Sweet's syndrome with idiopathic thrombocythemia

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Abstract

Diagnosis of paraneoplastic skin syndromes associating neoplastic processes is assumed as the crucial aspect of dermatological practice. Knowledge of clinical findings of dermatoses suggesting coincidence of malignant proliferative processes facilitates diagnostic and therapeutic procedures. We would like to present a case of Sweet's syndrome, qualified for comparative paraneoplastic skin syndromes. Sweet's syndrome, acute, febrile neutrophilic dermatosis, was first described by Robert Douglas Sweet in 1964 as a disorder characterized by fever, skin lesions of erythematous-infiltrative character, leukocytosis with neutrophilia and dense infiltrations of dermis by mature neutrophils. Sweet's syndrome aetiology is not fully understood, although cytokine abnormalities suggest that Th1 lymphocytes play an important role in pathogenesis of the dermatosis. Factors inducing Sweet's syndrome include: haematopoietic hyperplasia; neoplasms: genitourinary, breast, gastrointestinal; infections of the respiratory and alimentary system; inflammatory bowel diseases; drugs; pregnancy and vaccinations. Systemic corticosteroids are the "gold standard" of Sweet's syndrome treatment; potassium iodide or colchicine may also be used. Indomethacin, clofazimine, cyclosporine A and sulfones are the second-line drugs.

Key words: Sweet's syndrome, acute febrile, neutrophilic dermatosis, paraneoplasia, thrombocythemia.

Introduction

Knowledge of paraneoplastic skin syndromes (comparative and absolute) associating neoplastic processes is assumed as the crucial aspect of dermatological practice. Malignant neoplasms are identified in over 95% of patients as far as absolute markers are concerned. It is worth keeping in mind that paraneoplastic alterations refer not only to skin, but also result in functional disorders of other organs. Paraneoplasm pathogenesis is considered as very complex, and its development depends on the fundamental factor as a neoplasm influence on the immune system (autoimmunization, multinuclear leukocytes dysfunction) together with the endocrine system (hormonal and metabolic dysfunction). Knowledge of clinical symptoms of dermatoses suggesting coincidence of malignant proliferative processes facilitates diagnostic and therapeutic procedures [1].

Hereby, we would like to present a case of Sweet's syndrome (SS), qualified for comparative paraneoplastic skin syndromes.

Case report

A 67-year-old patient was admitted to our Clinic because of skin lesions of the trunk, face and upper limbs with concomitant fever, arthralgia and malaise. Skin changes had appeared 4 days before hospitalization and malaise together with arthralgia had been experienced for about 2 weeks. Idiopathic thrombocythemia (for 3 months), arterial hypertension and ischemic heart disease according to the patient's history. Due to aforementioned chronic diseases, the patient has used perindopril, bisoprolol, atorvastatin and acetylsalicylic acid. Because of malaise and fever during 2-week time before hospital

