Significant improvement of axillary artery stenosis in a 67-year-old woman with giant cell arteritis

Sirs,

We describe a 67-year-old woman with giant cell arteritis (GCA) presented with a month's history of intermittent claudication of the upper limbs and newly appeared Raynaud's phenomenon. The patient did not complain of headaches, shoulder or pelvic pain, nor did she have jaw claudication or visual impairment.

Her past medical history was unremarkable. The physical examination revealed absence of radial and brachial pulses bilaterally. Temporal arteries appeared normal on examination. Blood pressure was unrecordable in the upper limbs. The laboratory evaluation showed high erythrocyte sedimentation rate (ESR) (70 mm/h) and C-reactive protein (CRP) (80 mg/dl), as well as hypochromic and microcytic anemia (Hemoglobin 8.8 gr/dl). The rest of the laboratory tests were within normal limits. The color Doppler ultrasound study revealed a significant degree of bilateral axillary artery stenosis with excessively thickened endothelium Fig. 1A and B). The angiography of the aortic arch and its branches also showed extensive smooth appearance of stenoses of the axillary arteries bilaterally. The biopsy of the left temporal artery revealed histological lesions suggesting GCA.

Treatment with prednisolone 60 mg/day and methotrexate (MTX) 10 mg/week was started Four weeks later, the ESR and CRP had fallen to normal values (ESR 3 mm/h, CRP 1 mg/dl). and hemoglobin also returned to normal values, so the dose of prednisolone was tapered. One year later, her symptoms improved impressively, the blood pressure was recordable in both limbs and the color Doppler ultrasound studies showed a significant improvement of the axillary artery stenosis (Fig. 1C and D). At this time the dose of prednisolone was 10 mg every other day plus 10 mg MTX/week.

GCA targets extracranial branches of the carotid arteries preferentially but also affects the large arteries and especially the carotid, subclavian, and axillary arteries in almost a quarter of patients (1). The clinical presentation of the large vessel involvement includes claudication of the arms, absent or asymmetrical pulses, paresthesias, Raynaud's phenomenon and occasionally, peripheral gangrene (2, 3). Patients with the large-vessel variant of GCA may lack the clinical evidence of cranial involvement, as happened with our patient. Almost 50% of temporal artery biopsies are negative for vasculitis. In addition, large artery involvement in GCA may be complicated by aortic aneurysm, artery stenosis and/or aortic dissection increasing mortality (1).

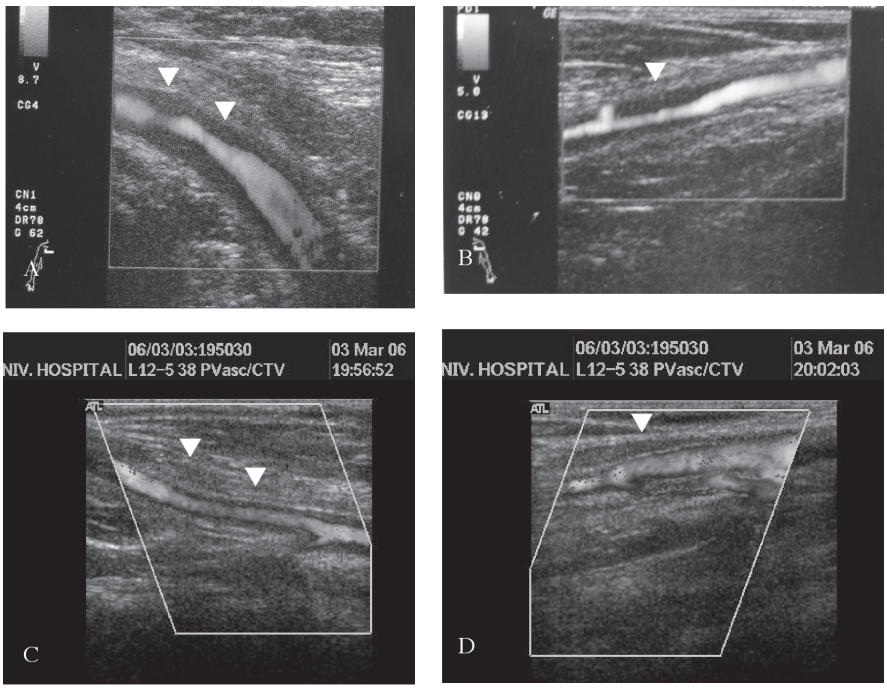

Fig. 1. Doppler ultrasound studies showed right axillary artery stenosis (**A**) and left axillary artery stenosis (**B**). After a year of treatment a significant degree of improvement were noted of both axillary arteries (**C** and **D** respectively).

