Sweet’s syndrome (acute febrile neutrophilic dermatosis), first described by Sweet in 1964, is characterized by fever, neutrophilic leukocytosis, and painful plaque-forming inflammatory papules on the limbs, neck, face and back. Histologically, the lesions display a heavy, diffuse dermal infiltrate, mainly of neutrophils. Perivascular leukocytoclasis is marked, giving the impression of vasculitis at low magnification. Sweet’s syndrome has been known to be associated with malignancy for many years (in 20% of cases), especially with myelodysplastic or myeloproliferative disorders such as idiopathic myelofibrosis, as in our patient. Sweet’s syndrome is usually treated with corticosteroids, colchicine, DDS, clofazimine, with fairly good results, but not in our case.

The association of spindle-cell thymoma (SCT) with myasthenia gravis (MG) is well-known, as is the association between SCT and immunological abnormalities such as Good’s syndrome, a poorly studied condition characterized by hypogammaglobulinemia and various alterations of cellular and seric immunity leading to respiratory infections. Here we present a case characterized by a singular constellation of the disease associations presented above. This patient posed difficult management problems, which were solved with the empiric decision to treat him with etretinate, the well-known aromatic retinoid active on leukocyte chemotaxis and on proliferation/differentiation of epithelial and lymphoid tissues. The clinical response to this uncodified extemporaneous treatment seemed quite favorable, with rapid disappearance of the plaque skin lesions, slight improvement of hematological parameters such as Hct, MCV, Hb level, RBC, WBC and lymphocyte absolute counts.

Case report
A 71-year-old man with typical Sweet’s syndrome (Figure 1 a,b,c) was referred to our Department. Clinical diagnosis was subsequently confirmed histologically. Presumably he could...
have been affected with idiopathic myelofibrosis (IMF, agnogenic myeloid metaplasia) since 1983, as documented by previous routine laboratory examinations (marked anemia, thrombocytosis, raised levels of LDH\textsubscript{2,3} isoenzymes), but a definitive diagnosis was posed only in 1991 when he underwent thymectomy with mediastinal radical lymphadenectomy through an anterior sternal split for a mediothoracic mass which proved to be a SCT. Before surgery, he had been suffering for months from typical MG, which persisted after thymectomy, although in milder
form (i.e. the neuromuscular disease could be easily controlled with prednisone 10 mg po on alternate days, and suspension of prostigmin administration had not been followed by relapse of the neuromuscular disease). At admission, physical examination revealed marked hepatosplenomegaly. Lymphadenopathy was absent. Body temperature was 38.5 °C.

Laboratory data of interest were as follows (normal range in brackets): RBCs 2.82×10¹²/L (4.2-5.8×10¹²); Hb 7.9 g/dL (13.5-17.0); Hct 22% (38-48); MCV 79.6 fl (80-100); platelets 586×10⁹/L (150-450×10⁹); WBCs 5.5×10⁹/L (3.5-10×10⁹), neutrophils 34%, eosinophils 0%, basophils 9% (myeloid series left-shifted), lymphocytes 30%, monocytes 3%, agranular and granular blasts 8%, neutrophilic promyelocytes 5%, neutrophilic myelocytes 4%, neutrophilic metamyelocytes 5%, orthochromatic erythroblasts 2%. RBC morphology: severe anisopoi-chilocytosis with the presence of dacryocytes, elliptocytes, spherocytes and acanthocytes, and rare Jolly’s bodies. Lactate dehydrogenase 37.2 𝜇kat/L (1.46-3.82). Indexes of kidney and liver function were normal, including alkaline phosphatase levels. Plasma proteins: total 53 g/L (60-80); albumin 54.7%; α1 6.3%; α2 8.4%; β 12.9%; γ 21.7%, with a true monoclonal IgG-λ peak (immunoelectrophoretic confirmation). IgG 12.85 g/L (8.0-18.0); IgA 1.01 g/L (0.80-4.20); IgM 0.36 g/L (0.50-3.0). C3 690 mg/L (550-1200), C4 190 mg/L (150-450). Serum iron 15 𝜇mol/L (9-31), TIBC 29 𝜇mol/L (45-82), ferritin 941 𝜇g/L (20-400). ESR 60 mm/hr (0-16). C-reactive protein 19 mg/L (0.0-10.0). Leukocyte alkaline phosphatase (LAP) 3+. Total lymphocyte count: 1600×10⁶/L (2000±1000). Lymphocyte subpopulations: CD2 54.4% (85±4), CD3 47.1% (74±7), CD4 12.5% (48±8), CD8 37.1% (19±7), CD4/CD8 ratio 0.33 (1.7±0.7), CD20 (panB) 2.9% (10±4), HLA-DR 38.5% (16±7), CD57 (NK) 19% (18±8), CD3-HLA-DR coexpression 12.0% (5±4). Bone marrow biopsy: mild dyserythropoiesis with stromal abnormalities typical of IMF. Ph₁-chromosome and other chromosomal abnormalities were absent. In the past this patient had been given four blood transfusions but HIV, HBV and HCV serology were negative. Skin cell immunity (patch-test; intradermal test) could not be assessed because of the severe cutaneous involvement. In vitro lymphocyte proliferation tests were not performed.

