Case Report

Recurrent Idiopathic Sweet Syndrome - Case Report and Literature Review

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ABSTRACT: Introduction. Sweet syndrome (SS), also denominated as acute febrile neutrophilic dermatosis, is a rare disease characterized by the sudden onset of painful, erythematous, firm skin lesions (papules, plaques, and nodules) which show, upon histologic examination, the presence of a diffuse infiltrate of mature neutrophils. The cutaneous manifestation typically involves the face, neck, trunk, and upper limbs and is associated with fever, general malaise, arthralgia. Case report. A female patient, 60 years old, attended the Dermatology Clinic due to the appearance of violaceous erythematous-oedematous infiltrated plaques, located on the face, neck, upper limbs, trunk and knees. The onset of the cutaneous manifestation had occurred 2 months prior, accompanied by pain, chills, flares of fever and arthralgia. The onset coincided with the surgical treatment of an umbilical hernia. From the medical history we note that the patient was diagnosed in 2014 with histiocytoid SS. She followed a treatment with methylprednisolone, with positive response, but had many relapses after the discontinuation of treatment. In 2017, due to a new episode, the histopathological examination was repeated, which revealed classical SS. She received treatment with Disulone and Colchicine. She had not been administered any treatment throughout the previous year. Laboratory tests revealed leukocytosis with neutrophils, increased ESR, elevated C4, hyperglycemia. The current histopathological examination revealed lymphocytic SS. Under treatment with methylprednisolone 32mg/day, the evolution was favorable. Discussions. The first case of SS was described by Robert Douglas Sweet in 1964. As known aetiological factors there have been described gastrointestinal and urinary tract infections, pregnancy, inflammatory bowel disease, drugs or malignancies. There have been described cases of SS that appeared after surgical treatment, as in our case, which registered a new outbreak following the umbilical hernia treatment. The histopathological variants of SS described in the literature are: subcutaneous, eosinophilic, histiocytoid, lymphocytic type. The first line-therapy consists in systemic corticosteroids, which induce a fast remission of lesions and general symptoms. Recurrence may occur in approximately 50% of patients and is common in idiopathic or paraneoplastic cases. Conclusions. In addition to the neutrophilic infiltrate that is typical for Sweet syndrome, different types of histological manifestations have been described in the literature: subcutaneous, eosinophilic, histiocytoid, lymphocytic. In our case, we noted that the histological profile changed over time, from a histiocytoid SS recorded in 2014, to a classical SS in 2017, followed by the appearance of lymphocytic SS in 2019. Due to the fact that SS can be associated with a numerous other disorders, our patient requires regular monitoring with a view to eliminate them, and potentially to make a diagnosis and initiate early specific treatment.

KEYWORDS: *Sweet Syndrome, recurrence, histopathological types, treatment.*

Introduction

Sweet syndrome, also described as acute febrile neutrophilic dermatosis, is a rare disease characterized by the sudden onset of painful, erythematous, firm skin lesions (papules, plaques and nodules) which show, upon histologic examination, the presence of a diffuse infiltrate of mature neutrophils.

The cutaneous manifestation typically involves the face, neck, trunk, and upper limbs and is associated with fever, general malaise, arthralgia [1].

The first line-therapy consists in systemic corticosteroids, which induce a fast remission of lesions and general symptoms [2].

Robert Douglas Sweet described the acute febrile neutrophilic dermatosis for the first time in 1964, which led to the name of Sweet syndrome (SS) [3].

It is a rare disease with an annual incidence of 2.7-3 new cases per 1000000 inhabitants. In 10-20% of cases it is associated with malignancy [4].

Gender distribution (F/M) is 4:1 in the classic type [5].

It affects people between the ages of 30-50 years, although cases of newborns of 5 days have been described.

However, in children SS is very rare and is associated in most cases with infections.

The disease is basically a reactive process characterized by the sudden onset of painful, red-to-purple papules and nodules that gather up as plaques.

