Churg-Strauss Syndrome: A brief case review

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Abstract

The authors present a case of a 76-year old man with a systemic vasculitis which, although not presenting the typical histological patterns, fits the classification criteria for Churg-Strauss Syndrome established by the American College of Rheumatology in 1990.

The case is presented not only due to the relative rarity of this syndrome, but also due to the relevance of some its diagnostic and therapeutic aspects. A brief review of the literature on this syndrome is also carried out.

Key words: Churg-Strauss syndrome, classification criteria.

Introduction

Churg-Strauss Syndrome (CSS) is a systemic vasculitis with clinical and pathological characteristics that frequently overlap with those of polyarteritis nodosa and Wegener granulomatosis.[1,2]

It was first described in 1951 by Churg and Strauss, who defined the characteristic histological aspects of this disease based on the results of autopsies in patients with severe asthma, systemic vasculitis and peripheral eosinophilia.

The strict adhesion of histological diagnosis to these criteria led to significant underdiagnosis of this disease, not only due to their low sensitivity, but also due to the major degree of overlapping with other vasculitis characteristics. Several authors then proposed that the diagnosis of this syndrome could be made even in the absence of traditional histological aspects, since its clinical pattern would be sufficiently specific to enable its identification.[3] Within this reasoning, the American College of Rheumatology, based on an analysis of seven hundred cases, proposed the adoption of six criteria for the classification of CSS, of which only one is histological, the presence of any four of these criteria being sufficient to obtain significant sensitivity and diagnostic specificity.[4]

The fact that the case presented here does not have the histological criterion highlights, in a concrete way, the need for early diagnosis of this disease, even in the absence of the histological criterion, in order to enable timely initiation of the appropriate treatment and prevent the irreversible visceral lesions.

Another interesting point of this case is the analysis of the treatment options, with a review of the therapeutic and prognostic concepts.

Clinical Case

A 76 year-old male patient, Caucasian, from Mozambique, residing in Lisbon, but with multiple stays in Mozambique and South Africa, was admitted to our Service due to dyspnea, peripheral neuropathy and accentuated eosinophilia.

The patient was diagnosed more than ten years ago with bronchial asthma and nasal polyposis, controlled with high doses of topical corticosteroids, xanthines, Beta-2-mimetics and i.m. corticosteroids in the acute phases, but in good health between crises.

Six weeks prior to admission, patient reports onset of asthenia and anorexia, with progressive weight loss (reduction of more than 10% of body weight), low fever in the afternoons (37-37.5ºC), myalgia and arthralgia of the lower limbs, which worsened to make autonomous walking impossible, due to pain and claudication.

Three weeks before admission, the patient noticed the onset of paraesthesia and painful, tactile hypoaesthesia in both hands, although stronger in the right and, and the appearance of skin lesions in both lower limbs, which were papular and painful to touch, non-confluent and non-pruritic.

One week before admission, there was a worsening of the respiratory condition, with frequent dyspnea

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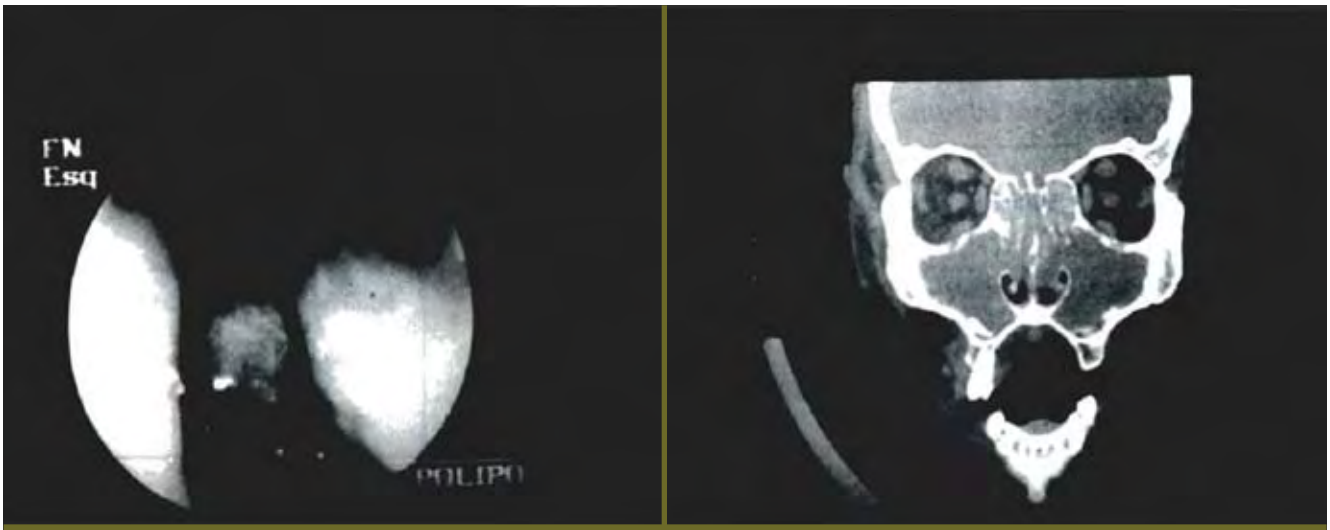