Other causes of Sweet’s syndrome and secondary myelofibrosis were ruled out, since careful history taking and appropriate investigations were not able to demonstrate occult infections, cancer, or previous exposure to aromatic hydrocarbons or other chemicals.

This patient had never undergone splenectomy because of either good hematological compensation or recurrent episodes of pneumococcal pneumonia and upper respiratory tract infections. Indeed his chest X-ray was clear at admission but during hospitalization another episode of pneumonia ensued, which was successfully controlled with penicillin. Response to antibiotic treatment was immediate, and spu-tum culture revealed the growth of Streptococcus pneumoniae; this circumstantial evidence allowed us to rule out a neutrophilic aseptic respiratory disease. The skin involvement was severe and treatment choice soon proved to be a thorny question. High doses of steroids (up to 100 mg/d methylprednisolone) as well as potassium iodide and clofazimine were tried but proved ineffective. Colchicine and DDS could have done further damage the hemopoietic marrow, so they were immediately ruled out. Thus we decided to treat this patient with etretinate (see below, Discussion). The effect of this drug (25 mg bid) on Sweet’s syndrome was spectacular, with regression of plaque lesions in less than 5 days. Moreover, lymphocyte and RBC absolute counts unexpectedly increased to 4000×10⁶/L and 3.29×10¹²/L, respectively (Figures 2-3), while the platelet count decreased to 330×10⁹. On the contrary, no substantial variations of immunoglobulin levels and pattern were observed and the CD4/CD8 ratio increased only slightly (Figure 4).

The patient was discharged on etretinate (50 mg/d) and methylprednisolone (25 mg/d), and has been doing well for 11 months. In particular, he has been free from respiratory infections since beginning etretinate treatment, and peripheral blood cell counts have steadily improved, ranging in the above mentioned lev-
Sweet’s syndrome and etretinate

Follow-up bone marrow biopsies have so far been refused by the patient.

Discussion

This unlucky patient was the meeting point for an astonishingly intricate constellation of unusual diseases. The associations between MG and SCT and between Sweet’s syndrome and IMF are well known. Moreover, Sweet’s syndrome itself can be associated with monoclonal gammopathy. In our case leukocytosis was not present, but this finding could be explained in terms of white series depression due to marrow disease, since white cell count did not reach $10^9/L$, even at the recurrence of pneumonia. SCT can be associated with several hematological diseases and thymic malignant lesions, such as multiple myeloma, various parenchymatous neoplasms, pure red cell aplasia, and immunoglobulin abnormalities.

A thorough bibliographic and MEDLINE search showed no previous reports linking myelofibrosis with SCT; in any case, our patient undoubtedly presented overt immunological alterations. The occurrence of recurrent upper respiratory tract infections and pneumococcal pneumonia coupled with the immunological laboratory pattern displayed by this patient prompted us to pose a diagnosis of associated Good’s syndrome, as a working hypothesis at least. Good’s syndrome, first described by Good in 1954, is a rare association of thymoma with hypogammaglobulinemia; clear-cut criteria for diagnosis have not been formulated because of its rarity, but typical elements of the syndrome are presentation with upper respiratory tract and lung infections, lymphopenia with a decrease of B and T4 lymphocytes and CD4/CD8 ratio inversion, cutaneous anergia, and eosinopenia.

Hypogammaglobulinemia in our patient was apparently restricted to IgM, but spuriously high values of total IgG could be due to the coexisting monoclonal IgG-λ gammopathy, as it was for IgM in the patient described by Jeandel and coworkers. Indeed immunoelectrophoretic findings were consistent with this interpretation. Moreover, six patients with
monoclonal gammopathy associated with a thymic tumor have been described.¹

The aromatic retinoid etretinate is widely used by dermatologists for its modulating effects on epithelial and lymphoid cell proliferation and differentiation. Moreover, it inhibits polymorphonuclear chemotaxis,¹⁰ enhances host immune defenses,¹¹ and antagonizes the action of proliferative polypeptide hormones.¹² In fact, this drug curtailed the clinical expression of Sweet's syndrome in our patient, and this was expected since retinoids are known to dampen the chemotactic processes leading to neutrophilic infiltration in Sweet's syndrome.¹³ The unexpected event was the significant and long-lasting improvement of the patient's general condition. Remarkably, the tendency to upper respiratory tract infection recurrences has completely vanished, the worsening trend in hematological parameters has reversed, and for the first time in years this patient has experienced a sense of physical well-being. Etretinate probably shares differentiation-influencing actions displayed by other retinoids used in leukemia chemotherapy, such as all-trans-retinoic acid (ATRA); however, etretinate has induced nothing resembling the retinoic acid crises caused by ATRA in leukemia patients.¹⁴ Our experience emphasizes the need for studies evaluating further potential applications of etretinate in oncohematology and in immunotherapy, and the importance of empiric decisions when treating intricate conditions for which codified therapy is unavailable.

References