10.12865/CHSJ.46.01.12

The lesions usually appear on the upper extremities, the face and the neck, and are classically associated with fever and peripheral neutrophilia.

The plaques can cause pain, burning, but not itching.

Systemic symptoms which accompany the cutaneous lesions include fever, arthralgia, malaise, headache.

As known aetiological factors there have been described gastrointestinal and urinary tract infections, pregnancy, inflammatory bowel disease, drugs or malignancies [6,7].

Case Report

We present the case of a female patient, 60 years old, which was admitted in May 2019, in the Dermatological Clinic of Emergency Hospital of Craiova after the onset of a new episode, consisting in the appearance of violaceous erythematous-oedematous infiltrated plaques, located on the face, neck, upper limbs (Figure 1), trunk (Figure 2) and knees (Figure 3).

The onset of the cutaneous manifestations had occurred 2 months prior this presentation, accompanied by pain, chills, flares of fever and arthralgia.

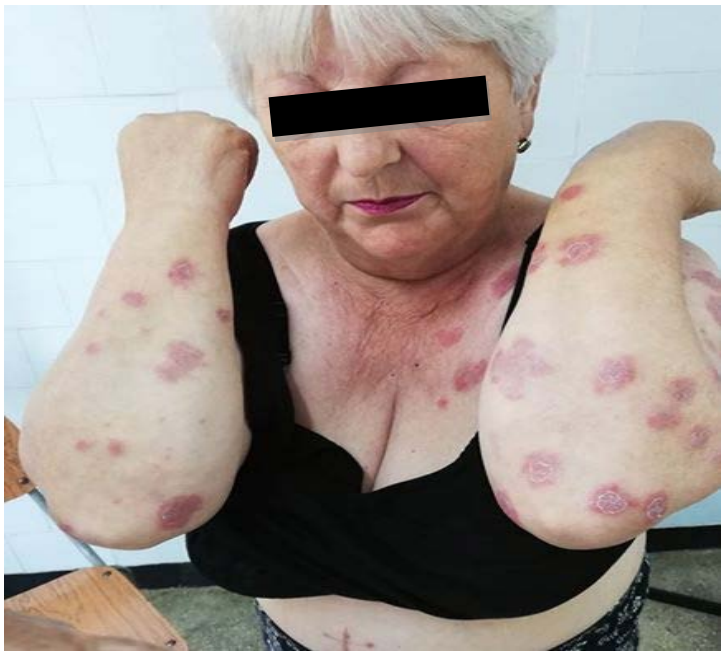

Figure 1. Violaceous erythematous-oedematous infiltrated plaques, located on the face, neck, upper limbs.

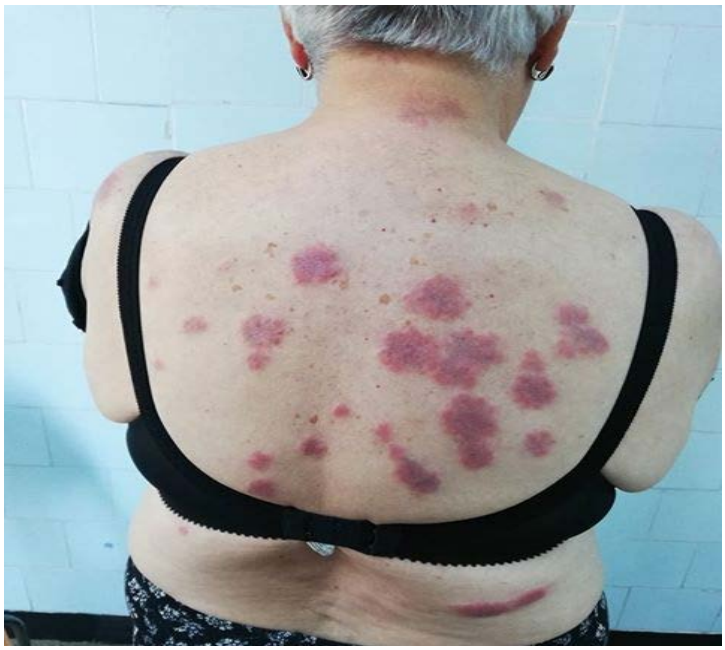

Figure 2. Violaceous erythematous-oedematous infiltrated plaques, located on the trunk.