Nasosinusal Polyposis – 1A – Endoscopy: Nasal polyps; 1B – CT of Paranasal Sinuses: Bilateral opacification of all Paranasal Sinuses and of most of the nasal fossae.

FIG. 1

crises, partially improving with bronchodilators. One day before admission, the dyspnea became almost permanent, with very poor response to therapy, therefore the patient was brought to the emergency service.

The patient was a non-smoker, and had a relevant history of arterial hypertension, known for one year, which was medicated with captopril 50mg daily + hydrochlorothiazide 25mg, and episodes suggesting immediate-type allergy to various non-steroidal anti-inflammatories and penicillin, with angioedema, urticaria and dyspnea.

Observation showed axillary temperature of 37.3°C, rhythmic, bounding and regular pulse of 110 ppm, but with frequent extrasystoles. BP 160/95 mmHg, moderate dyspnea, respiratory frequency of 28 cycles/minute, but with no peripheral or central cyanosis.

There was exuberant polyposis in the nasal fossae (*Fig 1A*) and the presence of candidiasis was observed in the oropharynx.

In the pulmonary observation, signs of bronchospasms and disperse rhonchi were observed. Cardiac and abdominal examinations were normal.

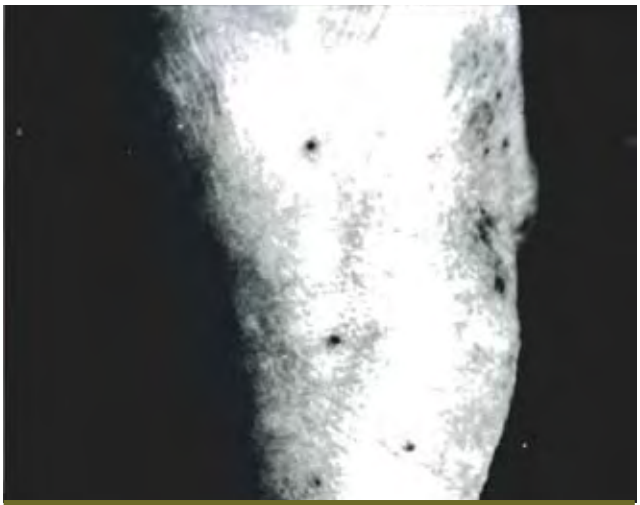
The limbs were painful to palpation of muscular mass and mobilization of both lower limbs; palpation of both tibiotarsal joints was also painful, but with no other signs of inflammation. Patient also presented some skin lesions spread across both lower limbs (*Fig. 2*), which were purple, papular and painful to touch, with ulcero-necrotic centers, suggestive of vasculitis.

Neurologic examination showed distal and asymmetric muscular atrophy of all four limbs, particularly evident in the thenar eminence of both hands, with decreased muscular strength in the movement of the hands and feet, more pronounced on the right: tactile, painful, thermal and vibrating stocking and glove hypoaesthesia and various errors in the assessment of postural sensitivity, also more pronounced on the right side. Osteotendinous and cutaneous reflexes, motor coordination tests and cranial nerve tests did not reveal any significant alterations.

Additional diagnostic tests

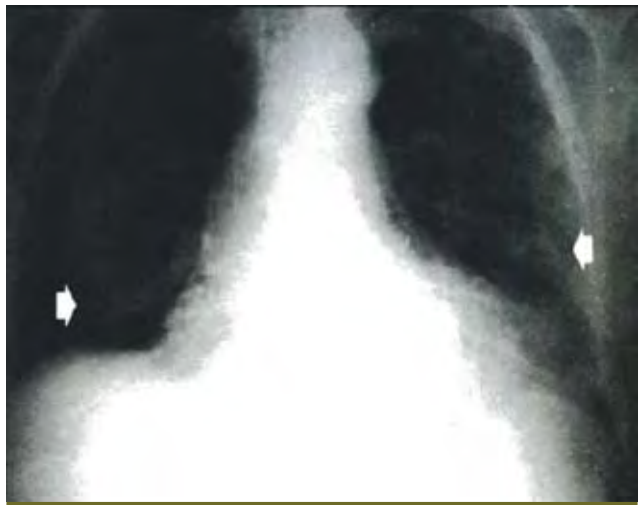
Blood count showed: erythrocytes 4,600,000/mm^3; hemoglobin 13.9 gr/dL; hematocrit 42%; mean globular volume 92 micra^3; leukocytes 28,000/mm^3 (N-43%, L-4%, E-52%, B-0%, M-1%); platelets 405,000/mm^3 and ESR 61mm/1st hour.

