	5.0		6.27	3.08	3.45	1.88	3.93	2.03
PLT [G/L]		148	241		176	208	192	209	153	153

*Detailed description in the text; IBD — inflammatory bowel disease; MDS-MLD — myelodysplastic syndrome with multilineage dysplasia; Hb — hemoglobin; WBC — white blood cells; ANC — absolute neutrophil count; PLT — platelets

While disease flared, findings from laboratory tests showed an elevated erythrocyte sedimentation rate (ESR): 120/h and C-reactive protein (0–5 mg/L): 78.4––137.1 mg/L. During a one-year observation period, repeated blood tests revealed a tendency towards anemia, and leukopenia with neutropenia (Table I). Interestingly, besides such laboratory peculiarities (leukopenia with neutropenia), only a few exacerbations were accompanied by raised temperature. Tumor markers and electrophoresis were within normal values. Screening for autoimmune diseases (ANAs, ENAs, anti-double-stranded DNA, anticardiolipin antibodies, c-ANCAs, p-ANCAs) yielded negative results. Serological tests for Yersiniosis anti-Yersinia enterocolitica IgA, IgG antibodies were negative. Neither abdominal not chest computed tomography scans were remarkable. Results of gastroscopy and colonoscopy were also inconspicuous. We performed two consecutive skin biopsies (2016, 2017) showing dermal infiltrates composed mainly of neutrophils, eosinophils, and myeloid cells (Figures 3A, B): lesional infiltrate labeled with myeloperoxidase and CD15 (polymorphonuclear neutrophils) and CD68 (myeloid cells). There was also some admixture of T lymphocytes (CD45$^+$ CD3$^+$) (Figure 3C).

Our patient met the criteria for SS. He had both major criteria (clinical manifestations, neutrophilic infiltrate without leucocytoclasia) and two minor criteria (associated disease, response to corticosteroid therapy). Because of the chronic, recurrent course and atypical clinical and laboratory features, the diagnostic work-up was broadened to include bone marrow aspirate smear and trephine biopsy. Bone marrow aspirate showed dysplasia of 10% of myeloid lineage cells (Figure 3D), whereas trephine biopsy revealed hypercellularity and features of multilineage

dysplasia. Cytogenetic examination of bone marrow found normal karyotype. Later, based on the investigations above and laboratory parameters, MDS with multilineage dysplasia (MDS-MLD) was diagnosed.

Initially, we started him on oral prednisone 0.5 mg/kg//day, with a good clinical response. Unfortunately, there were flares of SS on doses below 20 mg per day. Then, dapsone (100 mg/day) was added for three months, but with no benefit. Finally, we decided to give our patient 100 mg thalidomide/day along with a prophylactic dose of acetylsalicylic acid. Thalidomide (TH) led to complete resolution of the disease, and allowed for tapering and finally stopping steroids within one month. Due to somnolence and constipation, we had to reduce the dose to 50 mg/day after two months. During the whole observation period, we did not observe any adverse events. Importantly, TH also stabilized the patient's blood morphology. Nevertheless, we were unable to discontinue the TH because of recurrences of skin eruption. Currently, he is still on 25 mg of thalidomide every other day, which controls the disease (Table I).