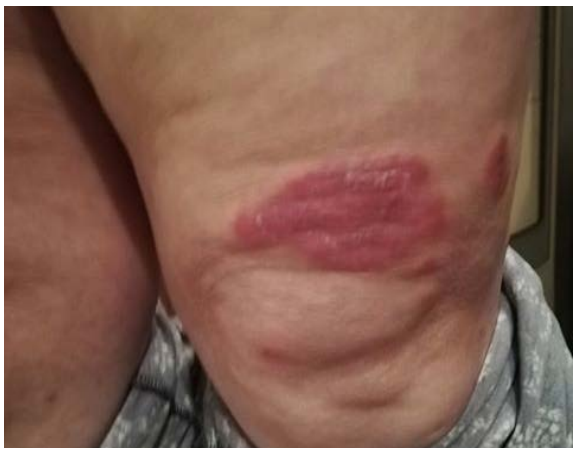

Figure 3. Violaceous erythematous-oedematous infiltrated plaques, located on the knees.

A written informed consent of the patient was obtained, agreeing with publishing these data.

Personal medical history: Umbilical hernia, treated by surgery 2 months prior.

Relevant behavior: does not smoke, does not drink alcohol.

Analysis of the case history revealed that the patient was first diagnosed with Sweet syndrome in 2014, during the hospitalization in another clinic. Based on the case history available from the patient, the results of the histopathological examination of the skin lesions at the time of initial diagnosis described:

-polymorphous inflammatory infiltrate, relatively dense, located at the level of the superficial and middle reticular dermis, comprised of neutrophils and neutrophilic nuclear dust, intricated with mononuclear cells with immature appearance, lymphocytes, and some eosinophils;

-inflammatory infiltrate with lymphocytes and some eosinophils with superficial perivascular location;

-important oedema at the level of the papillary dermis.

At that moment, in 2014, immunohistochemistry was also performed on the surgical specimen, resulting data showing: CD3-positive frequent small lymphocytes, CD20-positive rare small lymphocytes, CD30-negative infiltrate, CD-68 positive histiocytes and mononuclear histiocytoid cells, MPO-positive segmented granulocytes and mononuclear histiocytoid cells (immature granulocytes), and CD33-positive segmented and immature granulocytes.

Based on the clinical, histopathological, and immunohistochemical profile, the diagnosis of histiocytoid Sweet syndrome was made.

She followed a treatment with 32mg/day methylprednisolone, with positive response, but had many relapses after the discontinuation of the treatment.

In 2017, due to a new episode, the histopathological examination was repeated and revealed the following features: tegument fragment showing minimal surface parakeratosis, marked inflammatory lymphoplasmacytic infiltrate with a large number of perivascular neutrophils and areas of leukocytoclasis with periadnexal and interstitial location in the reticular and deep dermis, dilated blood vessels lined by endothelial cells with intraluminal bulging.

She received treatment with Disulone (which she did not tolerate) and Colchicine. She had not been administered any treatment throughout the previous year.

The onset of the current episode (2019) occurred following the treatment she received for umbilical hernia.

At *clinical examination*, we noticed a phototype II, normal weight female patient, having pains and crackling in the joints of knees and fingers on both hands.

Laboratory blood tests showed: leukocytes 12.5x1000/microL, neutrophils 72,5%, ESR (erythrocyte sedimentation rate) 32mm/1h, HBsAg negative, Anti-HCV antibodies-negativ, anti-Ro and anti-La antibodies-normal; complements C3 1.55g/L normal and C4 57mg/dl (10-40) elevated, anti-DNA antibody 5.4UI/ml (<25), CIC (circulating immune complexes) <2U/ml (2-20), glycaemia 111mg/dL (65-110), GOT 12UI/l, GPT 17UI/L, GGT 34UI/L (7-32), CK (creatin kinase) 38U/L (<145U/L), FR (rheumatoid factor) 8.2IU/ml (<14IU/ml).

