Churg-Strauss Syndrome

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Abstract

Churg-Strauss syndrome is a systemic ANCA-associated small- to medium-sized vessels vasculitis. Common clinical manifestations are marked blood eosinophilia, asthma, chronic sinusitis, cardiomyopathy, pulmonary infiltrates, gastrointestinal complaints and a multiplex neuropathy. Anti-MPO (antimyeloperoxidase) pANCA (ANCA with a perinuclear fluorescence pattern) is present in 38-59% of cases. Cardiac involvement is an important cause of morbidity and the leading cause of mortality in Churg-Strauss syndrome. The morphological substrate is an eosinophilic necrotizing vasculitis.

Treatment is based on corticosteroid therapy and immunosuppressive drugs (cyclophosphamide and azathioprine) and is determined according to prognostic criteria. Complete remission occurs in almost 90% of cases and relapses are frequent (25% of cases).

Key words: Churg-Strauss syndrome, ANCA, vasculitis.

INTRODUCTION

Churg-Strauss syndrome (SES) is a systemic vasculitis affecting small and medium vessels, and might eventually involve any organ, namely the lungs, peripheral nerves, skin, kidneys and less often the heart and gastrointestinal system. The disease is classically associated with allergic syndromes as asthma, rhinitis and sinusitis.[1]

EPIDEMIOLOGY

In average, SCS occurs in the fifth decade of life. Some studies indicate a slight predominance in the female gender,[1-3] others do not make evident any predominance regarding gender.[4] The incidence is of 1.8 to 6.8 cases per million in the general population,[5-7] although in asthmatic patients the value rises to 34.6 - 64.4 cases per million.[4,7] Regarding vasculitis ANCA (anti-neutrophil cytoplasmic antibodies), associated (SCS, microscopic polyangiitis and Wegener's granulomatosis), SCS is the rarest (Figure 1).[5-8]

By the end of the 90s, several studies suggest a link between the treatment of asthmatic patients with antileukotrienes and the disease development.[7,9,10]

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However, recent analyses consider that SCS "forme frustre" may exist at the beginning of the treatment, and the onset of symptoms is associated to the steroids therapy weaning off, responsible for suppressing the disease. The disease incidence is identical both in asthmatic patients undergoing therapy with antileukotrienes and in the asthmatic population which are not under such medication.[11,12]