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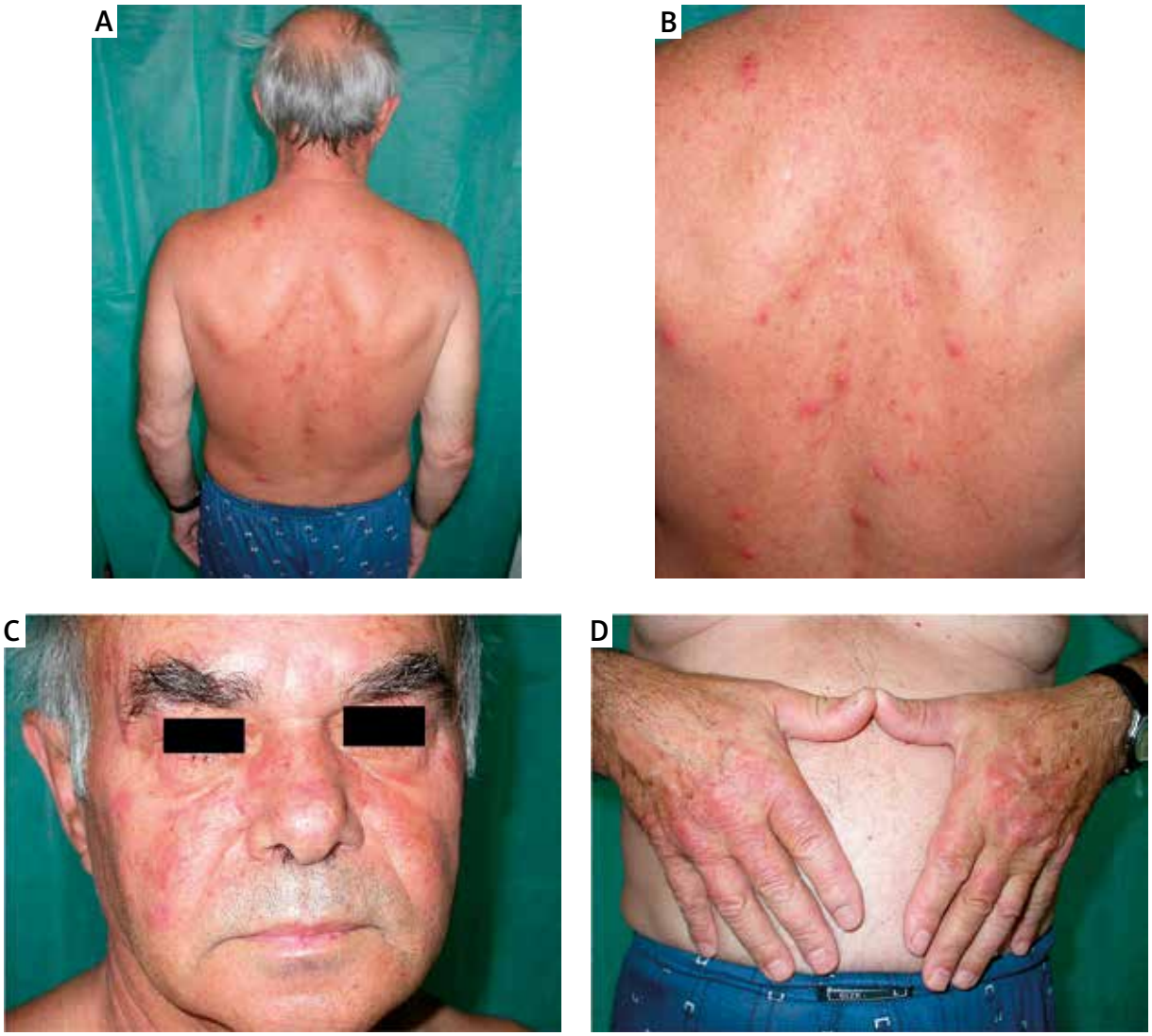

Figure 1 A–D. Erythematous-infiltrative and erythematous-oedematous lesions on the skin of the back, face and dorsal surfaces of the hands

admission, the patient had been administered amoxicillin, azithromycin and paracetamol. Physical examination on admission demonstrated blood pressure 120/60 mm Hg, heart rate 80/min, body temperature 37.5°C.

On general internal examination, the patient was competent regarding circulation and breathing, submandibular lymph nodes were palpable. No anomalies were detected in elementary neurological examination.

Erythematous-infiltrative and erythematous-oedematous lesions were experienced concerning the skin of the back, face and dorsal surfaces of hands (Figures 1 A–D). Laboratory tests revealed leukocytosis 8.56 G/l and in the following one 11.31 G/l with neutrophilia 72.3% and 77.1%, thrombocytosis 799 T/l and 821 T/l; erythrocyte sedimentation rate (ESR) 66/109 (after 1 and 2 h), C-reactive protein (CRP) 91 mg/l and 145 mg/l, alanine transaminase (ALT) 71U/l. Tumour markers CEA, AFP, PSA were normal and HBsAg, anti-HCV and anti-CMV tests were negative. There were no p-ANCA, c-ANCA and ANA antibodies detected in the patient's serum. The microbiologic test of blood was also negative. The results of laboratory tests are shown in Table 1.