Urinalysis findings: relatively frequent flat epithelial cells, relatively frequent leukocytes.

Faecal parasitology findings: normal.

Chest X-ray: heart within limits, without progressing pleural-pulmonary lesions.

Ultrasound examination of the abdomen and pelvis regions revealed liver with steatosis, left lobe measuring 71mm, right lobe 152mm.

Gallbladder reduces in size, two hyperechogenic images measuring 9 and 6mm respectively, suggesting the presence of stones, VP 7mm, main biliary duct 3mm, pancreas with infiltrate. Homogenous spleen, measuring 100mm along the long axis. Kidneys with normal size, without dilatations. Urinary bladder with soft walls. Uterus measuring approximately

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46/38mm, homogenous structure, without fluid in the peritoneal cavity.

Under local anesthesia induces by 1% Lidocaine biopsies were performed from representative lesions located on the forearm and right arm.

The surgical specimen was fixed in 10% buffered formalin, processed for routinely paraffin embedding, sectioning and Hematoxylin-Eosin (HE) staining) in the Pathology Department of the same hospital.

The histopathological examination showed:

-abundant lymphoid cells, rare eosinophils and PMN with leukocytoclasis (Figure 4),

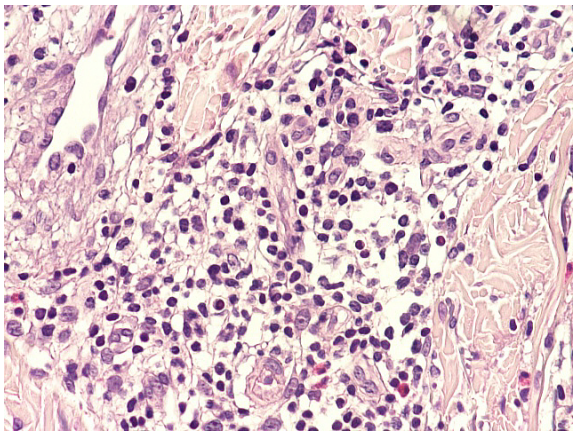

Figure 4. Lymphoid cells, rare eosinophils and PMN with leukocytoclasis, haematoxylin and eosin, 40x.

-inflammatory infiltrate in the dermis around the capillaries with turgescent endothelial cells (Figure 5).

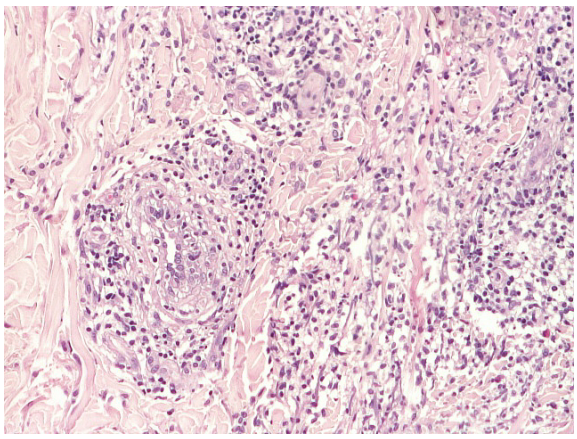

Figure 5. Inflammatory infiltrate in the dermis around the capillaries with turgescent endothelial cells, hematoxylin and eosin, 20x.

-tegument with orthokeratosis and inflammatory infiltrate in the dermis (Figure 6).

