Mononeuropathy multiplex in a Churg-Strauss syndrome patient – case report

Filipe Gonçalves, Fernando Esculcas, Pedro Cunha, Jorge Cotter

Abstract

A 44 year-old male with asthma and allergic to grass pollen came to our Emergency Department with dyspnea, productive cough, paresthesia, dysaesthesia and dysphonia. He was admitted with a diagnosis of community-acquired pneumonia. An acute axonal polyneuropathy has developed preventing the patient from walking becoming totally dependent on others. In spite of exhaustive investigation the aetiology was not ascertained. Peripheral blood eosinophilia and P-ANCA positivity with myeloperoxidase specificity led to the diagnostic hypothesis of ANCA associated vasculitis, namely Churg-Strauss syndrome. Treatment with prednisolone and cyclophosphamide achieved significant improvement, albeit a disabling neuropathy persisting and not responding well to intravenous immunoglobulin and rituximab.

Key words: Churg-Strauss syndrome, ANCA-associated vasculitis, mononeuropathy multiplex.

CASE REPORT

A 44-year-old man with personal background of bronchial asthma, allergic to grass and high blood pressure, came to the Emergency Service referring the onset two weeks previously of dyspnea, paraesthesias and dysaesthesia in the feet, forearms and dysphonia. He presented a progressive degeneration of dyspnoea associated with fever and productive mucopurulent haemoptoic coughing. Besides of his usual medication consisting of inhaled terbutaline and salbutamol, he had been prescribed 7 days previously with amoxicillin/clavulamic acid and prednisolone in a lower dose without improvement.

He had the following vital endpoints: heartbeat of 152 bpm, BP 152/68 mmHg, respiratory rate 28 cycles per minute, peripheral saturation of oxygen of 90% and axillary temperature of 39.5°C. In the physical exam there was only to highlight, in the pulmonary auscultation, the presence of sparse wheezing.

Internal Medicine Service. Alto do Ave Hospital Center – Guimarães Unit. Guimarães.

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The blood tests showed leukocytosis (15,000/µL) with eosinophilia (5,400/µL), hypoxemia (63,2 mmHg) and increases of C-reactive protein (52,7 mg/L). The thorax X-ray has shown opacity with left aerial perihilar bronchogram.

He was admitted and medicated with levofloxacin, nebulisation of ipratropium bromide and salbutamol, and prednisolone as it was done previously (5 mg/day/Oral route) but on the first date of admission it was increased to 75 mg/per day for the asthma treatment. He presented improvement and subsequent resolution of respiratory symptoms. Through computerized tomography (CT scan) it was demonstrated condensation with aerial bronchogram on the upper segment of the left lower lobe, which was also solved. There was no bacterial isolation in the blood and sputum culture tests. He presented however a worsening of dysphonia and progressive decrease of muscular strength and sensitivity in the four limbs, with higher intensity on the right, predominantly distal, in one and a half glove; he was totally dependent on others and unable to walk. Motor and sensitive changes were not confined to the territory of one nerve or several nerves individually, escaping to a stem or radicular systematization. Cranial-encephalic CT scan has shown signs compatible with maxillary, sphenoidal and some ethmoid cells sinusitis. Electromyography has shown signs of severe acute axonal polyneuropathy predominantly motor and distal reaching all the limbs (more markedly on the right-hand side). The otorhinolaryngology observation has shown paralysis of the left vocal cord, without anatomical

TABLE I

Initial aetiologic investigation, of the acute axonal neuropathy

Neuropathy associated to HIV infection	Negative HIV serology
Guillain-Barré Syndrome	Non suggestive clinical history; No protein in the CSF
Neuropathy associated to porphyria	Normal urinary excretion of porphyrin
Toxic neuropathies	Without history of pharmacological or occupational exposure
Paraneoplastic Neuropathy	Thorax-abdominal-pelvic CT scan without suggestive changes Bronchofibroscopy: paralysis of the left vocal cord; without other changes Cytology of the bronchial aspirate: inflammation Normal PSA
Amyloidosis	Search of amyloid substance of rectal mucosa, after staining through the Congo red method: negative
Nutritional deficits	Normal Vitamin B12
Hypothyroidism	Normal TSH and free T4
Autoimmunity	Negative antinuclear antibodies, normal C3 and C4, total IgE = 2360KU/L (<120), ANCA-P 1/640, anti-myeloperoxidase = 74.4EU/mL (<6.0)

changes. *Table 1* shows the initial investigation of the polyneuropathy aetiology, results of which were obtained. From the remaining analyses carried out it should be highlight the presence of proteinuria of 936 mg/day with a preserved renal function (creatinine clearance = 97.4 mL/min/L, 73 m²) and urinary sediments without changes.