Color Doppler ultrasonography demonstrates a characteristic picture in GCA showing a hypoechoic mural thickening in the acute phase of the disease due to edema of the vessel wall with subtotal or total occlusion of the involved vessel. In the chronic stage or after treatment, the mural thickening becomes hyperechoic due to fibrosis. Thus, Doppler ultrasonography permits accurate assessment of the involved vessels at specific sites (4).

Angiography, computed tomography, and magnetic resonance angiography delineate characteristic patterns in large-vessel GCA (5).

High-dose of corticosteroids is the treatment of choice for large-vessel GCA (2). Early diagnosis and treatment enables a good response avoiding vascular complications. However, angioplastic revascularization is required in cases with arterial occlusion not responsive to corticosteroid therapy, while the addition of aspirin may help maintaining the angioplastic results (6). Despite a tendency to restnoses, balloon angioplasty of the upper-extremity artery, in combination with immunosuppressive treatment, is an efficient method for the treatment of extracranial GCA (7, 8). Although the use of MTX in temporal arteritis is controversial, it seems to be an effective corticosteroid-sparing agent for the treatment of GCA (9, 10). However, the most important finding in this case is the significant improvement of axillary artery stenosis after a year of early treatment with prednisone and MTX. Thus, in patients with upper limb ischemia, the possibility of large-vessel GCA must be considered. Early diagnosis and treatment enables a good clinical response and avoidance of large-artery complications.

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Henoch-Schönlein purpura associated with pidotimod therapy

Sirs,

Henoch-Schönlein purpura (HSP) is a small-sized vasculitis affecting mainly children and young adults. The mean age of patients is six years; 90% of patients are under ten years of age (1, 2).

A wide variety of drugs, pathogens and other environmental exposures have been associated with HSP. Although the precise etiology of the disease is unknown, it is clear that antigenic stimuli causing elevation of circulating Immunoglobulin A (IgA) have a pivotal role in the pathogenesis of HSP (3).

The clinical manifestations of HSP are a consequence of widespread vasculitis resulting from IgA deposition in vessel walls and the renal mesangium (3, 4). HSP is characterized by palpable, non-thrombocytopenic purpura, arthritis and/or arthralgia, abdominal pain, gastrointestinal haemorrhage and/or nephritis (2).

We report the first case of HSP associated with treatment with pidotimod.

A nine-year-old female came under our observation in January 2007 for a non-pruritic palpable purpuric rash with lower limb predominance, diffuse abdominal pain and arthritis involving knees and ankles; the arthritis was painful and inhibited walking.

Laboratory analysis showed a white blood cell count of $8.45x10^3/mm^3$ and a platelet count of $357x10^3/mm^3$. Serum IgA were slightly increased. C-reactive protein, erythrocyte sedimentation rate, kidney function and urine sediment were normal. Antistreptolysin was not increased. Antinuclear antibodies, cryoglobulins and antineutrophilic cytoplasmic antibodies (perinuclear and cytoplasmic patterns) were negative.

The patient had started treatment with pidotimod 400 mg per day eight days before her visit due to recurring tonsil infections and adenoid-tonsillar hypertrophy.

She had had her last infection three months earlier, and she was living with her parents who were in good health.

Pidotimod ((R)-3-[(S)-(5-oxo-2-pyrrolidinyl) carbonyl]-thiazolidine-4-carboxylic acid, PGT/1A, CAS 121808-62-6) is a synthetic biological response modifier which acts by stimulating cell-mediated immunity (5) and which has been shown to enhance several immune parameters in humans, both *in vitro* and *in vivo* (6, 7). Pidotimod is active on T-lymphocytes in early maturation stage (8) and is able to enhance peripheral blood mononuclear cell proliferation through an increased interleukin-2 production (IL-2) (7). IL-2 has been shown to induce interleukin-5 (IL-5) production by T-lymphocytes, in a dose-dependent manner, and IL-5 induces IgA production from B-lymphocytes and is also recognized by its activity as an IgA-enhancing factor (9).

She was diagnosed with drug related HSP and discontinuation of the drug led to a complete resolution of the disease; abdominal pain was resolved in four days, purpuric rash disappeared within ten days and arthritis improved over the following two weeks. The occurrence of HSP was probably related to pidotimod therapy.

There was a close temporal relationship between drug ingestion and onset of symptoms and when its intake was interrupted the patient's clinical picture improved.

For this reason, and on the basis of the Naranjo algorithm (10), adverse drug reaction could be considered possible and we believe that our patient may represent the first clear evidence of a relationship between HSP and pidotimod treatment.

Although this is the first report of HSP associated with pidotimod, clinicians should be aware of a possible association between HSP and the intake of pidotimod; it is also possible that the intake of cell mediated immunity stimulating drugs may trigger the development of cell mediated immunity diseases in genetically predisposed patients.

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