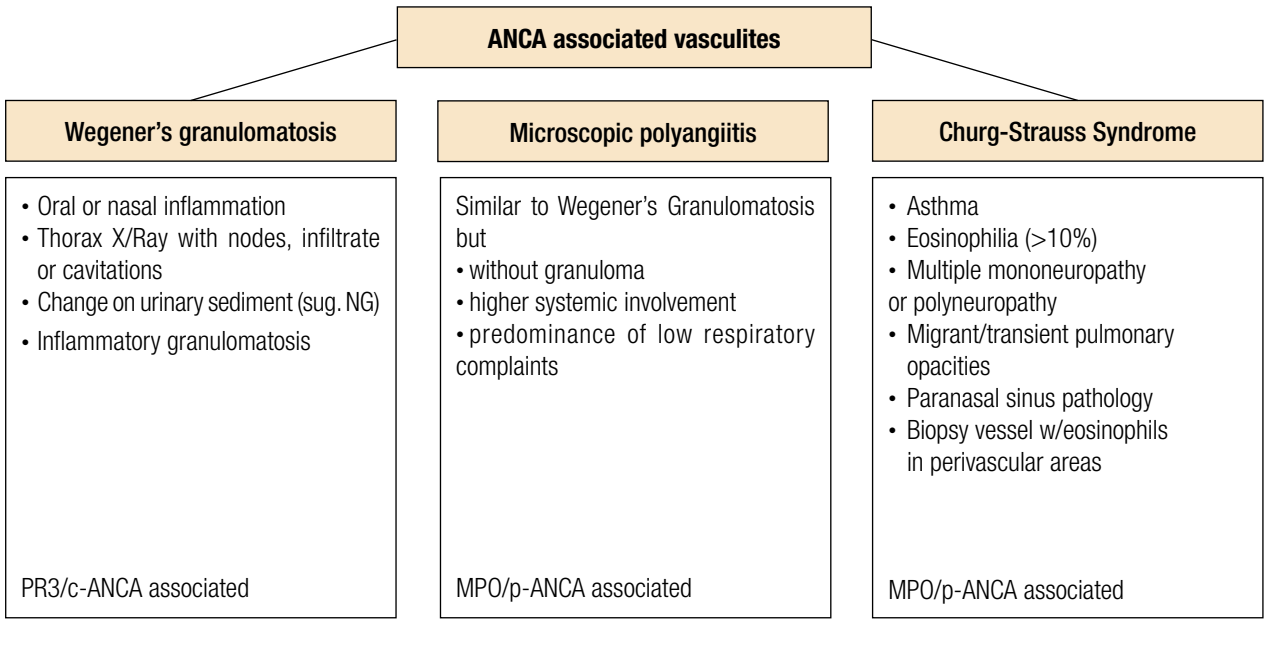
PATHOPHYSIOLOGY

The aetiology is unknown. The association with asthma and atopy is typical, although there are cases described where there is not a history of previous asthma.[13] In a simpler way it is thought that an infectious agent or an exogenous antigen, possibly inhaled, can trigger an allergic inflammatory reaction in a genetically prone individual, leading to the development of rhinosinusitis and asthma, followed by eosinophils tissue infiltration. The endothelial adhesion and leukotrienes activation lead to the vascular inflammation and subsequently to necrotising vasculitis in the different organs and affected system.[14]

The role of autoimmunity in the development of the disease is evident, with a presence of hypergammaglobulinaemia, increase on the levels of E immunoglobulin, rheumatoid factor and anti-neutrophil cytoplasmic antibodies.

DIAGNOSIS

Since the initial description by Churg and Strauss in 1951 that the disease definition suffered several changes. The initial triad – small and medium vessels necrotising vasculitis, infiltration of vessels and tis-



ANCA associated vasculites.

FIG. 1

sues by eosinophils and the presence of extravascular granuloma – more specific criteria were added but are still a target of criticism.[15–17]

The American College of Rheumatology has defined the SCS as likely when four out of the following six criteria are identified: a) asthma; B) eosinophilia; C) neuropathy, mononeuropathy, polyneuropathy; D) Pulmonary infiltrates; E) Changes of the paranasal sinus; F) extravascular and tissue infiltration of eosinophils.[18] (*Table I*).

However the diagnosis remains a clinical one being desirable the pathological anatomy confirmation.

The typical patient is a middle age adult starting complaining of allergic rhinitis and/or asthma, of progressive deterioration and hard to control – the first stage of the disease or prodromal, followed by a second stage featured by eosinophilia in the peripheral blood and eosinophilic infiltration of tissues. Lastly it emerges a stage of full blown vasculitis.

In the prodromal stage, the allergic rhinitis is usually the first evidence of the disease, occurring in around 70% of patients, being usually severe and can be associated to nasal polyps or recurrent sinusitis.

Nasal perforation, pain or purulent or bloody rhinorrhea are usually associated to Wegener granulomatosis being rare in the SCS.[16,17]

The most affected systems of organs are (on decreasing order) the respiratory, the peripheral nervous system, the skin, cardiovascular, gastrointestinal, kidneys and central nervous system (*Table II*).