Discussion

Sweet's syndrome (acute febrile neutrophilic dermatosis) belongs to a heterogeneous group of neutrophilic dermatoses (NDs), which are characterized by histologically evidenced neutrophilic infiltrate [2]. Hematologic disorders account for 85% of MASS. The most prevalent are acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) [3]. The less frequently reported ones are myeloproliferative diseases, CLL, and paraproteinemias. Solid tumors constitute 7–15% of associated cancers [1]. Myelodysplastic syndromes are a group of clonal hematopoietic stem
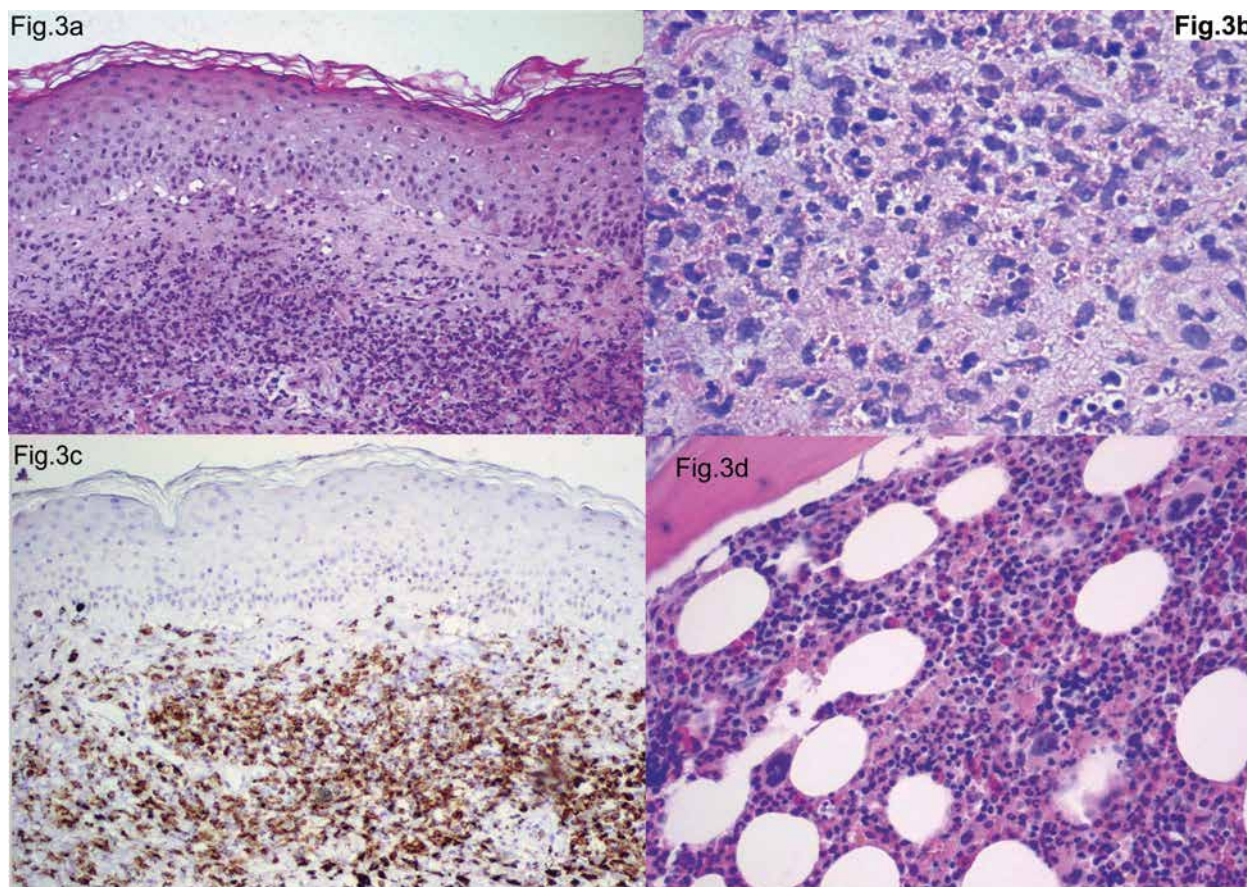
Figure 3A, B. Infiltration of the skin composed of neutrophils, eosinophils and myeloid cells; **C.** The lesional infiltrate showing positive immunostaining for CD68; **D.** Myelodysplastic syndrome with multilineage dysplasia in trephine biopsy of patients with Sweet's syndrome

cell diseases with cytopenia(s) and dysplastic features in one or more myeloid lineage [4].

Our patient presented with lesions of widespread distribution (Figure 1), which is considered by some authors to be a potential sign of underlying malignancy [1]. Notably, crops of cutaneous lesions were accompanied by oral ulcerations (Figure 2), which are not only extremely rare in SS but also possibly indicative of MASS [5]. Malaise and low-grade fever parallelled the exacerbations, but without arthralgias or other constitutional symptoms. Lack of joint complaints and afebrile disease have both been found to be more prevalent in the paraneoplastic variant [6]. Unfortunately, besides anemia, only a few findings have been consistently reported to differ between cancer-associated SS and the classic idiopathic form [2]. Data from case series indicates, however, that a combination of chronicity and refractoriness to treatment [7] plus initially lymphocytic infiltrates on skin biopsy, especially in older males, could potentially indicate a distinct group of SS patients at higher risk of developing MDS [8, 9]. Clearly, in our case, there was gradually increasing anemia, and the disease had a chronic, remittent course. Moreover, the first biopsies

showed predominantly lymphocytic infiltrate. Our findings seem to parallel observations from published case series, which have described 'initial' lymphocytic and 'late' neutrophilic patterns [8].