It was verified the development of muscular atrophy around five weeks later, and he has been undergoing physiatrics treatment.

Having improvement on the respiratory function and stable from a neurological point of view, and while waiting for the results of sural nerve biopsy, amyloid substance search in the rectal mucosa, dosing of urinary porphyrin and autoimmunity, he was discharged from hospital and referred to the Internal Medicine clinic and Physical Medicine and Rehabilitation.

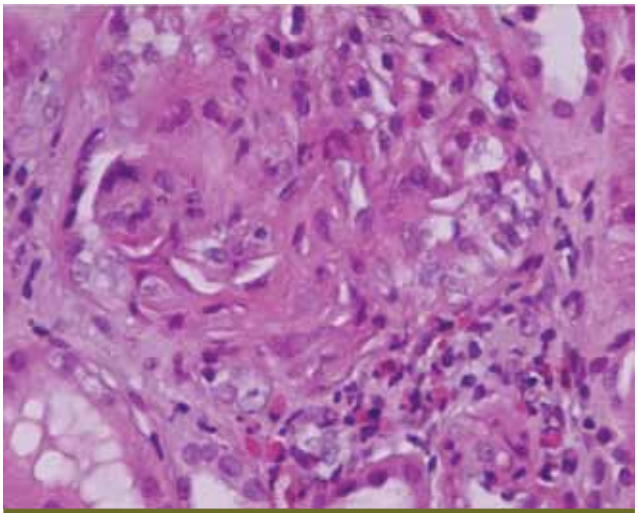
Around three weeks later after being discharged, he went back to the Emergency Service due to dyspnea and mucopurulent sputum in productive coughing which had not improved with cefprozil and clarithromycin which had been prescribed to him as an outpatient. It was also being medicated with hydroxyzine, prednisolone in weaning of schedule, esomeprazole and inhaled terbutaline.

He was readmitted due to the suspicion of pneumonia, with new opacity on the right lower lobe and medicated with prednisolone on (25 mg every eight hours), pantoprazole, ipratropium bromide and budesonide in nebulisation. In the blood tests it was highlighted the presence of eosinophilia (4,200/µL).

His respiratory symptomatology and pulmonary infiltrate were solved. He kept high blood pressure (<160/100 mmHg). Culture tests in the blood and sputum were negative. The histological exam of the sural nerve has shown very severe lesions of acute axonal neuropathy, thickening and hyalinization of the endoneurial capillary walls. An ANCA-P titer of 1/640 was obtained. A brief urine test showed erythrocyturia (10 to 25 erythrocytes/field) and proteinuria (++) which was quantified in 1.403 mg/24 hours.

The integration of all the clinical information obtained led to the formulation of a diagnosis hypothesis of vasculitis associated to ANCA, namely Churg-Strauss Syndrome (SCS). Once the blood pressure was controlled with slow absorption nifedipine and excluding renal circulation aneurysms by magnetic resonance, a renal biopsy was carried out demonstrating an increase of cells and mesangial matrix, presence of several tubular interstitial inflammatory foci with eosinophilic infiltrate and arteriole with chronic sclerotic changes compatible with vasculitis sequelae (*Fig. 1*). This biopsy was carried out seven weeks after the initial presentation.

The prednisolone dose was increased to 1 mg/kg/



Kidney optical microscopy.

FIG. 1

day adding after 10 days cyclosphosphamide mg/kg/day, by oral route.

10 days after starting cyclophosphamide it was verified a return of eosinophilia (*Table 2*). At four months he presented haemorrhagic cystitis, being cyclophosphamide administered in monthly pulses by intravenous route, associated to mesna. He did not show this complication again. Cystoscopy was impossible due to a urethral stenosis.

On the evaluation after one year in therapy with cyclophosphamide it was verified that the patient did not show again respiratory symptoms, the pulmonary auscultation was always normal, he presented a gradual and slow improvement on the motor and sensitive deficits recovering claudicating gait and with a wider support base although keeping amyotrophy of the limbs predominantly distal and the hands intrinsic muscles, with the consequent dependency on a third person for his daily life activities. From the laboratorial point of view, eosinophils were kept in the normal number, proteinuria regressed progressively for a trace value (156 mg/day), and urinary sediment becoming normal. Electromyography showed compatible signs with severe mixed sensitive and motor polyneuropathy.