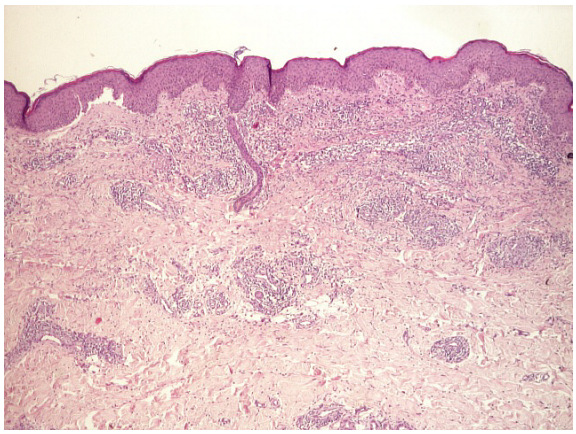

Figure 6. Tegument with orthokeratosis and inflammatory infiltrate in the dermis, haematoxylin and eosin, 5x.

Based on the case history, on the objective clinical examination, and on the histopathological and immunohistochemical findings the diagnosis of ***recurrent idiopathic Sweet syndrome*** was supported.

We initiated the treatment with 32mg methylprednisolone 1 tablet/day in the morning, topical Clobetasol ointment, 10mg Rupatadine-1 tablet/morning, 1mg Ketotifen-1 tablet/evening, with positive response.

Discussions

In a 2011 retrospective study, of 23 patients (of which 2 children) diagnosed with SS in the period 1995-2009, the age of patients was between 2 and 75 years, with an average of 44.5 years. 17 women and 6 men were diagnosed.

The lesions mostly affected the trunk and upper limbs, the face, neck and lower limbs were also involved.

Fever was the most common systemic manifestation (65% of cases), followed by arthralgia and myalgia (17%), conjunctivitis (13%), arthritis (8.6%).

The most commonly identified triggering factors were upper respiratory tract infections (60% of cases).

Ulcerative colitis, erythema nodosum, systemic lupus erythematosus were other associated conditions.

Associated neoplasia was present in 30% of patients, especially hematological (70%), with chronic myeloid leukemia as the most common [8].

Etiology

SS is divided into 3 types:

1. *Classical/idiopathic SS* usually occurs in middle-aged women, sometimes in association with upper respiratory tract or gastrointestinal tract infections, pregnancy (2%) or inflammatory bowel disease (Crohn's disease and ulcerative colitis in 16% of cases). Other associated diseases are: SLE, rheumatoid arthritis, Behcet syndrome, Sjogren's syndrome. Rare causes: thyroiditis, erythema nodosum, sarcoidosis. Cases have been reported in patients with bone marrow or kidney transplantation [9,10].

In a study of 176 patients, classical SS was the most common (>71% of cases). SS associated with malignancy accounted for approximately 27% of cases.

2. *Drug-induced SS (5%)*-most frequently occurs in patients receiving G-CSF. Other causative drugs are: antibiotics, antiepileptic drugs, antihypertensive drugs, oral contraceptives and retinoids (all-trans retinoic acid) [11,12].

3. Paraneoplastic SS, seen in patients with hematological malignancies or solid cancers. It can be the initial sign of internal malignancy, thus all suspected patients need to be adequately investigated. It can precede, follow or occur concurrent with diagnosis of underlying malignancy [13]. Malignancy accounts for 10-20% cases of SS. Most common hematological malignancies associated are acute myeloid leukemia and myelodysplastic syndromes. Around 15% cases of paraneoplastic SS are due to solid tumours involving genitourinary tract, breast and gastrointestinal tract [14]. Paraneoplastic SS differs from classical SS in being more persistent, widespread and resistant to treatment. Relapses after treatment are also more frequent. Lesions more commonly turn bullous, ulcerative and may mimic pyoderma gangrenosum. The treatment of the underlying malignancy represents the treatment of choice in the management of paraneoplastic SS. Recurrence of lesions may suggest recurrence of malignancy [15,16].

In a retrospective study (Mayo Clinic, 2013) on 77 patients with SS, between 1992-2010, the mean age at onset was 57 years. Of the 77 cases, 43 (56%) were men. In 18 patients, SS was preceded by infection. A total of 41 (53%) were classified as having classic SS, 27 (35%) had associated neoplasms (21 patients with haematological tumors and 6 patients with solid tumors). In 9 cases (12%), SS was drug induced. Systemic corticosteroid treatment was the most commonly used treatment (70%) [17].

