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IM - CASE RECORD

A sweet fever

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Case presentation

Dr. Lombardi

An 87-year-old woman was admitted to the emergency department (ED) because of a 7-day history of high fever (up to 39 °C) responsive to paracetamol. She exhibited also severe myalgia mainly localized to neck, shoulders and inferior limbs, but denied any additional symptom, such as sore throat, cough, abdominal pain, nausea, vomiting, diarrhoea, urinary disorders or joint swelling.

Her past medical history included small-cell lymphocytic lymphoma successfully treated with rituximab and bendamustine with negative follow-up, mild aortic insufficiency, arterial hypertension and anxious-depressive syndrome.

At the time of admission, she was on therapy with nebivolol/hydrochlorothiazide, olmesartan/amlodipine, sertraline and bromazepam. No allergy was recorded.

After few hours since ED admission, a cutaneous eruption appeared. It was characterized by diffuse small popular–nodular smooth monomorphic elements, of increased consistency, neither painful nor itchy. The day after, skin lesions increased in number and dimension, and the biggest ones acquired a targetoid appearance (Fig. 1).

The very first clinical examination at the ED was unremarkable other than the above-mentioned cutaneous manifestation, a 2/6 intensity systolic murmur at cardiac auscultation, more intense at the mitral auscultation point, and a small palpable non-tender axillary lymphadenopathy. Blood tests showed elevated C reactive protein (CRP 18 mg/dL, normal value < 0.5 mg/dL) and erythrocyte sedimentation rate (ESR 85 mm/h, normal value < 20 mm/h) without leucocytosis and normal haemoglobin and platelets count. Procalcitonin, renal function electrolytes, hepatobiliary enzymes and coagulation were normal. Also, urine sediment did not show any alteration. A chest X-ray study revealed no abnormalities.

Because of persistent fever, an empirical antibiotic treatment with levofloxacin was started, and the patient was then moved to the Internal Medicine Unit to continue her diagnostic and therapeutic course.

Differential diagnosis

Dr. Tiraboschi, Dr. Boccoli

As the patient was admitted to our department, we focused on her two main symptoms, fever and skin lesions.

Based on our patient's clinical presentation and strictly according to definition of fever of unknown origin (FUO) by Petersdorf and Beeson in 1961, this case could not be considered as FUO, defined by 3-week history of fever including 1 week of in-hospital studies. Likewise, we would not be able to promptly identify the underlying cause of her fever. However, as previously reported, for practical purposes, we consider the clinical features of FUO (roughly definable as persistent fever without clear symptoms and signs of specific organ involvement) applicable to the case of our patient [1]. All fever etiologies can be categorized into four main groups: infectious, malignant/neoplastic, rheumatic/inflammatory and miscellaneous disorders.

Concerning infective etiology, as the patient was transferred to the Internal Medicine Unit, we discussed the need for antibiotic treatment, given normality of procalcitonin, lack of clinical and chemical improvement after 2 days of levofloxacin treatment and considering that antibiotic therapy could affect microbiologic analysis. Thus, levofloxacin

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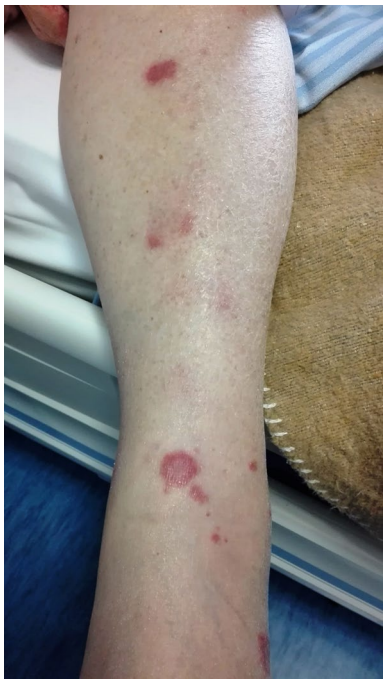

Fig. 1 Erythematous papules and plaque-type skin lesions on the lower extremities

was stopped, and other bloods tests were taken, confirming her inflammatory state (a slight elevation of acute-phase proteins alpha-1 and alpha-2 globulins and CRP 25 mg/dL). A wide panel of microbiologic tests was also performed (urinary and blood cultures, nasal swab for respiratory viruses, pharyngeal swab for beta haemolytic group A *Streptococcus*, serology for Cytomegalovirus, Epstein–Barr virus, Varicella Zoster virus, Herpes Simplex 1 and 2 virus, Widal, Weil–Felix and Wright reactions), with negative results.

