Churg–Strauss syndrome associated with montelukast therapy

Sir,

A 47-year-old woman had a 4-year history of severe asthma. Because asthma continued to deteriorate, montelukast therapy was instituted in April 2007. On September 2007, the patient presented with painful cutaneous manifestations of 1-month duration that had progressively developed, involving her elbows and hands. On admission, the patient was febrile (38°C). Physical examination revealed diffuse sibilant rales, bilaterally. Cutaneous examination demonstrated skin nodules involving her elbows and the back of her hands (Figure 1). The patient also complained of both pain and paresthesias in her lower limbs. Laboratory findings disclosed: erythrocyte sedimentation rate 34 mm/h, C-reactive protein 15 mg/l, white blood cell count 44.8 × 10⁹/l with 55% eosinophils (calculated eosinophils were 24.6 × 10⁹/l), platelet count: 455 × 10⁹/l. Other routine biochemical tests, including renal and liver tests, were normal. Blood cultures, urinalysis, bacterial (Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella) and viral (cytomegalovirus, influenza viruses) serologies were negative. Autoantibody screening yielded negative results for: rheumatoid factors, antinuclear antibodies and cryoglobulin; it was positive for perinuclear antineutrophil cytoplasmic antibodies (ANCA) with myeloperoxidase (MPO)-ANCA levels at: 30 IU/l. Serum IgE level was elevated: 2136 IU/ml (N < 20). Biopsy specimens of skin nodules were performed; histological examination of skin biopsy specimens showed: eosinophil-rich inflammatory infiltrates with granuloma formation around blood-vessel walls (Figure 2); histiocyte infiltration around vessel was confirmed by immunostaining, showing angiocentric CD68-positive staining; immunostaining was negative for: cytokeratine, CD1a, PS100 and CD31. Pulmonary function tests revealed airflow limitation with improvement after administration of inhaled bronchodilator. Lung CT-scan showed bilateral patchy pulmonary infiltrates. Electromyogram revealed an acute neuropathy involving both fibularis superficialis nerves.

A diagnosis of Churg–Strauss syndrome was made. Montelukast therapy was discontinued. Combined therapy of methylprednisolone (pulses of 500 mg/day, during 3 consecutive days) and oral prednisone (1 mg/kg per day initially) was instituted, which resulted in improvement of both pulmonary and neurological clinical symptoms; cutaneous lesions completely healed within 3 weeks after initiation of steroid therapy.

Churg–Strauss syndrome is a rare diffuse vasculitis, characterized by severe refractory asthma, peripheral blood eosinophilia, and specific histological features such as granulomas in both the vascular and extravascular lesions.¹ Systemic complications of Churg–Strauss syndrome are variable, including especially the lungs (97.9%), peripheral nerves (77.1%), sinus (61.1%), skeletal muscles (54.2%), gastrointestinal tract (31.2%), kidneys (26%), heart (12.5%), pancreas and gallbladder (1%).¹⁻⁴ In a recent series, skin involvement has also been reported to occur in 49% of patients with Churg–Strauss syndrome, more often occurring during the course of the disease.² Among cutaneous manifestations, palpable non-thrombocytopenic purpura is considered to be the most frequent sign of Churg–Strauss syndrome, being encountered in about one-third of patients; other cutaneous manifestations of Churg–Strauss syndrome are more uncommon, i.e. patchy and migratory urticarial rashes, livedo reticularis, erythematous papules and macules, fingertip vesicles, aseptic pustules, necrotic bullae,
pinna chondritis or ulcerations.1–4 In the work of Guillevin et al.,3 cutaneous and/or subcutaneous nodules have been reported in 18% of patients. In this instance, skin involvement (i.e. cutaneous nodules) revealed Churg–Strauss syndrome; lesions’ onset, with subsequent skin biopsies, therefore resulted in early diagnosis of Churg–Strauss syndrome. Our findings indeed confirm that cutaneous lesions are a significant diagnostic feature of Churg–Strauss syndrome.

Furthermore, in the present case report, our patient interestingly developed Churg–Strauss syndrome-related cutaneous manifestations, about 3 months after montelukast therapy initiation; our data, in fact, suggest that this later therapy may have deteriorated underlying Churg–Strauss syndrome, resulting in cutaneous and neurological symptoms’ onset. The literature review also suggests that there has been some concern that leukotriene-receptor antagonists might precipitate the onset of Churg–Strauss syndrome.5–10 In a recent series of 78 patients with Churg–Strauss syndrome, Hauser et al.7 have reported that montelukast use was associated with a 4.5-fold higher risk of Churg–Strauss syndrome onset within 3 months after therapy institution; nevertheless, the authors pointed out that the montelukast–Churg–Strauss syndrome association observed may be, in part, explained by the increasing use of this medication over time.7 Moreover, other investigators have postulated that the association of Churg–Strauss syndrome with leukotriene-receptor antagonists may be either coincidental to disease progression (despite steroid therapy) or be related to oral steroid withdrawal, because of the efficacy of leukotriene-receptor antagonists in improving airway obstruction such patients with severe asthma.5,6,8–10 Finally, further prospective series are warranted to determine the role of leukotriene-receptor antagonists in Churg–Strauss syndrome’ onset; indeed, post-marketing surveillance appears to be a major tool for early detection of safety problems with a new drug.

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