The systemic symptoms may be prominent, namely fever, weight loss, fatigue, asthenia and arthralgia.[1,3]

The respiratory involvement is practically universal (96 – 100%) and asthma is an early manifestation preceding vasculitis with an average of eight years.[16,17] Its severity usually increases with time and may paradoxically improve when the vasculitis stage settles in. Although rare, there are cases described where

TABLE I

American College of Rheumatology Criteria (1990)[18]
Likelihood when 4 out of the following are present

- Asthma;
- Eosinophilia;
- Neuropathy, mononeuropathy, polyneuropathy;
- Pulmonary infiltrates;
- Nasal sinus changes;
- Eosinophils extravascular and tissue infiltration

TABLE II

Multi-systemic involvement in 3 groups of patients

	Guillevin n=96 (%)[1]	Lanham n=16 (%)[36]	Solans n=32 (%)[28]
Asthma	96 (100%)	16 (100%)	
Rhinitis		12 (75%)	32 (100%)
Pulmonary Infiltrate	36 (37,5%)	10 (62,5%)	20 (62,5%)
Monon multiplex	75 (78,1%)	12 (75%)	16 (50%)
Skin disease	49 (51,0%)		26 (81,3%)
Nodes	19	2 (12,5%)	2
Purpura	30	9 (56,3%)	16
Erythema	8	9 (56,3%)	
Arthralgia Myalgia	52 (54,2%)	11 (68,8%)	14 (43,8%)
Cardiovascular			12 (37,5%)
HTA	12	12 (75%)	7 (25%)
CCI	9	4 (25%)	
Pericarditis/Per.effusion		2 (12,5%)	1
ECG Change		8 (50%)	
Gastrointestinal	32 (33,3%)		14 (43,8%)
Abdominal pain	29	7 (43,6%)	10
Diarrhea		5 (31,3%)	4
Bleeding	9	4 (25%)	
Renal	25 (26,0%)		4 (12,5%)
Mild Kidney failure		14 (87,5%)	
Chr.Kidney failure	5	1 (6,25%)	1
Nephrotic Syndrome		3 (18,75%)	
CNS	8 (8,3%)		2 (6,2%)
CVA	6	4 (25%)	1

asthma appears only in this stage of the disease. [13]

The occurrence of haemoptysis due to alveoli hemorrhage is a rare situation but potentially severe. Pleural effusion can be found but presents a poor clinical expression, just an exudate with a predominance of eosinophils.

The involvement of the nervous system is very frequent and may manifest itself through peripheral neuropathy, being mononeuropathy multiplex the most common presentation, as it affects the vasa vasorum, being sensitive motor and predominantly of distal topography, in the lower limbs.[20-22]

The involvement of the central nervous system is not very frequent, with the cerebral vascular accident, both ischaemic as haemorrhagic, the most common manifestation, and they are an important cause of morbidity and mortality.[19-23]

Skin lesions are common in the vasculitis stage and may have several presentations (erythematous lesions, maculopapular, pustules or nodes). Lesions are predominant in the extremities, especially in the lower limbs. In the biopsy the most common findings are the necrotising extravascular granuloma and leukocytoclastic vasculitis.[17, 24]

Cardiac complications of the disease are the main cause of death and include acute pericarditis, constrictive pericarditis, myocarditis and myocardial infarction. Arterial hypertension and electrocardiographic changes are also reported in around 50% of cases.[17]

The gastrointestinal involvement it is usually expressed by abdominal pain. Eosinophilic infiltration of the intestine wall can produce symptoms similar to an eosinophilic gastroenteritis. The submucosa and mucosa infiltration can lead to diarrhoea and haematochezia, and when it reaches the muscle layer may lead to obstruction; at serosa level it can trigger peritonitis with ascitic fluid that typically has a high concentration of eosinophils. Any part of the digestive system can be affected, including the gallbladder.[17-19, 25]

Less than half of the patients present kidney involvement, being this in the majority of cases light to moderate and seldom evolving to terminal chronic renal failure. The main manifestations were serial creatinine and urea increase, proteinuria and microscopic hematuria. In the renal biopsy a focal and segmental glomerulonephritis with necrosis and/or crescent formations, pauci-immune could be seen.[16-19, 26,27]

LABORATORY AND DIAGNOSIS ADDITIONAL TESTS

The laboratory evaluation reveals typically a nor-

mocytic, normochromic anaemia with leukocytosis, eosinophilia and a response to the acute stage with an increase on C-reactive protein, fibrinogen, α-2 globulin and erythrocyte sedimentation rate.[1,28] IgE levels are also increased in over half of the patients.