Moreover, given the concomitant presence of fever, heart murmur and skin nodules suggestive of Osler's nodules, although not painful, we thought of infectious endocarditis (IE).

The advent of transesophageal echocardiography (TE) has revolutionized the diagnosis of definite IE, and TE is considered the first-line imaging modality in suspected IE according to current international guidelines [2–4]. Nevertheless, despite improvement in imaging techniques, this pathologic condition remains a clinical challenge, and not infrequently is only a post-mortem finding [5]. So, since the above-mentioned microbiologic tests were negative, the patient underwent a TE which ruled out IE, revealing only mild mitral and moderate aortic insufficiencies.

At this point, a dermatological consultation was obtained, and suggested a reactivation of the haematological disease with a new skin localization. Despite negative follow-up, the patient underwent both a PET scan, which did not demonstrate any localization of high glucose metabolism, and a punch biopsy of a cutaneous lesion.

To complete the diagnostic workout, the patient was tested for autoimmune diseases, suspected because of the presence of fever, diffuse myalgia, skin lesions and nonspecific increase in inflammatory markers. Anti-nuclear, anti-extractable nuclear antigens (ENA), anti-neutrophil cytoplasmic antibodies and rheumatoid factor were negative and C3 and C4 resulted within normal ranges.

Diagnosis and therapy

Prof. Fracanzani, Dr. Marzano, Dr. Genovese

After 2 weeks of persistent high fever, despite no antibiotic therapy, the temperature progressively decreased to 37.5 °C, the cutaneous lesions improved, becoming less intense in colour and the CRP dropped down from 25 to 5 mg/dL.

We asked for a second consultation from a dermatologist, who, on the basis of the patient clinical evolution, hypothesized an urticarial vasculitis versus Sweet Syndrome versus Wells Syndrome. Waiting for the histological result, the specialist recommended only topical steroid treatment.

Finally, histopathological evaluation revealed a dermal infiltrate consisting of neutrophils, histiocytes, lymphocytes, giant cells foreign bodylike, and occasional eosinophils, with focal signs of leukocytoclastic vasculitis (Fig. 2). This picture of interstitial dermatitis was compatible with either Sweet Syndrome or Wells Syndrome, despite Sweet Syndrome being more probable due to the acute onset and the presence of systemic symptoms, notably fever and also myalgias.

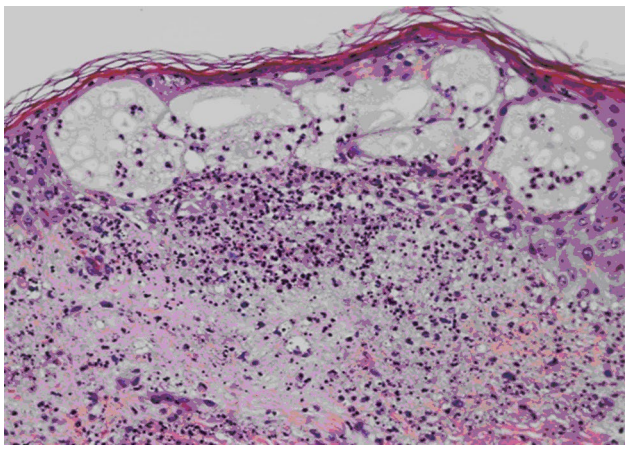

Fig. 2 Histology showing an upper dermal edema, and, in the entire dermis, a dermal inflammatory infiltrate mainly consisting of neutrophils

The patient progressively improved, the fever disappeared and only dyschromic skin sequelae persisted. She was discharged with a dermatological outpatient appointment for follow-up.

Discussion

Prof. Fargion, Dr. Marzano

Sweet's syndrome (SS), also named Acute Febrile Neutrophilic Dermatosis, is an uncommon inflammatory skin disease characterized by fever, neutrophilia and typical skin lesions with a dense dermal neutrophilic infiltrate, responsive to corticosteroids in the absence of infection.