No abnormalities were detected in ultrasonography of lymph nodes and thyroid gland. As recommended by the haematologist, ticlopidine hydrochloride was implemented of 250 mg, 2 × 1 tablet.

Skin biopsy, taken from dorsum of hands and face lesions, showed presence of dense, extensive inflammatory infiltrations in dermis composed mainly of neutrmophils (Figure 2). The final diagnosis of SS was established on the basis of clinical findings and laboratory tests. The patient received prednisone at a daily dose of 60 mg, metamizole

Table 1. Results of laboratory tests

Complete blood count		
Haemoglobin [g/dl]	11.8	11.1
Hematocrit [%]	35.7	34.1
Erythrocytes [T/l]	3.66	3.5
Leukocytes [G/l]	8.56	11.31
Thrombocytes [T/l]	799	821
Peripheral blood counts		
Neutrophils [%]	72.3 (6.2 G/l)	77.1 (8.03 G/l)
Lymphocytes [%]	13.2	
Monocytes [%]	12.3	
Eosinophils [%]	1.8	
Basophils [%]	0.4	
Inflammatory markers		
ESR	66/109 (after 1 h and 2 h)	
CRP 91 [mg/l]	145	25.9 after treatment
Biochemical diagnostics		
Creatinine [mg/dl]	1.1	
AST [U/l]	31	
ALT [U/l]	71	
Glucose [mg/dl]	85	
Cholesterol [mg/dl]	108	
HDL [mg/dl]	37	
LDL [mg/dl]	46	
TG [mg/dl]	125	
LDH [U/l]	224	

(antipyretic) and dexamethasone topically. The state of mind and body temperature normalized for several hours after the treatment. In the next few days, we noticed improvement of the skin condition (Figures 3 A–D).

Discussion

Acute, febrile neutrophilic dermatosis, also called Sweet's syndrome, was first described by Robert Douglas Sweet in 1964 as a disorder characterized by fever, skin lesions of erythematous-infiltrative character, leukocytosis with neutrophilia and dense infiltrations of dermis by mature neutrophils [2]. The lesions have a predilection for occurring on the upper extremities, head and neck and may be characterized by some variation, ranging from the typical oedematous papules, often in confluent plaque, to erythematous macules and pustules. Rarely seen vesicular and bullous lesions are most commonly associated with haematological malignancies [3, 4]. The plaques vary from about 1 cm to 4 cm in diameter and

