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Short communication

Intracerebral haemorrhage, a possible presentation in Churg-Strauss syndrome: Case report and review of the literature

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ABSTRACT

Churg-Strauss syndrome (CSS) is a rare systemic vasculitis, almost invariably accompanied by asthma, nasal polyposis, paranasal sinus abnormalities, and increased peripheral blood eosinophil count. Neurological involvement as peripheral neuropathy is a common feature, whereas cerebral involvement is extremely rare. Herein, we report the case of a young man who presented with sudden onset of right-side emiparesis and aphasia, whose head CT scan showed the presence of large haemorrhage in the left striatum nucleus involving part of the temporal lobe. Based on clinical and laboratory findings (asthma, eosinophilia >10%, paranasal sinus abnormalities and mononeuritis multiplex) a diagnosis of CSS was made. Cerebral angiography resulted normal, excluding the presence of vascular malformations or signs of vessel abnormalities. Pharmacotherapy with (intravenous and afterwards oral) corticosteroid and immunosuppressors (cyclophosphamide and then azathioprine) was initiated. The outcome was good with neurological follow-up showing a nearly complete recover. Our case points out that intracerebral haemorrhage can be, despite rare, a presenting feature of CSS. Previously reported patients affected by cerebral haemorrhage and CSS are summarized and briefly reviewed.

1. Introduction

Churg-Strauss syndrome (CSS) is a rare systemic disease characterized by necrotising eosinophilic vasculitis of medium- to small-sized blood vessels, involving nearly all major organs and almost invariably accompanied by asthma, nasal polyposis, paranasal sinus abnormalities and increased peripheral blood eosinophil count. Neurological involvement is extremely common, usually manifesting as peripheral neuropathy [1]. Conversely, central nervous system (CNS) is seldom affected by CSS, and cerebral ischemic infarctions are the most common reported events [2,3]. Herein, we report the case of a young man affected by CSS, presenting with spontaneous intracerebral haemorrhage (ICH).

2. Case presentation

A 29-year-old man presenting with sudden onset of right-side emiparesis and aphasia was admitted to the Department of Neurology in November 2006. Over the preceding month he had suffered from diffuse arthralgias, persistent slight fever, erithematous vesiculopapular skin rash at four extremities, painful swelling and erythema of right leg due to lymphangitis and numbness with paresthesias at the dorsal surface of the right foot and, subsequently, at the ulnar surface of the right hand. A long history of allergic bronchial asthma, rhinitis complicated by severe nasal polyposis, and raised blood eosinophilia was reported. He denied smoking or assumption of illegal substances. No other vascular risk factors were referred in the past medical history.

Neurological examination on admission disclosed a global aphasia and marked right emiparesis with omolateral Babinski at plantar cutaneous stimulation. Subtle atrophy at right-hand muscles and reduction of supinator and achilles tendon reflex at right limbs were also observed.

Blood pressure was normal (130/80 mm Hg) and general examination was significant for vasculitic bullous lesions distributed at hands and vesicles at the dorsal surface of right foot. No signs of pulmonary involvement were detectable.

Head CT scan showed the presence of large haemorrhage in the left striatum nucleus involving part of the temporal lobe, with intraventricular extension, and mild mass effect (Fig. 1).

Cerebral angiography, performed in the acute phase, resulted normal, excluding particularly the presence of vascular malformations. Signs of vessel abnormalities consistent with vasculitis of large-to-medium arteries were not detected.