Asthma is in itself a disease associated with eosinophilia, although less marked than in the SCS. Values over 800/μL are not frequent in asthma, and values above 1.500/μL or 10% of the leukocyte count are even rarer and therefore very suggestive of SCS. However it should be remembered that circulating eosinophils can be suppressed by corticotherapy.[1,14]

ANCA (antineutrophil cytoplasmic antibodies) are antibodies directed against neutrophil enzymes. Two patterns can be identified through indirect immunofluorescence: a pattern with perinuclear distribution – P – ANCA and another dispersing through the neutrophils cytoplasm – c– ANCA. The main p–ANCA antibodies antigen is the myeloperoxidase (MPO) while the c–ANCA is proteinase 3 (PR3). In the SCS from 38 to 59% of patients are ANCA positive, being that these ¾ present antibodies against myeloperoxidase with a distribution pattern p-ANCA.[27, 29-31]

In the thorax teleradiography is possible to identify multi-focal bilateral pulmonary infiltrate, transient, [17] that in CAT scan correspond to a parenchymal opacification. These nodes contrary to what happens in Wegener granulomatosis, seldom cavitate. CAT scan of paranasal sinus can also reveal the presence of sinusitis. ECG and echocardiogram as well as endoscopic exams are useful to evaluate the cardiac and gastrointestinal involvement, respectively.

The EMG can reveal an axonal neuropathy, featured by a normal transmission speed and a decreased or absent action potential.[32]

PATHOLOGICAL ANATOMY

SCS is a vasculitis reaching mainly small and medium-size vessels: arterioles, venules and capillaries. In the acute stage of the disease there is fibrinoid necrosis in the tunica media and intraparietal and perivascular infiltration, pleomorphic with a predominance of eosinophils.[33]

Extravascular lesions can occur in any organ and are featured by an inflammatory infiltrate rich in eosinophils forming granulomas with a necrotic core surrounded by histiocytes in picket fence and multinucleate giant cells. It is not always possible to observe and are not pathognomonic to the disease.[16,25,34]

The coexistence of three kinds of lesion: necrotising vasculitis, eosinophilic infiltration and extravascular granuloma are rare and not compulsory for the histological diagnosis.[17,32]

The biopsy must be performed preferentially in organs presumably affected. The places where more frequently histological manifestation of the disease are found are the skin (67.4%), nerves (65.7%) and muscles (47.9%).

TREATMENT

The treatment of ANCA associated vasculitis consists in two stages: the initial stage inducing the remission and the subsequent stage of maintenance (*Table III*).

Systemic steroids are the first line of treatment. Prednisolone in a dose of 1 mg/kg can be started in patients who are not presenting a serious multi-organic involvement.[35] In patients with multi-organic involvement it can be administered 1 g of methylprednisolone IV for three days, followed by 40 to 60 mg/day of prednisolone. After the beginning the therapy it should be expected a decrease on the vasculitis symptoms and the inflammatory endpoints. ANCA are not considered reliable markers of disease activity.[36]

Cyclophosphamide should be added to the treatment with corticosteroids, in patients with a severe systemic involvement. It can be administered in endovenous pulses (every two weeks in the first three administrations and then monthly – 0,6 g/m2/ month) or in a continuous form, oral route, in low dosage (2 mg/kg/day).[37] Recent studies indicate that pulse administration presents a reduction on the drug adverse effects, with an equal rate of remission although within increases on the recurrence rate.

The main treatment side-effects with cyclophosphamide are haemorrhagic cystitis, bladder fibrosis, bone marrow suppression, neoplasms and infections. Haemorrhagic cystitis can be prevented through the appropriate hydration and mesna administration before and after each treatment; prophylaxis with trimethoprim and sulphamethoxazole three times a week is recommended.[28,38]

The cyclophosphamide dosage can be reduced in 25 mg in patients over 60 years of age.