Biochemical values showed normal liver and kidney functions, urine II without alterations, lactate dehydrogenase 436 UI/L, total protein 6.1 gr/dL with electrophoresis showing polyclonal increase in gamma-globulin levels (27%). Immune-electrophoresis revealed normal levels of IgG, IgA, and IgM, and an IgE value of 1980 KU/L. The Kappa and Lambda



Vasculitis of the lower limbs.

FIG. 2



Transitory lung infiltrates.

FIG. 3

chains presented normal values. Arterial blood gas showed: pH 7.43; pO2 67 mmHg (sat 92%); pCO2 43 mmHg; and HCO3- 27mmol/l.

The patient had undergone previous exams (*Table I*), showing evident progressive elevation of total IgE values for around eight months and eosinophilia for about twenty days prior to admission.

ECG showed sinus tachycardia with slight, non-specific alterations of ventricular repolarization.

Chest X-ray *(Fig. 3)* showed cardiomegaly and heterogeneous, poorly-defined lung infiltrate in both pulmonary fields.

Patient had also undergone exams 15 days earlier: Ultrasound – ejection fraction 32%, non-dilated cavities; abdominal ultrasound with no alterations; Facial CT of the paranasal sinuses (Fig. 1) – extensive nasosinusal polyposis with opacification of all paranasal cavities, as well as nasal fossae. During hospital stay, the following complementary diagnostic tests were carried out:

Myelogram – increase in the no. of eosinophils (40% of total cells) in all phases of maturity, with no other alterations.

Autoimmune Assay – ANA, antiDNA, anti Sm, anti RNP, anti Ssa, anti Ssb, anti-centromere, anti Scl70, RA test, c-ANCA and p-ANCA, all negative. Negative circulating immune complex assay; normal C3, C4 and CH100 assays; hepatitis B serology –AcHBs, AcHBe and AcHBc positive (IgM negative); AgHBs and AgHBe negative.

Skin tests and aspergillosis precipitin test – negative.

Chest x-ray – repetition of the x-ray carried out in the emergency service showed the same aspects, but repetitions after the 5th day of hospitalization no longer revealed lung infiltrates.

Chest CT – carried out on the 5th day of hospitalization, did not show any alterations.

Skin biopsy – the biopsy of one of the lesion zones of the lower limb showed the presence of vasculitis, but with no granuloma or eosinophil infiltration.

Lung biopsy – this was only possible around two weeks after hospital admission and already under therapy. Histological exam did not show any alterations.

Electromyogram – pattern compatible with multiple mononeuropathy, more intense on the right side.

Faced with a systemic vasculitis with characteristics suggestive of CSS, on the 5th day of hospitalization we initiated treatment with prednisolone 2 mg/kg/day, observing a rapid improvement in the patient's general health, breathing difficulty and skin complaints – no new skin lesions emerged, and the existing lesions began to recede -, accompanied by evolution of laboratory results, as shown in *Table 1*, with the disappearance of eosinophilia and subsequently, of the leukocytosis, and a reduction in ESR

TABLE I

Evolution of laboratory values

	24-11-92	25-05-93	08-07-93	28-07-93*	09-08-93**	28-09-93	30-03-94	28-09-94
Erythrocytes	5060000	5310000	5090000	4600000	4220000	4210000	4980000	4880000
HG	14.9	16.9	16.1	13.9	12.8	12.8	14.5	14.3
Leukocytes	7000	8700	13000	28000	13.540	8900	7600	5500
% Neutr	60	79	41	43	77	72	70	65
% Eosin	4	2	37	52	3	2	2	3
% Basop	0	0	0	0	0	1	0	1
% Lymphoc	33	13	14	4	12	16	21	28
% Mono	3	6	8	1	8	9	7	3
Platelets	352000	303000		403000	461000	392000	410000	
ESR	14	2	28	61	37	15	16	12
IgE (kU/l)	163	1085		1980	427	235	180	205

*Date of admission: 28/07/93
**Start of corticosteroid therapy: 01/08/93

and total IgE values. The neurological complaints in the lower limbs showed a significant improvement from the first week of treatment, with autonomous walking capacity being re-established, but it was observed that the complaints of bilateral hypoaesthesia of upper limbs continued, and the patient still had great difficulty carrying out fiddly activities involving sensitive-motor coordination.