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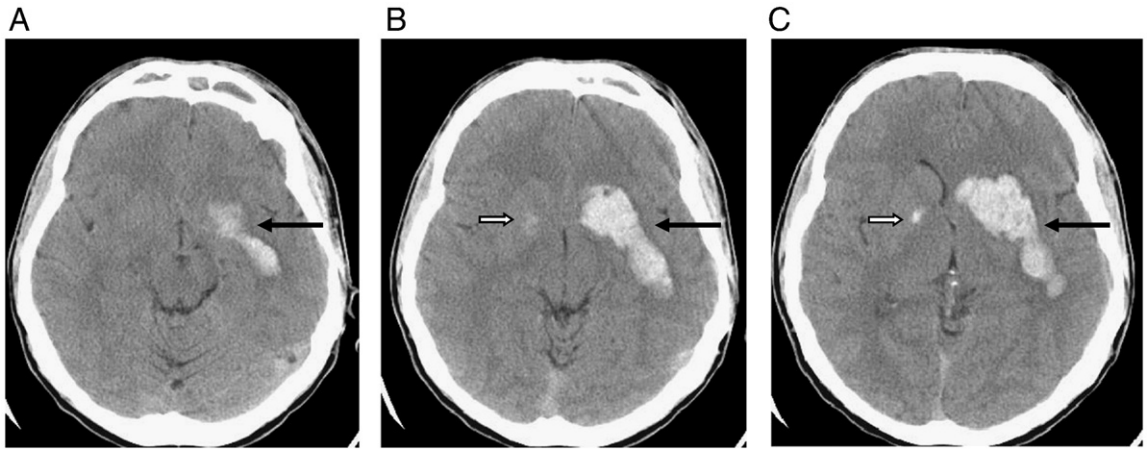

Fig. 1. Axial CT images (A, B, C) showing an intraparenchymal haemorrhage in the left striatum nucleus (black arrow) involving part of the temporal lobe. The light hyperdensity in the right globus pallidus represents a calcification (white arrow).

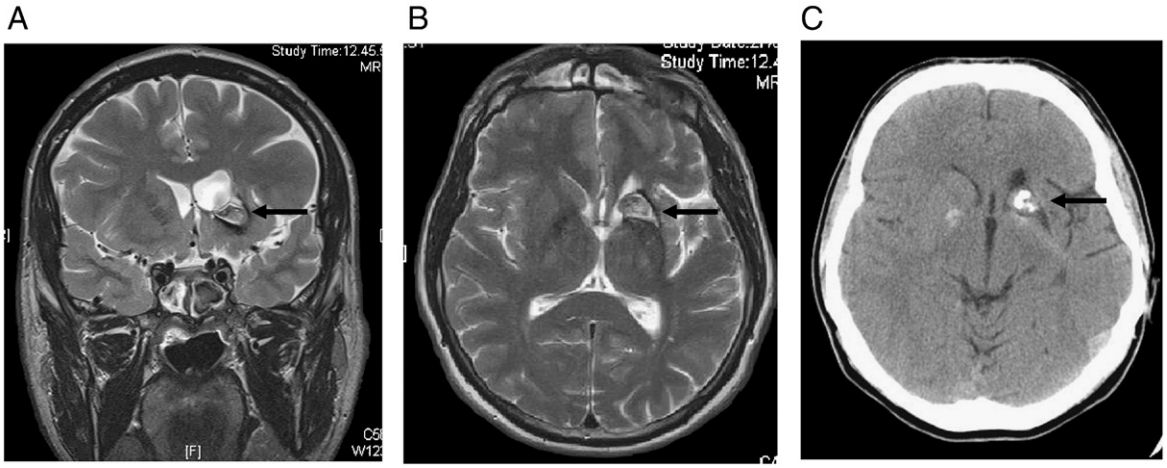

Fig. 2. Follow up T2 MR images (A, coronal and B, axial planes) and CT image (C) showing calcification and haemosiderin debris in the left striatum nucleus (black arrow) with ventricular compensatory dilation.

Electrocardiogram was normal, whereas echocardiogram revealed a small pericardial effusion.

Chest radiography and CT did not show significant parenchymal or interstitial infiltrates. Spirometry was normal. CT of paranasal sinuses disclosed the presence of a massive chronic hypertrophic pansinusopathy.