In patients without severe systemic involvement, cyclophosphamide can be replaced by methotrexate.

Remission is usually achieved in 3 to 6 months, starting the maintenance stage in which cyclophos-

TABLE III

Treatment (summary)

Induction (3-6 months)
Patients without a severe systemic involvement
Corticoids – Prednisolone 1mg/kg/day
Methotrexate – 20 mg/week IV or Oral route
Patients with systemic involvement or a bad prognosis
Corticoids – Methylprednisolone 1g for 3 days followed by prednisolone 1mg/kg/day,
Associated with
Cyclophosphamide – Oral 2 mg/Kg/day or IV in monthly pulses 0,6 g/m^2
Maintenance (minimum 18 months)
Azathioprine – 2mg/Kg/day 3 to 6 months, followed by a gradual dosage decrease.
Corticoids – Progressive reduction on the induction dosage.

phamide should be replaced by azathriopine and should be administered for a minimum period of at least 18 months.[38]

When the renal involvement is not significant, serum creatinine < 1.7 mg/dL, mycophenolate mofetil,[39] methotrexate[40] and leflunomide [41] may can be used as alternatives for the maintenance therapy.

Plasmapheresis has been used as adjuvant to the induction therapy, however in the meta-analysis performed to 140 patients it has not demonstrated any additional benefit.[42]

Alpha interferon seems to be effective and well tolerated while inducing the remission in patients with refractory SCS, although presented studies report only to small groups of patients.[43]

The depletion of B cells resorting to rituximab, was suggested as beneficial in the treatment of ANCA associated vasculitis, however its use is described only in series or isolated cases.[44]

Recurrence is defined as occurrence or recurrence of SCS clinical manifestations. Persistent asthma or isolated increases on eosinophils count are not considered recurrence.[38]

In a refractory or persistent disease, one may as alternative use the following induction therapies: endovenous immunoglobulin, 15 – deoxyspergualin, anti-thymocyte globulin, infliximab, mycophenolate mofetil and rituximab.[38]

PROGNOSTIC

Before using corticosteroids in SCS treatment, the mortality rate was 50% within three months. After its introduction there was an important mortality reduction with a survival rate of 90% within one year and 50% at seven years.[17-19] Associated factors to a bad prognosis and high mortality rate are the cardiac involvement, gastrointestinal, central nervous system, proteinuria > 1 g/24 hours, serum creatinine > 1.6 g/dL. Over 90% of patients reach remission. Recurrences occur in about ¼ cases, and half of these occurred in the first year, usually preceded by an increase of the eosinophils count. [1]

The neurological deficits recovery degree is unpredictable and it might also occur complete regression. Motor deficits suffer a regression more rapidly than the sensitive component, tending to have a slower evolution and sequels in the form of paresthesia. [28]

References

1. Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrouse B, Cassaus P. Churg-Strauss Syndrome: Clinical study and long term follow up of 96 patients. Medicine 1999; 78:26-37.

2. Abril A, et al. The Churg Strauss Syndrome (Allergic Granulomatous Angiitis): Review and Update. Seminars in Arthritis and Reumatism 2003; 33 (2):106-114.

3. Finan MC, Winkelmann RK. The cutaneous extravascular necrotizing granuloma (Churg-Strauss granuloma) and systemic disease: a review of 27 cases. Medicine (Baltimore). 1983;62(3):142-158.

4. Harrold LR, Andrade SE, Go AS, Buist AS, Eisner M, Vollmer WM, Chan KA, Frazier EA, Weller PF, Wechsler ME, Yood RA, Davis KJ, Platt R. Incidence of Churg-Strauss syndrome in asthma drug users: a population-based perspective. J Rheumatol. 2005;32(6):1076-1080.

5. Watts RA, Curruthers DM, Scott DGI. Epidemiology of systemic vasculitis: Changing incidence or definition? Semin Arthritis Rheum 1995;25:28-34.