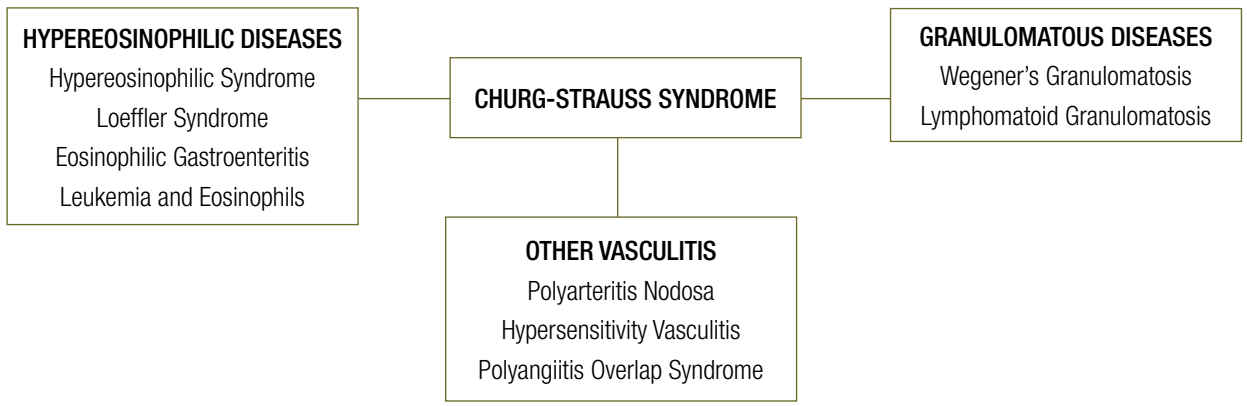
In view of the marked improvement in general health, and the absence of significant visceral lesions, it was decided not to start any other immunosuppressant therapy. The patient was discharged three weeks after admission, with a regimen of very gradual reduction of the systemic corticosteroid therapy.

About two months after discharge from hospital, still under corticosteroid therapy, the peripheral neuropathy once again worsened, with severe functional limitation – loss of the ability to grip with the hands, with only palm pressure possible, and significant deterioration in cardiac function (EF 22%, dilatation and global hypokinesis of the left cavities), with no alteration in rhythm, accompanied by intense fatigue and general malaise. There was no evidence of renal lesion. Based on this evolution, the patient was admitted and treatment was started with cyclophosphamide 2 mg/kg/day e.v., subsequently changed to oral route, which was maintained for eleven months, and then suspended due to haematologic toxicity (pancytopenia). During this treatment, a marked recovery was seen in general condition, with gradual recovery of ejection fraction values (EF 34% at 6 month) and regression of neuropathic complaints, with recovery of all the movements of the hands and fingers, though still with mild hypoesthesia in both hands. It is also interesting to note that during the treatment with cyclophosphamide, a more pronounced clinical and radiological regression was observed of the nasosinusal polyposis which had never been achieved previously, even with the use of systemic corticosteroids.

Discussion

Churg-Strauss Syndrome (CSS), also known as allergic granulomatous angiitis, is a systemic necrotizing vasculitis which affects mainly small and medium-caliber vessels, frequently leading to the emergence of granulomas.

The identification of a vasculitis with intense eosinophilia and significant lung manifestations dates back to 1939, when Rackeman and Greene[1] identified a subgroup of patients with these characteristics, diagnosed as polyarteritis nodosa (PAN). However, it was only in 1951, with the works of Churg and Strauss[2], that CSS was definitively highlighted as an autonomous diagnostic entity distinct from PAN. This diagnosis was made possible with the identification of



Relationships between the Churg-Strauss Syndrome and other pathologies with common clinical and pathological aspects.

FIG. 4

the Churg-Strauss lesion, consisting of three histological aspects: necrotizing vasculitis, tissue infiltration by eosinophils and extravascular granulomas. The differential diagnosis is thus made, in particular, with hypereosinophilic diseases, granulomatous diseases and other vasculitis. The relations between them are shown in the diagram in *Fig. 4*.