Neurophysiological examination of right limbs showed absence of sensory action potential of sural, superficial peroneal and ulnar nerves and marked reduction of amplitude of compound muscle action potential of ulnar, common peroneal, and tibialis posterior nerves. Nerve conduction studies of left limbs resulted all normal. Needle examination displayed absence of voluntary activity in right-hand

Table 1
Clinical features of previously reported patients with Churg-Strass syndrome and cerebral haemorrhage.

Case reference	Age	Sex	Type and site of haemorrhage	Angiography	Hypertension	Bronchial asthma	Allergic rhinitis and/or nasal polyposis	Nasal and paranasal sinus abnormality
Maloon et al., 1985	39	F	Recurrent spinal and cerebral SAH	Not executed	No	Yes	Yes	Not reported
Chang et al., 1993	47	F	SAH and IV haemorrhage	Not executed	Not reported	Yes	No	Yes
Liou et al., 1997	27	M	ICH (Right parieto-occipital and left parietal)	Not executed	Yes	Yes	Yes	Yes
Ojeda et al., 2001	48	M	ICH (Left putamen)	Not executed	No	Yes	No	Yes
Calvo-Romero et al., 2001	47	F	SAH	Vasculitis	No	Yes	Yes	Yes
Tyvaert et al., 2004	47	F	SAH and ICH (Right occipital and left parieto-occipital)	Vasculitis	No	Yes	Yes	Yes
Sakamoto et al., 2005	36	F	SAH	Vertebral dissecting aneuyrism and vasculitis	No	Yes	Yes	Yes
Mishra et al., 2007	45	M	ICH (Right occipital), with SA and IV extension	Normal	Yes	Yes	Yes	Yes
Sheerin et al., 2008	37	F	SAH	Vasculitis	Yes	No	No	No

Legend: M, male; F, female; SAH, subarachnoid hamorrhage; ICH, intracerebral hamorrhage; IV, intraventricular hamorrhage; ERT, erythrocyte sedimentation rate; CRP, C-reactive protein; ANCA, antineutrophil cytoplasm antibodies.

muscles innervated by ulnar nerve and mild chronic neurogenic changes with reduced recruitment in right tibialis anterior and sural triceps muscles. These findings were consistent with a sensory-motor mononeuritis multiplex.

Electroencephalogram showed slow abnormalities in left hemisphere and diffuse parossistic abnormalities, but not the presence of clear epileptic discharges.

Blood tests showed leukocytosis (19.100/mm^3, normal value 4.0–10.0), raised eosinophil count (35%, normal value 0–10), slight elevation of CRP (1.19 mg/dL, normal value < 0.5), and mild hypergammaglobulinemia (22.4% of total proteins, normal value 11.1–18.8). Liver and kidney function were normal and the coagulation parameters were all in the normal range. Anti-nuclear, anti-extractable nuclear, anti-DNA, anti-phospholipid, and antineutrophil cytoplasm antibodies (ANCA) were negative. In particular, ANCA were investigated by indirect immunofluorescence and by ELISA against proteinase-3 and myeloperoxidase as previously described [4].

Cardiovascular monitoring during whole hospitalization confirmed a condition of well-controlled arterial pressure. No pathological cardiac events were recorded.

Based on clinical and laboratory findings (asthma, blood eosinophilia >10%, paranasal sinus abnormalities and mononeuritis multiplex) a diagnosis of probable CSS was made, according to the American College of Rheumatology Criteria [5]. Thus, a 3-day intravenous pulse therapy with a daily dose of 1000 mg methylprednisolone was initiated, followed by daily oral prednisone 1 mg/kg. During hospitalization neurological conditions gradually improved. In particular, the severe right-side emiparesis completely resolved and the aphasia markedly improved. Examination at discharge (on the 12th day from onset) revealed only mild aphasia and presence of signs of peripheral neuropathy as atrophy with mild weakness of right-hand intrinsic muscles (MRC = 4), hypoesthesia at ulnar surface of right-hand and dorsal surface of right foot.