Albeit our patient never presented a rise in neutrophils count, she fulfilled both the two main criteria (typical skin lesions and characteristic histological features) and three of the minor criteria listed for the diagnosis of SS (fever, rise in CRP and ESR), thus making this diagnostic scenario likely (see Table 1 with diagnostic criteria). We could not evaluate the response to systemic corticosteroids because only topical therapy was prescribed.

SS can be classified into classic/idiopathic, malignancy associated and drug induced. The neoplastic conditions associated with SS include both haematological and solid tumours, while granulocyte colony-stimulating factor (G-CSF) is the most widely reported-related medication.

Classic or idiopathic SS, which constitutes the majority of cases, is defined by the fulfilling of the established diagnostic criteria in the absence of malignancy or drug exposure. It may be associated with infections (especially of the upper respiratory tract or gastrointestinal tract), inflammatory bowel disease (IBD) or pregnancy.

Despite the past history of haematologic malignancy, she was in clinical remission, and the PET scan excluded any new disease localization. Moreover, the patient was not exposed to any known SS-inducing drugs, and the association with the haematological malignancy seemed improbable; thus, we classified the SS as idiopathic.

Classic or idiopathic SS is characterized by the abrupt onset of tender, elevated, sharply limited, intensely red papules or coalescent plaques, variable in size and irregular in shape. Some lesions may have a vesicle-like appearance, or they may have a targetoid aspect mimicking erythema multiforme. The eruption is often distributed asymmetrically, usually predominating on the face, neck, upper trunk and upper limbs, and typically spares mucosae. SS lesions, either spontaneously or after treatment, usually resolve without scarring.

Arthralgias, malaise, headache, and myalgias are rather frequent additional symptoms.

Our patient's skin lesions perfectly mirrored the typical presentation of this disease, exception made for not being painful. In addition, she complained also of diffuse myalgia, as often reported.

SS histopathological examination usually reveals an infiltrate consisting predominantly of mature neutrophils located in the upper dermis, without evidence of vasculitis. An oedema of the papillary dermis is frequent, sometimes resulting in subepidermal vesiculation. The neutrophilic infiltrate may extend into the subcutaneous tissue with septal or lobular involvement. Other typical histological features may include a mixture of lymphocytes and eosinophils, vascular endothelial swelling and erythrocyte extravasation [6].

Table 1 Diagnostic criteria for Sweet's syndrome [6]

Major	
Clinical	Rapid onset of skin lesions which may be typical as tender erythematous plaques and nodules or atypical as bullae and targetoid lesions
Histological	Dense neutrophil infiltration without leukocytoclastic vasculitis
Minor	
Clinical	Fever (> 38 °C)
	History of upper respiratory tract or gastrointestinal infection
	The presence of hematologic or solid neoplasia or inflammatory bowel diseases or pregnancy
	Good response to corticosteroid
Laboratory	Erythrocyte sedimentation rate > 20 mm/h
	White blood cells $> 8 \times 10^9$/L
	Neutrophils > 70%
	High C-reactive protein

The diagnosis requires all major criteria and at least three minor criteria

Conclusion

Prof. Fargion

The overall clinical picture consisting of erythematous papule, nodules coalescing into plaque in some areas of the body accompanied by fever and rapidly responsive to topical corticosteroids, strongly suggested a diagnosis of SS, which was confirmed by histology showing a pattern of dermal neutrophilic dermatosis. Sweet syndrome is a prototype of dermal or plaque-type neutrophilic dermatosis regarded as autoinflammatory in its origin, as supported by the overexpression in lesional skin of SS patients of interleukin (IL) 1, which is pivotal in autoinflammation [7]. In the present case, a form of SS associated with the underlying leukemia might be hypothesized. In reality, a pathogenetic link to the underlying leukemia does not seem to be conceivable, since SS associated with hemopathy usually shows a widespread and aggressive presentation, manifesting also as blistering or necrotic skin lesions in addition to classic plaque-type elements. Moreover, she was in clinical remission, and the PET scan excluded any disease localization, also ruled out by the absence of neoplastic lymphocytes on skin histology, which can be seen in SS associated with lymphoproliferative disorders [8].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights This article does not contain any studies with animal or human subjects performed by any of the authors.

Informed consent Informed consent obtained from the patient for her anonymized data to be published.

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