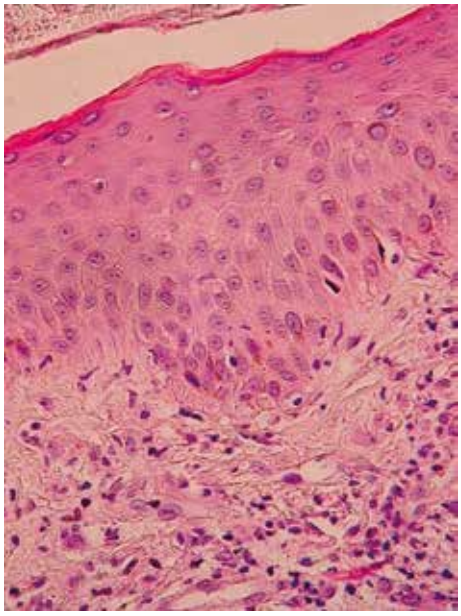

Figure 2. Dense inflammatory infiltrations composed mainly of neutrophils

typically heal without scarring [5]. The disease can also present extra-cutaneous manifestations like acute sterile arthritis, arthralgias, encephalitis, aseptic meningitis, Guillain-Barre syndrome, blepharitis, keratitis, conjunctivitis, iridocyclitis, retinitis, glomerulonephritis, pancolitis, hepatosplenomegaly, cardiomegaly, bronchiolitis, aphthous-like lesions, bullae and vesicles in the mouth, gingival hyperplasia [3, 6, 7]. The presence of oral involvement in the case of SS is often associated with haematological disorders. It seems that SS has two age peaks of appearance: infancy and middle age [8]. The disease is more common in females (F : M – 5 : 1) with the highest incidence between 30 and 60 years of age [5].

Sweet's syndrome aetiology has not been fully understood, although cytokine abnormalities (high concentrations of interleukins 1α and 1β (IL-1α and IL-1β), IL-2 together with interferon γ (INF-γ) and normal concentrations of IL-4) suggest that Th1 lymphocytes play an important role in pathogenesis of dermatosis [3, 9–11]. Recently, neutrophilic dermatoses have been included in the group of autoinflammatory diseases, which classically comprises genetically determined forms due to mutations of genes regulating innate immune response [12]. According to Anzalone and Cohen, photosensitivity may have a role in pathogenesis of SS [13].

The most popular factors inducing SS are: haematopoietic hyperplasia (usually acute myeloid leukaemia); neoplasms: genitourinary, breast, gastrointestinal; infections of the upper part of the respiratory system (particularly streptococcal) and digestive tract (*Salmonella* spp., *Yersinia* spp.); inflammatory bowel diseases (Crohn disease, ulcerative colitis); drugs (antiepileptic drugs, oral contraceptive