Discharge and one month follow-up cerebral CT scan controls showed a normal evolution of haemorrhagic lesion, which was completely reabsorbed one month later (Fig. 2C). A follow-up MRI, including gradient echo sequences, did not show signs of amyloid angiopathy, venous malformation, or tumors (Fig. 2A and B).

Cutaneous and other systemic symptoms also completely resolved, except for appearance of hypoesthesia on left ulnar surface and a progressive worsening over the following month of strength in right and left hand (MRC = 2 bilaterally). Control electroneuromyography confirmed worsening of sensory and motor nerve conduction at upper limbs and at right leg. A pulse therapy with cyclophosphamide was then introduced to induce symptoms remission. A low dose regimen (600 mg/week) effective in lupus nephritis treatment [6] was chosen since the patient refused the standard treatment. Four pulses only were carried out, then the patient denied further treatment. The patient continued to assume oral prednisone, which was slowly tapered down until the lowest dose for maintenance (2.5 mg every other day) and azathioprine was added up to 200 mg daily. Laboratory markers (blood eosinophilia and inflammatory markers) and clinical disease signs remained stable over time. Also strength and sensitive deficit due to multineuropathy slowly recovered over the following year, lasting only mild weakness at left hand (MRC = 4.5), slight atrophy of both hand muscles and subtle hypoesthesia at dorsal surface of right foot fingers. A 3-year follow-up confirmed a stable remission of symptoms and signs of the disease.

3. Discussion

CSS is a rare systemic disorder characterized by multi-organ vasculitic involvement. Despite its frequent involvement of peripheral nerves, it rarely involves CNS. Prevalence of CNS involvement is estimated to be around 6–10% in largest series, and cerebral infarction and diffuse encephalopathy are by far the most frequently features described [2,3].

Cerebral haemorrhages have been seldom associated with CSS. Subarachnoid haemorrhage (SAH), caused by vasculitic involvement of major arterial vessels or by rupture of dissecting aneurysm, has been reported in few patients affected by CSS [7–9]. ICH in association with CSS is equally extremely rare [10–13]. Furthermore a case of recurrent spinal SAH [14] and one of SAH and intraventricular haemorrhage caused by necrotizing vasculitis of choroid plexus [15] have been reported.

CNS involvement is a rare complication also of other ANCA-associated systemic vasculitides, being reported in 2–8% of patients affected by Wegener's granulomatosis [16] and in 11% of patients with microscopic polyangiitis [17]. Cerebral haemorrhage, in particular, is anecdotally reported [18,19], whereas ischemic cerebrovascular events secondary to vasculitis, seizures, diffuse encephalopathy, pituitary gland involvement, chronic hypertrophic pachymeningitis and cranial neuropathies are the most common manifestations [20,21].

We describe the case of a young man referring to our hospital because of spontaneous ICH that induced the diagnosis of CSS.

Reviewing previously described patients that presented cerebral haemorrhage in association with CSS, it comes out that cerebral involvement was nearly always preceded by a long history of asthma and atopy. Common systemic CSS features (e.g., weight loss,

Pulmonary infiltrates	Neuropathy	Eosinophil count	ERT (mm/h)	CRP (mg/dL)	ANCA	Therapy	Outcome
Yes	No	Not reported	Not reported	Not reported	Not reported	Oral prednisone and cyclophosphamide	Death
Yes	Yes	22.040/mm^3 (76% of WBC)	Not reported	Not reported	Not reported	Oral prednsione	Death
Yes	Yes	4.274/mm^3 (31% of WBC)	132	4.5 (n.v. < 0.5)	Present (pANCA)	Intravenous methylprednisone plus cyclophosphamide and oral prednisone	Remission
Yes	No	6.750/mm^3 (37% of WBC)	63	Not reported	Absent	Oral prednisone and cyclophosphamide	Remission
No	Yes	15.200/mm^3 (46% of WBC)	78	13 (n.v. < 5)	Present (pANCA)	Oral prednisone and cyclophosphamide	Remission
No	Yes	5.600/mm^3 (34.4% of WBC)	110	11.2 (n.v. < 0.4)	Present (pANCA)	Intravenous methylprednisone plus cyclophosphamide and oral prednisone	Not reported
No	Yes	9.515/mm^3 (38.4% of WBC)	Not reported	1.2 (n.v. < 0.4)	Absent	Coil embolization and oral prednisone	Remission
No	Yes	14.600/mm^3	Raised	Not reported	Absent	Cyclophosphamide and prednisone	Improvement
No	No	Normal	82	42 (n.v. < 5)	Present (pANCA)	Intravenous methylprednisone	Remission