There have been described cases of *SS that appeared after surgical treatment*, as in our case, which registered a new outbreak following the umbilical hernia treatment. Minocha R et al. described a 47-year-old man diagnosed with SS that initially appeared at the operating site, 4 weeks after a right tibial osteotomy, who recovered after treatment with Disulone [18].

SS has also been described after spinal column operations and excision of an actinic keratosis. Post-surgical SS was correlated with trauma to the skin, with post-seizure or puncture cases, application of bran and post-biopsy [19].

Pathophysiology

SS is a hypersensitivity reaction that occurs as a response to some systemic triggers, such as hematologic pathology, infection, administration of different drugs, inflammation, or vaccination. The disease seems to be mediated by neutrophils, and this is also supported by its histopathologic appearance where it associates neutrophilia, and by the fact that medication that affect neutrophil activity also modulates the pathology [1].

The development of SS after administration of granulocyte colony-stimulating factor (G-CSF) also supports the role of neutrophils and associated cytokines in this process [20,21].

It has been showed that G-CSF suppresses apoptosis and favours the survival of neutrophils in an in-vivo environment, for a population of $CD34^+$ cells. G-CSF levels are also increased in the blood of patients with the active SS, supporting the idea that high levels of G-CSF correlate with the pathological and clinical disease activity [22].

The functional state of neutrophils, is believed to be of essence, as the patients with SS and G-CSF increased levels, develop lesions while the number of neutrophils increases steeply. A stem cell donor woman developed SS 4 days after receiving G-CSF at a dose of 10 micrograms/kg/day [23].

Moreover, other studies have suggested roles for other cytokines such as interleukin IL-1, IL-2, and IFN-γ acting together with Th1. This is especially apparent in the paraneoplastic form, in patients receiving G-CSF, INF-gamma and all-trans retinoic acid and who develop characteristic lesions [24].

A possible genetic connection with HLA-B54 has been suggested in the Japanese population [25].

10.12865/CHSJ.46.01.12

A published report of two brothers who developed Sweet syndrome in the neonatal period shed more support for this genetic predisposition. Structural modifications at the level of the long arm of chromosome 3 have been linked with SS [26].

Positive diagnosis

The final positive diagnosis is based on both clinical and histopathological data. Characteristics features that separate the lesions of Sweet syndrome from other neutrophilic dermatoses are the healing of the lesions without scarring and the absence of vasculitis.

In the classical type, the histopathological examination highlights:

-neutrophilic infiltrate in the superficial dermis along with edema of the papillary dermis. Leukocytoclastic nuclear debris is typically present interstitially;

-true vasculitic modifications are missing (dilation of the postcapillary venule wall with fibrin deposition);

-eosinophils and lymphocytes are present in some cases, with neutrophils usually predominating in all cases;

-spongiosis and subcorneal pustule formation can be seen in the epidermis [1,2].

In addition to the skin, aseptic neutrophilic infiltrate may exist in organs such as the lungs, brain, eyes, heart.

Different histological variants were presented in the literature. Jordaan described variations of cell infiltrate, including lymphocytes, and years later, lesions rich in lymphocytes and histiocytoids (immature myeloid cells misdiagnosed as histiocytes) that were linked to myelodysplastic syndrome. In a study of 37 patients (Jordaan et al. 1989), lymphocytes were present in 100% of cases, whereas neutrophils were absent in some cases. The lymphocytes had a perivascular distribution, the neutrophils being dispersed interstitially [27].

In a study of 9 patients diagnosed with SS (Kazlouskaya, 2018), lymphocytes were present in all biopsies in varying amounts, often exceeding the number of neutrophils. The inflammatory infiltrate was composed of lymphocytes, neutrophils and frequently eosinophils. Also, the perivascular component was composed predominantly of lymphocytes, while the interstitial inflammatory infiltrate was mostly neutrophilic. The cases did not have a history of myelodysplastic syndrome at the time of examination nor after a period of evolution of 2-6 years [28].

