Case report

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. Paraneoplasms 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...
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 neutrophils (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...
Sweet’s syndrome with idiopathic thrombocythemia

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 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, pancytopenia, 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

Table 1. Results of laboratory tests

|                     | Complete blood count |           | Peripheral blood counts | Inflammatory markers | Biochemical diagnostics |
|---------------------|----------------------|-----------|-------------------------|----------------------|-------------------------|
|                     | 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                     |                      |                         |
| 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                  |           |                         |                      |                         |
| ESR                 | 66/109 (after 1 h and 2 h) | 145      | 25.9 after treatment |                      |                         |
| CRP 91 [mg/l]       | 145                  |           |                         |                      |                         |
| 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                  |           |                         |                      |                         |

Figure 2. Dense inflammatory infiltrations composed mainly of neutrophils
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 erythematosus, 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.

References
1. Outerbridge CA. Cutaneous manifestations of internal diseases. Vet Clin North Am Small Anim Pract 2013; 43: 135-52.
2. Sweet RD. An acute febrile neutrophilic dermatosis. Br J Derm 1964; 76: 349-56.
3. Cohen PR, Kurzrock R. Sweet’s syndrome. A review of current treatment options. Am J Clin Dermatol 2002; 3: 117-31.
4. Burgdorf WHC, Plewig G, Wolff HH, Landthaler M. Dermatologia Braun Falco, Lublin, Poland 2010; 513.
5. McKee PH, Calonje E, Grantner SR. Pathology of the skin. Elsevier Mosby 2005; 679-82.
6. Cohen PR. Sweet’s syndrome—a comprehensive review of an acute febrile neutrophilic dermatosis. Orphanet J Rare Dis 2007; 2: 34.
7. Cohen PR, Kurzrock R. Extracutaneous manifestations of Sweet’s syndrome: steroid responsive culture-negative pulmonary lesions. Am Rev Respir Dis 1992; 146: 269.
8. Kibbi AG, Zaynoun ST, Kurban AK, Najjar SS. Acute febrile neutrophilic dermatosis (Sweet’s syndrome): case report and review of the literature. Pediatr Dermatol 1985; 3: 40-4.
9. Burral B. Sweet’s syndrome (Acute febrile neutrophilic dermatosis). Dermatol Online J 2012; 5: 8.
10. Cohen PR, Kurzrock R. Sweet’s syndrome: a neutrophilic dermatosis classically associated with acute onset and fever. Clin Dermatol 2000; 18: 265-82.
11. Giasuddin AS, El-Orfi AH, Ziu MM, et al. Sweet’s syndrome: is the pathogenesis mediated by helper T-cell type 1 cytokines. J Am Acad Dermatol 1998; 39: 940-3.
12. Marzano AV, Ishak RS, Saibeni S, et al. Autoinflammatory skin disorders in inflammatory bowel diseases, pyoderma gangrenosum and Sweet’s syndrome: a comprehensive review and disease classification criteria. Clin Rev Allergy Immunol 2013; 45: 202-10.
13. Anzalone CL, Cohen PR. Acute febrile neutrophilic dermatosis (Sweet’s syndrome). Curr Opin Hematol 2013; 20: 26-35.
14. Ali M, Duerksen DR. Ulcerative colitis and Sweet’s syndrome: a case report and review of the literature. Can J Gastroenterol 2008; 22: 296-7.
15. Shimizu T, Yoshida I, Eguchi H, et al. Sweet syndrome in a child with aplastic anemia receiving recombinant granulocyte colony stimulating factor. J Pediatr Hematol Oncol 1996; 18: 282-4.
16. Bologna JL, Jorizzo JL, Rapini RP. Dermatology. Elsevier 2008; 380-3.
17. Ma EH, Akikusa JD, MacGregor D, et al. Sweet’s syndrome with postinflammatory elastolysis and Takayasu arthritis in a child: a case report and literature review. Pediatr Dermatol 2012; 29: 645-50.
18. Sánchez Conejo-Mir J, Perez Bernal A, Camacho F. Acute febrile neutrophilic dermatosis (Sweet’s syndrome) associated with melanoma. MED Cut Ibero Lat Am 1990; 18: 155-8.
19. Díaz-Corpas T, Mateu-Puchades A, Morales-Suárez-Varela MM, et al. Retrospective study of patients diagnosed with Sweet syndrome in the health area of a tertiary hospital in the autonomous community of Valencia. Actas Dermosifiliogr 2012; 103: 233-7.
20. Su WP, Liu HN. Diagnostic criteria for Sweet’s syndrome. Cutis 1986; 37: 167-74.
21. Von den Driesch P, Gomez RS, Kiesewetter F, et al. Sweet’s syndrome: clinical spectrum and associated conditions. Cutis 1989; 44: 193-200.
22. Cohen PR, Almeida L, Kurzrock R. Acute febrile neutrophilic dermatosis. Am Fam Physician 1989; 39: 199-204.
23. Fett DL, Gibson LE, Su WPD. Sweet’s syndrome: systemic signs and symptoms and associated disorders. Mayo Clin Proc 1995; 70: 234-40.
24. Haliasos E, Soder B, Rubenstein DS, et al. Pediatric Sweet syndrome and immunodeficiency successfully treated with intravenous immunoglobulin. Pediatr Dermatol 2005; 22: 530-5.
25. Brodkin RH, Schwartz RA. Sweet’s syndrome with myelofibrosis and leukemia: partial response to interferon. Dermatology 1995; 190: 160-3.
26. Altomare G, Capella GL, Frigerio E. Sweet’s syndrome in a patient with idiopathic myelofibrosis and thymomamasythenia gravis-immunodeficiencycomplex: efficacy of treatment with etretinate. Haematologica (Pavia) 1996; 81: 54-8.
27. Browning CE, Dixon JE, Malone JC, et al. Thalidomide in the treatment of recalcitrant Sweet’s syndrome associated with myelodyplasia. J Am Acad Dermatol 2005; 53: 135-8.
28. Yamauuchi PS, Turner L, Lowe NJ, et al. Treatment of recurrent Sweet’s syndrome with coexisting rheumatoid arthritis with the tumor necrosis factor antagonist etanercept. J Am Acad Dermatol 2006; 54: 122-6.