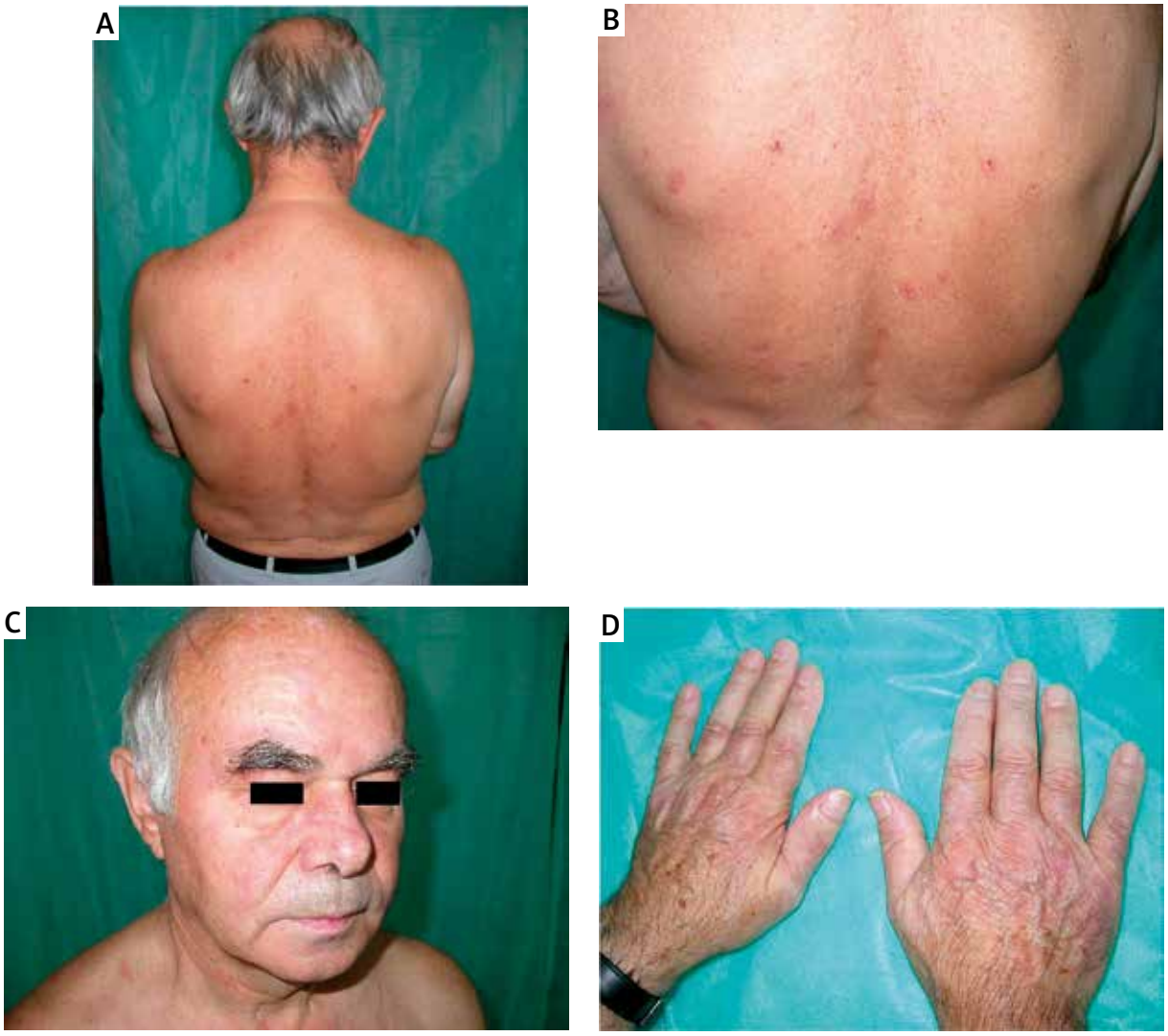

Figure 3 A – D. 9th day of the treatment. Skin lesions were flattened

drugs, furosemide, minocycline, co-trimoxazole, tretinoin, granulocyte-macrophage colony-stimulating factor (GM-CSF) propylthiouracil); pregnancy; vaccinations [5, 6, 14–16].

It is also believed that SS may be accompanied by Behcet's disease, erythema nodosum, rheumatoid arthritis, sarcoidosis, Grave's disease, Hashimoto's disease, Takayasu's disease and skin melanoma [6, 15–18]. In 2012, Diaz-Corpas *et al.* described the first case of SS induced by infliximab in a 51-year-old male with psoriatic arthritis. The symptoms appeared after the second intravenous infusion. The drug was withdrawn, and no further recurrences were observed [19]. Recently, there have been papers describing bortezomib-induced SS [13].

Certain criteria underlie SS diagnosis, proposed by Su and Liu [20] in 1986 with modifications made by Von den Driesch *et al.* between 1989 and 1990 [21]. The presence of both major criteria and two of the four minor criteria is required in order to establish the diagnosis of SS.

Major criteria: i) abrupt onset of painful erythematous plaques or nodules; ii) histopathologic evidence of dense neutrophilic infiltrates without evidence of leukocytoclastic vasculitis. Minor criteria: i) fever over 38°C; ii) association with underlying hematologic or visceral malignancy, inflammatory disease, or pregnancy, or status preceded by the upper respiratory or gastrointestinal infection or vaccination; iii) excellent response to treatment with systemic corticosteroids or potassium iodide; iv) abnormal laboratory tests results (three of four): ESR > 20 mm/h; high CRP concentration; leukocytosis > 8000G/l; neutrophilia > 70%. All major (points 1 and 2) and 3 minor (points 2–4) criteria were present in the described patient.

Differential diagnosis of SS should include such skin conditions as erythema multiforme, erythema nodosum, acute urticaria, erythema elevatum diutinum, granuloma

faciale, leukocytoclastic vasculitis, polyarteritis nodosa, cellulitis, erysipelas, cutaneous lymphomas, Behcet's disease, dermatomyositis, lupus erythematous, pyoderma gangrenosum, allergic contact dermatitis [6].