The histopathological variants of SS described in the literature are: subcutaneous, eosinophilic, histiocitoid, lymphocytic type [29].

In *subcutaneous SS*, lymphocyte infiltrate predominates in the upper parts of the dermis, whereas the typical neutrophilic infiltrate can be seen in the deep dermis. The lymphocyte component may help to differentiate SS from neutrophilic urticaria, which does not contain a significant lymphocyte population.

In a 2007 study, Boeckler et al. described 2 men aged 60 and 75, respectively, diagnosed with SS associated in one case with myelodysplastic syndrome and the other with chronic lymphocytic leukemia.

These two patients had typical SS edematous plaques. Histopathological examination revealed superficial and deep perivascular lymphocyte infiltrate into the dermis at 5 repeated biopsies, before the characteristic SS with neutrophils appeared, recorded after 2 and 4 years of progression, respectively [30].

Histiocitoid SS (H-SS) is a histological variant of SS that differs from classical neutrophilic SS (N-SS) by a dermal infiltrate composed mainly of MPO+lymphocytes and histiocitoid cells. In a 2016 study in Baltimore (Ghoufi L), on 62 patients histopathologically diagnosed with SS between 2005 and 2014, 22 (35.5%) and 40 (64.5%) patients had histopathological diagnosis of H-SS and N-SS, respectively.

Mean age, sex ratio, and skin lesions, respectively, were similar in the 2 groups.

The frequency of extra-cutaneous manifestations was 50% versus 37.5%.

Recurrent forms were more common in H-SS than in N-SS (21% vs. 2.5%).

Hematologic malignancy was diagnosed in 22 patients, 12 (55.5%) with H-SS and 10 (25%) with N-SS.

Hematological malignancy had myeloid origin in 8/22 respectively 5/40 patients and lymphoid origin in 4/22, respectively 4/40 patients and an N-SS patient of mixed origin. MDS was diagnosed in 7/22 H-SS, respectively 1/40 N-SS.

Hematologic disease was diagnosed before (in 8 H-SS and 3 N-SS) or during skin lesions (1 H-SS and 7 N-SS). However, in 3 H-SS patients with MDS, skin lesions preceded haematological disease by approximately 6 months [31].

According to the diagnostic criteria given by Von den Driesch (1994), the presence of both

major and two of the minor criteria is required for making the diagnosis.

Major criteria:

- ❖ abrupt onset of painful erythematous plaques or nodules;
- ❖ histopathological evidence of a dense neutrophilic infiltrate without evidence of leucocytoclastic vasculitis.

Minor criteria:

- ❖ fever >38°C;
- ❖ association with an underlying haematological or visceral malignancy, inflammatory disease or pregnancy, or preceded by an upper respiratory or gastrointestinal infection or vaccination;
- ❖ excellent response to treatment with systemic corticosteroids or KI;
- ❖ abnormal laboratory values at presentation (3 of 4): positive C reactive protein, >8000 leucocytes, VSH >20mm/h, >70% neutrophils [32].

Several criteria need to be carefully considered. For example, in cancers that induce neutropenia, leukocytosis may not occur. Some authors consider these criteria less useful in clinical practice.

We emphasize that in our case we witnessed a change in the histopathological profile, passing through the forms of histiocitoid SS (2014), classical SS (2017), then lymphocytic (2019).

The Differential diagnosis is made with: leukemia cutis, cellulite, Behcet syndrome, erythema multiforme, erythema nodosum, pioderma gangrenosum, allergic contact dermatitis, eruptions given by drugs, leukocytoclastic vasculitis [1,2].

Evolution and prognosis

Generally, SS is remitted within a few weeks of treatment, unless there are underlying diseases or uses of drugs that induce this syndrome. Without treatment, the lesions can persist for weeks or months and usually disappear without leaving scars.