Three monthly cycles were performed of human immunoglobulin on doses of 0.4 g/kg/day for five days, without any neuropathy changes. Lymphocyte B depletion before 2 pulses of 1 g of rituximab separated by 15 days has not presented any effect.

DISCUSSION

The clinical case presented corresponds to a typical presentation of SCS, fulfilling all the six classification criteria of the American College of Rheumatology (ACR). In spite of that, the rarity of the disease has contributed to delay the diagnosis. The disease has showed itself, in a generalized way, according to the classification of severity levels of the European League Against Rheumatism (EULAR),[1] justifying the therapeutic association of glucocorticoids and cyclophosphamide. Oral cyclophosphamide was used, continuously, considering the fears of a higher risk of recurrence same with endovenous therapy by pulses. Proteinuria > 1 g/day remains one of the five factors of a bad prognosis defined by the French group of the vasculitis study, and the same authors argue that the presence of at least one of these factors of bad prognosis indicates the need for associating immunosuppressants. [2]

SCS evolves usually in three successive stages: the prodromic stage corresponding to the onset of

TABLE II

Eosinophilia, C- reactive protein (CPR), erythrocyte sedimentation rate (ESR) and ANCA-P laboratorial progression

		Starting cyclophosphamide	Following day	5 days later	10 days later	1 and half months later	2 and half months later
Eosinophils	4.200/mL		100/mL	1.400/mL	0	0	100/mL
CRP	9,4 mg/L		4,4 mg/L	4,5 mg/L	—	1,5 mg/L	—
ESR	18 mm		—	—	—	8 mm	—
ANCA-P	1/640		—	—	—	1/80	negative
CPR normal value <5.0mg/L							

asthma rapidly corticoid dependent; blood and tissue hypereosinophilia features the second stage; finally it emerges on the third stage, systemic vasculitis.

In our case it is possible to describe a first stage featured by asthma, followed one year afterwards of a second stage causing the admission where it was presented in a simultaneous way both hypereosinophilia and vasculitis. The presence or absence of ANCA has been referred as able to discriminate between two SCS subtypes: the first case predominating renal involvement, peripheral neuropathy and purpura; on the second case the cardiac involvement, non-haemorrhagic pulmonary infiltrate and fever. [3,4] In our case, ANCA presence did not discriminated clearly between these two subtypes. Reaching the cranial pairs seldom happens (1%).[5] Our patient had an involvement of the vagal nerve, regressing totally after therapy.

On the patient's general evaluation one year after therapy, a disabling neuropathy was persistent and it was verified the deterioration of the electromyographic changes, leading to introduce human immunoglobulin. Some authors argue in favor of and are carrying out clinical trials on the use of such drug as a second-line therapy, particularly in cases of neuropathy and/or myopathy resisting to conventional therapy. [6] In some patients with SCS it was demonstrated the reduction of vasculitis sequela, as persistent and disabling neuropathy, through the combination of the conventional regime (glucocorticoid and cyclophosphamide) and the plasmapheresis synchronized with human immunoglobulin, as first line therapy. [2]

Due to the inefficacy of human immunoglobulin, we opt out for treating with rituximab with base in references to the effective treatment of some patients with SCS refractory using such drug.[7] Several casuistries were published coming to the conclusion of rituximab efficacy in the treatment of vasculitis, positive for ANCA, more prevalent then SCS, namely Wegener granulomatosis and microscopic polyangiitis, refractory or with frequent recurrences. [8-10] Recently two random studies emerged comparing rituximab with cyclophosphamide. RAVE study has demonstrated the non-inferiority of rituximab when related to the daily cyclophosphamide for the remission induction in severe ANCA positive vasculitis, and can be higher in the recurrent disease. [11]

RITUXVAS came to the conclusion that the remission rates supported of renal vasculitis ANCA positive are high both in the group of patients treated with rituximab as in the endovenous cyclophosphamide.[12] In our case, we did not get any improvement of the neuropathy therefore the current changes can also be a sequela.

The authors thought relevant to report this case due to its severe and mutilating presentation, in a 38-year-old individual, with refractory manifestations to therapy both to the first and second line consensually. In spite of that, a defined and presented therapeutic intervention, had the result of a partial recovery of autonomy. ■

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