neuropathy related symptoms, cutaneous manifestations, typical haematological findings) were generally evident at the time of haemorrhage, as we observed in our patient. An exception to this statement is the case reported by Sheerin et al., where SAH occurred 8 months before appearance of hypereosinophilia, chronic rhinitis, asthma, and lung infiltrates [9]. It's noteworthy that in almost all patients, included our case, cerebral bleeding occurred in phases of disease activity, as pointed out by the presence of increased blood inflammatory markers and/or marked leucocytosis.

ANCA, which have been reported to be present in 38–50% of all CSS patients [22], were absent in our patient's serum. Moreover, considering previously reported CSS patients with cerebral haemorrhage, ANCA were present in only four cases out of seven. Hence, we could infer that ANCA detection is only partially helpful in identification of CSS associated cerebral bleeding. Angiographic evaluation in our patient did not show abnormal vessels. However, in the reported cases angiography was performed in five patients and it resulted consistent with cerebral vasculitis in four of them, whose three were affected by SAH and one by both ICH and SAH. Only one of the patients with ICH underwent angiography and he had a normal aspect of cerebral vessels as it was in our case. Although only few cases are available in literature, one might presume that involvement of large cerebral arteries is a predisposing factor to SAH, while ICH generally occurs when small arteries are predominantly affected.

Regarding size and site of ICH, haemorrhages were multiple and bi-hemispheric in two cases, whereas in the other cases, including ours, were single. Bleeding occurred in the basal ganglia in two patients, as well as in the patient here reported, while it was lobar in the others. In the case reported by Tyvaert et al., ICH and SAH were concomitant [12].

All patients underwent an immunosuppressive therapy with steroid (intravenous, oral or both) and cyclophosphamide and clinical course was good in all of them, except the case described by Maloon et al. [14], who died after the third episode of bleeding and the rapidly fatal case reported by Chang et al. [15].

Pathological findings of CSS associated cerebral bleeding are reported only in the case of SAH described by Chang et al. [15], in which the presence of fibrinoid necrosis and transmural inflammatory neutrophilic and eosinophilic infiltrates in vessels of the choroid plexus was evidenced. Surprisingly, no vasculitic alteration in parenchymal or leptomeningeal vessels was found.

Clinical features of patients with cerebral haemorrhage and CSS reported in literature are reported in detail in Table 1. Pathogenetic mechanism of cerebral bleeding in CSS remains unclear.

Some authors pointed to a close relationship between vessel abnormalities and hypertension, which is a common feature in CSS cases [23]. Hypertension in CSS patients has been attributed to renal vasculitic involvement or dysautonomia due to small fiber neuropathy [23,24]. Differently from some of the previous case reports [9,10,13], our patient did not present hypertension, suggesting that probably other agents such as genetic or environmental factors predisposed to haemorrhage.

Since common causes of spontaneous cerebral haemorrhage, such as vascular malformations, coagulation abnormalities, substance abuse, were ruled out by anamnestic, clinical and instrumental data, we suppose that cerebral haemorrhage in our patient can be related to a vasculitic process. Clear features of active systemic vasculitis involving skin and peripheral nervous system support this hypothesis. Indeed, the inflammatory process could likely involve also the cerebral district, despite typical vessel abnormalities were not detected at cerebral angiography. However, since vasculitic process tends to involve medium- to small-sized blood vessels, conventional cerebral angiography could not detect vessel alterations.