6. Kurland LT, Chuang TY, Hunder GG: The epidemiology of systemic arteritis, in Lawrence RC, Shulman LE, (eds): The epidemiology of the Rheumatic Diseases. New York, Gower 1984:196-205.

7. Martin RM, Wilton LV, Mann RD. Prevalence of Churg-Strauss syndrome, vasculitis, eosinophilia and associated conditions: retrospective analysis of 58 prescription-event monitoring cohort studies. Pharmacoepidemiol Drug Saf. 1999;8(3):179-189.

8. Haugeberg G, Bie R, Bendvold A, Larsen AS, Johnsen V.; Primary vasculitis in a Norwegian community hospital: a retrospective study. Clin Rheumatol. 1998;17(5):364-368.

9. Franco J, Artés MJ. Pulmonary eosinophilia associated with montelukast. Thorax. 1999;54(6):558-560.

10. Wechsler ME, Garpestad E, Flier SR, Kocher O, Weiland DA, Polito AJ, Klinek MM, Bigby TD, Wong GA, Helmers RA, Drazen JM. Pulmonary infiltrates, eosinophilia, and cardiomyopathy following corticosteroid withdrawal in patients with asthma receiving zafirlukast. JAMA. 1998;279(6):455-457.

11. Wechsler ME, Finn D, Gunawardena D, Westlake R, Barker A, Haranath SP, Pauwels RA, Kips JC, Drazen JM. Churg-Strauss syndrome in patients receiving montelukast as treatment for asthma. Chest. 2000;117(3):708-713.

12. Weller PF, Plaut M, Taggart V, Trontell A. The relationship of asthma therapy and Churg-Strauss syndrome: NIH workshop summary report. J Allergy Clin Immunol. 2001;108(2):175-183.

13. Chen KR, Ohata Y, Sakurai M, Nakayama H. Churg-Strauss syndrome: report of a case without preexisting asthma. J Dermatol. 1992 ;19(1):40-47.

14. Noth I, Strek ME, Leff AR. Churg-Strauss syndrome. Lancet. 2003 ;361(9357):587-594.

15. Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, Hagen EC, Hoffman GS, Hunder GG, Kallenberg CG et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum. 1994;37(2):187-192.

16. Churg J, Strauss L. Allergic Granulomatosis, Allergic Angiitis, and Periarteritis Nodosa Am J Pathol. 1951;27(2):277-301.

17. Lanham JG, Elkon KB, Pusey CD, Hughes GR. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. Medicine (Baltimore). 1984;63(2):65-81.

18. Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, Calabrese LH, Edworthy SM, Fauci AS, Leavitt RY et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum. 1990;33(8):1094-1100.

19. Chumbley LC, Harrison EG Jr, DeRemee RA. Allergic granulomatosis and angiitis (Churg-Strauss syndrome). Report and analysis of 30 cases. Mayo Clin Proc. 1977;52(8):477-484.

20. Moore PM, Calabrese LH. Neurologic manifestations of systemic vasculitides. Semin Neurol. 1994;14(4):300-306.

21. Namora J., Santos FM, Morais T et al. Síndrome de Churg-Strauss – Caso Clínico. Acta Reuma Port. 2000; 98:19-23.

22. Oliveira S., Mendonça C., Ambar J., Mendes B. Síndroma de Churg-Strauss – a propósito de um caso clínico. Rev Port Pneumol. 2005; XI (1): 73-83.

23. Hattori N, Ichimura M, Nagamatsu M, Li M, Yamamoto K, Kumazawa K, Mitsuma T, Sobue G. Clinicopathological features of Churg-Strauss syndrome--associated neuropathy. Brain. 1999;122 (Pt 3):427-439.

24. Davis MD, Daoud MS, McEvoy MT, Su WP. Cutaneous manifestations of Churg-Strauss syndrome: a clinicopathologic correlation. J Am Acad Dermatol. 1997;37(2 Pt 1):199-203.