Given the frequency of systemic vasculitis with asthma and eosinophilia which did present the three histological aspects, several authors began to propose the adequacy of the clinical pattern for recognizing CSS[3]. Within this pattern, there are often three phases whose sequential emergence was also observed in this patient: a prodromal phase, that lasts several years, which consists of an allergic disease (asthma, rhinitis), emerging in adulthood and with no atopic family history; a second phase, characterized by the emergence of eosinophilia and eosinophilic tissue infiltration; and a third phase with systemic vasculitis and multi-organ lesions, during which improvement of the asthma is frequently observed. However, in about 20% of cases, worsening of the asthma coincides with the vasculitis phase.

At the culmination of the evolution of diagnostic concepts are the classification criteria produced by the American College of Rheumatology[4] in 1990 (*Table II*), which established six criteria: clinical, laboratory, radiological and histological. The presence of at least four of these criteria gives a diagnosis of significant sensitivity and specificity, making the diagnosis viable even in the absence of typical histological lesions.

In the present case, five of the six proposed criteria were present. The histological manifestation was not verified, either in the skin biopsy (which is relatively common, except when there are subcutaneous nodules and these are submitted to biopsy) or in the lung biopsy, which could only be made about a week after the start of corticosteroid therapy. Nerve and muscle biopsies, had the patient authorized them, may also have been positive. Renal biopsy was not carried out, since there were no alterations in renal function or sediment.

The history of CSS therapy can be roughly divided into three phases: the first, pre-corticosteroid therapy, which invariably ended in the death of the patient;

TABLE II

Classification criteria 1990 - American college of rheumatology (Churg- strauss syndrome)

1. Asthma
2. Eosinophilia of peripheral blood > 10%
3. Transitory or migratory lung infiltrates in chest x-ray (Fixed infiltrates are excluded)
4. Paranasal sinus abnormalities
6. Biopsy containing vessels with accumulation of eosinophils in extra-vascular areas
4 Or more criteria: sensitivity = 85%; Specificity = 99.7%

the second, with the introduction of systemic corticosteroid therapy, which enabled control the disease in the majority of patients; and the third, with the advent of immunosuppressants – particularly cyclophosphamide or azathioprine, generally in association with systemic corticosteroid therapy, enabling better control of severe forms with extensive visceral involvement. Various authors advocate the use of isolated corticosteroid therapy in moderate forms, due to its lower toxicity[5], while others recommend the early addition of other immunosuppressants, even in less severe forms of CSS.

In the severe forms of CCS, or those with insufficient response to corticosteroid therapy, there is a consensus on the need to use immunosuppressive drugs; however there is no unanimity as to the choice of drug, dose, or length of treatment.

Plasmapheresis is not currently recommended for the treatment of CSS, since its association does not offer any consistent advantage. [6]

In this patient, the treatment initially established was Prednisolone 2mg/kg/day. Corticosteroids had been the therapeutic basis and responses were usually good, generally with marked improvement of general and allergic symptoms, as well as of the vasculitis symptoms in the very first week, the response of the peripheral neuropathy being somewhat slower. Reduction of this corticosteroid therapy must always be done slowly and gradually, defined by the evolution of the general state and cardiac and renal functions.

As soon as worsening of peripheral neuropathy and cardiac function were observed, the scheme recommended by Fauci[7] was adopted, with 2mg/kg/day cyclophosphamide, and possibly changing to azathioprine in the same dose of 2mg/kg/day after twelve months of treatment, due to its lower toxicity.

With the immunosuppression, the re-establishment of cardiac function and a very significant reduction of the neuropathic involvement were achieved, restoring a functional autonomy in the patient that had been lost.

After interruption of the treatment with cyclophosphamide, due to haematologic toxicity, there was no clinical or laboratorial evidence of recurrence, in particular, reemergence of eosinophilia or increase in IgE values, which is considered one of the earliest markers of reactivation of the disease.[3] Late recurrences, although rarer than in other systemic vasculitis, can occur, but if they are detected early on, they show good response to the reintroduction of immunosuppression.

Nowadays, the prognosis is considered to be good. In the series Mayo Clinic, the five-year survival was 62%, with an average survival of nine years, cardiac involvement being responsible for about 50% of deaths.[8] Other, smaller series report a five-year survival of 80%. The emergence of a vasculitis condition soon the onset of the respiratory condition appears to give a worse prognosis.

The morbidity of this pathology is essentially related to the cardiac involvement, persistence of the neurologic lesions, manifestations of nasal and bronchial allergies, and the frequent presence of arterial hypertension, normally requiring two or more drugs for its control. ■

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