Systemic corticosteroids are the "gold standard" of SS treatment, potassium iodide or colchicine may also be used. Indomethacin, clofazimine, cyclosporine A and sulfones are helpful in SS treatment and as second-line therapy [6, 9, 22, 23]. The underlying disease should be treated [4, 6]. When the disease is associated with infection, such as caused by *Streptococcus*, *Yersinia* or *Staphylococcus* species, treatment of the underlying infection may result in improvement [16]. Antipyretic drugs are also advisable. Topical therapy is of minor importance, but in the early period corticosteroids and suspensions containing zinc may be used [4]. In the case of single skin lesions, topical or intralesional high potent corticosteroids or topical calcineurin inhibitors are applied.

First-line therapy:

- corticosteroids:
  - prednisone 1 mg/kg/day (30–60 mg) *p.o.* within 4 to 6 weeks taper dose to 10 mg/day; some patients may require 2–3 months of treatment,
  - methylprednisolone intravenously administered (up to 1000 mg/day, for 3 to 5 days);
- potassium iodide:
  - 3 times each day 300 mg *p.o.* (daily dose 900 mg) or as a saturated solution (1 g/ml of water) of potassium iodide (Lugol's solution);
- colchicines:
  - orally at dose 0.5 mg 3 times each day (daily dose of 1.5 mg).

Second-line therapy:

- indomethacin:
  - 150 mg/day for 7 days and then 100 mg/day for next 14 days, orally;
- clofazimine:
  - 200 mg/day for 4 weeks and then 100 mg/day for next 4 weeks, orally;
- cyclosporine A:
  - initial dose ranges from 2–4 mg/kg/day to 10 mg/kg/day orally, from 11th day the dose should be reduced by 2 mg/kg/day every 2 days and stopped on treatment day 21;
- sulfones:
  - as monotherapy or in combination therapy,
  - 100–200 mg/day, orally.

Other systemic drugs have also been effective for the treatment of SS such as chlorambucil, cyclophosphamide, immunoglobulin [24], interferon α [25], etretinate [26] and thalidomide [27]. Yamuauchi *et al.* described successful treatment with tumour necrosis factor antagonist (anti-TNF-α), etanercept for recurrences of SS coexisting with rheumatoid arthritis [28]. In another paper, the therapy with etanercept was highly effective in the treatment of the arthritis and SS, but it took 6 months for the skin disease to respond [29]. Rahier *et al.* reported excellent regression of the cutaneous lesions after infliximab treatment in a patient with Crohn's disease and SS [30]. Anti-TNF-α therapy is very effective but it should be used with caution because some patients with SS have malignancy background. Kluger *et al.* reported the efficacy of anti-interleukin-1 receptor antagonist (anakinra) in the case of a 66-year-old male patient who had a 5-year history of SS refractory to various conventional treatments [31].

Sweet's syndrome is considered as benign dermatosis, that might last for weeks or months without any treatment [16]. Spontaneous remission of SS has been observed in some cases so far [2, 32]. Recurrences occur in approximately 30% of patients and occur even more often in those with hematologic disorders (approximately 50%) [5]. The duration of remission is variable between recurrent episodes of the dermatosis. In some SS patients who had dermatitis associated with tonsillitis, solid tumours, or renal failure, surgical or nephrological intervention resulted in resolution of dermatosis [33]. Patients with SS can develop complications which are either directly related to mucocutaneous lesions or indirectly related to SS associated conditions or both [6]. Because of underlying medical conditions, the follow-up is an important part of treatment and its results decide about further patient management with other specialists co-operation. For instance, recent observations in paediatric patients suggest an evaluation of dermatosis-related cardiac involvement in children suffering from post-SS cutis laxa [34].

Not fully understood aetiology, wide spectrum of clinical findings and therapeutic options show that SS is a very complex disease sometimes difficult to diagnose and requiring co-operation with doctors of various specialities.

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