25. Lie JT. Limited forms of Churg-Strauss syndrome. Pathol Annu. 1993;28 Pt 2:199-220.

26. Clutterbuck EJ, Evans DJ, Pusey CD. Renal involvement in Churg-Strauss syndrome. Nephrol Dial Transplant. 1990;5(3):161-167.

27. Reid AJ, Harrison BD, Watts RA, Watkin SW, McCann BG, Scott DG. Churg-Strauss syndrome in a district hospital. QJM. 1998;91(3):219-229.

28. Solans R, Bosch JA, Pérez-Bocanegra C, Selva A, Huguet P, Alijotas J, Orriols R, Armadans L, Vilardell M. Churg-Strauss syndrome: outcome and long-term follow-up of 32 patients. Rheumatology (Oxford). 2001;40(7):763-771.

29. Schmitt WH, Csernok E, Kobayashi S. Churg Strauss syndrome serum markers of lymphocyte activation and endothelial damage. Arthritis Rheum 1998; 41:445.

30. Hasley PB, Follansbee, WP, Coulehan, JL. Cardiac manifestations of Churg-Strauss syndrome: Report of a case and review of the literature. Am Heart J 1990; 120:996.

31. Sinico RA, Di Toma L, Maggiore U et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. Arthritis Rheum 2005; 52:2926.

32. Lhothe F, Cohen P, Guillevin L. Syndrome de Churg et Strauss. Maladies et syndromes systémiques. 5e édition. Médecine-Sciences, Flammarion. Paris, 2008; 652-673.

33. Lie JT. Histopathologic specificity of systemic vasculitis. Rheum Dis Clin North Am, 1995; 21:883-910.

34. Jennette JC, Falk RJ. Small-vessel vasculitis. N Engl J Med. 1997 Nov 20;337(21):1512-23.

35. Silva M, Garrido N, Alves P et al. Efeitos diferenciais da terapêutica córtico--imunossupressora nas diversas manifestações da síndrome de Churg-Strauss: a propósito de um caso clínico. Med Interna, 2005; 12(3): 154-158.

36. Lanham JG. Churg-Strauss syndrome. Br J Hosp Med. 1992;47(9):667-673.

37. Groot, K., Adu, D. The value of cyclophosphamide in ANCA-associated vasculitis: Meta-analysis and critical review. Nephrol. Dial. Transplan. 2001;16: 2018-2027.

38. Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, Hauser T, Hellmich B, Jayne D, Kallenberg CG, Merkel PA, Raspe H, Salvarani C, Scott DG, Stegeman C, Watts R, Westman K, Witter J, Yazici H, Luqmani R; European Vasculitis Study Group. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis. 2009;68(3):310-317.

39. Langford CA, Talar-Williams C, Sneller MC. Mycophenolate mofetil for remission maintenance in the treatment of Wegener's granulomatosis. Arthritis Rheum. 2004 15;51(2):278-283.

40. De Groot K, Rasmussen N, Bacon PA, Tervaert JW, Feighery C, Gregorini G, Gross WL, Luqmani R, Jayne DR. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2005;52(8):2237-2242.

41. Metzler C, Fink C, Lamprecht P, Gross WL, Reinhold-Keller E. Maintenance of remission with leflunomide in Wegener's granulomatosis. Rheumatology (Oxford). 2004;43(3):315-320.

42. Guillevin L, Cevallos R, Durand-Gasselin B et al. Treatment of glomerulonephritis in microscopic polyangiitis and Churg-Strauss syndrome. Indications of plasma exchanges, Meta-analysis of 2 randomized studies on 140 patients, 32 with glomerulonephritis. Ann Med Interne (Paris) 1997;148(3):198-204.

43. Metzler C, Schnabel A, Gross WL, Hellmich B. A phase II study of interferon-alpha for the treatment of refractory Churg-Strauss syndrome. Clin Exp Rheumatol. 2008;26(3 Suppl 49):S35-40.

44. Jones RB, Ferraro AJ, Chaudhry AN et al. A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2009 ;60(7):2156-2168.