Recurrence may occur in approximately 50% of patients and is common in idiopathic or paraneoplastic cases. In rare cases, the lesions reappear and may persist forever.

Patients with chronic SS may have high levels of proinflammatory cytokines or chemotaxins that drive neutrophils to the skin or may have an aberrant, hyperactive cytokine response to minor skin trauma. Patients with chronic SS have been described, who developed myelodysplastic syndrome a few years later. Initial biopsies in these patients were usually histologically atypical and found lymphocytic or histiocytoid infiltrates, as opposed to classical SS characterized by neutrophilic infiltrate into the dermis. Despite visualization of lymphocytic or histiocytoid infiltrates, MPO+, chronic SS has been diagnosed without an underlying cause being discovered. It is important that these studies looked at the association between chronic SS and MDS subsequently, which was diagnosed up to 13 years after the diagnosis of SS. The chronic form may also be present as a distinct entity [33].

Treatment

Both systemic and skin lesions respond rapidly to systemic corticosteroids or K. iodide.

Colchicine has also been used as first-line therapy in a 90-patient study, with good results [34]. Other used treatments are: indomethacin, Disulone, cyclosporine, etretinate, pentoxifylline [1,35].

Also, in some cases treated with doxycycline, metronidazole, isotretinoin, methotrexate, cyclophosphamide, chlorambucil, infliximab, Ig iv, alpha-interferon, encouraging results were obtained [36-38].

Thalidomide was administered in SS associated with MDS, resulting in lesion remission within one month after corticosteroid, metronidazole and dapsonone therapy failed [39].

In a number of studies, etanercept has been used to treat SS in rheumatoid arthritis patients [40].

Rituximab and adalimumab have also been helpful in some resistant cases [41,42].

In a retrospective study (Maillard et al) between 1984-1996, 20 patients treated with colchicine (12 F and 8 B aged 29-93) were analyzed. Colchicine was introduced 2-8 days after the onset of SS at 1.5mg/day over an average of 15 days. Skin lesions were attenuated in 18 patients in 2-4 days, with fever disappearing. After completion of treatment, 9 patients underwent relapse [43].

In 1997, Jeanfils et al. described the efficacy of indomethacin as a first line treatment in 17 of 18 patients with SS, at a dose of 150mg for 7 days, then 100mg for another 2 weeks [44].

Von den Driesch obtained complete remission in 6 patients treated with clofazimin. Patients had chronic SS resistant to methylprednisolone (200mg/4 weeks, then 100mg another 4 weeks) [32].

Disulone has been used successfully in 2 patients at a dose of 100mg 2 times daily. Two women aged 40 and 43 respectively, with SS, achieved clinical improvement after 7 days of

10.12865/CHSJ.46.01.12

treatment, which continued for another two weeks [45].

Nicolas Kluger (2011, Helsinki), treated a 66-year-old man with 5-year chronic SS, refractory to other therapies, with an anti-Il-1 receptor antagonist (Anakinra). The patient had not responded to prednisone, colchicine (1mg/day), methotrexate (15mg/week), disulone (50-150mg/day), rituximab (375mg/m²/week) therapy. Anakinra was administered at a dose of 100 mg/day for 6 months subcutaneously, resulting in lesion remission [46].

Conclusions

In addition to the neutrophilic infiltrate that is typical for Sweet syndrome, different types of histologic manifestations have been described in the literature: subcutaneous, eosinophilic, histiocytoid, lymphocytic.

In this case, we noted that the histological profile changed over time, from a histiocytoid SS recorded in 2014, to a classical SS in 2017, followed by the appearance of lymphocytic SS in 2019.

Due to the fact that SS can be associated with numerous other disorders, our patient requires regular monitoring with a view to eliminate them, and potentially to make a diagnosis and initiate early specific treatment.

Conflict of interests

None to declare.

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 10.12865/CHSJ.46.01.12