Many studies have revealed a strong association between myelodysplasia and autoimmune and inflammatory conditions (AIMs) [10]. AIMs can appear before, during, or after the diagnosis of MDS [10]. In the lymphocytic variant of MDS-associated SS, cutaneous disease has been found to appear between 6 months and 8 years (median 3.5 years) [8, 9] before myelodysplastic syndrome. Patients with typical histopathology described by Kulasekararaj et al. [7] had MDS diagnosed at a median of 1.5 years following the development of SS.

Our findings are in agreement with previous studies in showing that skin lesions of SS can precede by months, or years, a diagnosis of MDS. In the presented patient, it was three years from the beginning of the SS to the confirmation of MDS.

The pathogenesis of SS is complex and multifactorial. Recent research has revealed that neutrophil-rich cutaneous inflammation might be a consequence of an overactive

innate immune system [11] and excessive synthesis of interleukin 1 (IL-1) family members [12, 13]. Paraneoplastic inflammation implicated in MDS includes abnormal expression of distinct inflammatory cytokines and chemokines, which are produced by the immune, stromal, and malignant cells. There are also qualitative and quantitative differences in inflammatory cell recruitment [14]. Remarkably aberrant innate immune activation (specifically, NLRP3 inflammasome formation and pyroptosis) is now believed also to be a key driver of ineffective hematopoiesis in MDS [15]. In the setting of cancer-associated Sweet syndrome, the underlying myeloid dysfunction may disrupt networks of cytokine and stimulating factors, which in turn could exaggerate neutrophil chemotaxis and activation [16].

Thalidomide and its derivates belong to a group of therapeutic agents collectively called immunomodulatory drugs (IMIDs). Research carried out in recent years has identified the anti-proliferative, anti-angiogenic, and immunomodulatory potential of IMIDs [17]. Modulation of the immune system may be the primary mode of action of thalidomide in SS. Thalidomide may act via modulation of cytokine secretion. For example, it is best known for the downregulation of tumor necrosis factor alpha. TH may also decrease levels of IL-1, IL-6 [18] via inhibition of the caspase-1-NLRP3 inflammasome axis [19, 20]. Studies suggest that TH affects neutrophil chemotaxis and inhibits granulocyte-mediated tissue injury [21, 22]. Inhibition of phagocytosis and reduced expression of matrix metalloproteinases (MMP) may also translate into the efficacy of TH in ND [16, 18, 23].

Only a handful of reports have described the use of thalidomide in SS [8, 24]. It has mainly been used in patients with the hemopathy-associated form because of steroid-dependency or refractoriness to other drugs. In the vast majority of cases, it shows high effectiveness. Unfortunately, despite an excellent response, TH also causes a high drop-out rate due to adverse events.

Two important observations emerge from our case. Firstly, knowledge of the specific phenotype of hemopathy-associated SS prompted us to closely and regularly monitor the patient and then introduce increasingly invasive procedures (trephine biopsy) when blood parameters just reached the threshold considered to be diagnostic for MDS. Secondly, it is increasingly acknowledged that MDS and autoimmune and inflammatory diseases (AIDs) are interconnected and reciprocally influence each other [25]. Due to substantial cross-talk between the mediators and cytokines in the local tumor microenvironment and systemic circulation, it is plausible to assume that targeting of cancer-related inflammation has the potential to affect both the underlying neoplasm and the associated skin disease [26].

We believe that thalidomide, at its lowest but effective dose, allowed for control of both diseases without any adverse events. Notably, 25 mg daily dosing of TH has been considered relatively safe in respect to neuropathy [27]. Another point is that even low or ultra-low doses of thalidomide could be a valuable option in anemic MDS patients [28].

Conclusions

The presented case emphasizes the importance of including myelodysplastic syndrome into the diagnostic work-up in patients with SS. While most patients with SS respond to corticosteroid therapy, treatment of the disease in the setting of myeloid malignancy can be challenging, with a high incidence of steroid dependence and relapse. Thalidomide should be considered as an alternative, third-line agent in the treatment of such patients.

Authors' contributions

BW — article concept, data collection, writing of article. DK — critical revision of article, final approval of article. DJ, AP, JS — critical revision of article. JS — pathomorphological analysis.

Conflicts of interest

The authors declare that they have no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for Manuscripts submitted to Biomedical Journals.

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