Without a clear radiological or pathological confirmation, we cannot state with certainty that cerebral vasculitis is the cause of the haematoma in our patient. Moreover, given the high frequency of hypertension in CSS patients, we cannot completely exclude that, for a few days before the bleeding occurred, the patients has undergone hypertensive peaks that blunted cerebral vessels predisposing him to haemorrhage, although normality of blood pressure at the acute stage makes this hypothesis improbable.

In conclusion, our case points out that ICH can be, despite rare, a presenting feature of vasculitis associated with CSS. Thus, CSS vasculitis should be considered in differential diagnosis of ICH and investigation of vasculitis systemic signs and symptoms should be performed in patients presenting with ICH, after exclusion of other possible causes, given the reported benefit obtained with a prompt start of an adequate treatment with steroids or immunosuppressors. This is particularly important since cerebral involvement is a major cause of morbidity and mortality, differently from the overall prognosis of CSS, which is generally good [25].

In addition, in consideration of the risk of cerebral haemorrhage, CSS patients should be intensively monitored to avoid that risk factors such as hypertension could facilitate a devastating event as cerebral bleeding.

References

[1] Noth I, Strek ME, Leff AR. Churg-Strauss syndrome. Lancet 2003;361:587–94.
[2] Sehgal M, Swanson JW, DeRemee RA, Colby TV. Neurologic manifestations of Churg-Strauss syndrome. Mayo Clin Proc 1995;70:337–41.
[3] Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P. Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. Medicine 1999;78:26–37.
[4] Boomsma MM, Stearns-Kurosawa DJ, Stegeman CA, Raschi E, Meroni PL, Kurosawa S, Tervaert JW. Plasma levels of soluble endothelial cell protein C receptor in patients with Wegener's granulomatosis. Clin Exp Immunol 2002;128:187–94.
[5] 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;33:1094–100.
[6] Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, de Ramon Garrido E, Danieli MG, Abramovicz D, Blockmans D, Cauli A, Direskeneli H, Galeazzi M, Gül A, Levy Y, Petera P, Popovic R, Petrovic R, Sinico RA, Cattaneo R, Font J, Depresseux G, Cosyns JP, Cervera R. The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide. Ann Rheum Dis 2010;69:61–4.
[7] Calvo-Romero JM. del Carmen Bonilla-Gracia M, Bureo-Dacal P. Churg-Strauss syndrome presenting as spontaneous subarachnoid haemorrhage. Clin Rheumatol 2002;21:261–3.
[8] Sakamoto S, Ohba S, Eguchi K, Shibukawa M, Kiura Y, Okazaki T, Kajihara Y, Arita K, Kurisu K. Churg-Strauss syndrome presenting with subarachnoid hemorrhage from ruptured dissecting aneurysm of the intracranial vertebral artery. Clin Neurol Neurosurg 2005;107(5):428–31.
[9] Sheerin UM, Barreto J, Brown MM, Brew S, Losseff NA. Subarachnoid haemorrhage as the first clinical manifestation of Churg-Strauss syndrome. J Neurol 2008;255:607–8.
[10] Liou HH, Liu HM, Chiang IP, Yeh TS, Chen RC. Churg-Strauss syndrome presented as multiple intracerebral hemorrhage. Lupus 1997;6:279–82.
[11] Ojeda E, Auzmendi A, Teresa Unanue M, Fathi O. Cerebral hemorrhage in Churg-Strauss syndrome. Med Clín 2001;116:118–9.
[12] Tyvaert L, Devos P, Deloizy M, Belhadia A, Stekelorom T. Peripheral and central neurological manifestations in a case of Churg Strauss syndrome. Rev Neurol 2004;160:89–92.
[13] Mishra S, Das CP, Das A, Prabhakar S. Intracerebral hemorrhage in a patient with Churg-Strauss syndrome. Neurol India 2007;55:416–8.
[14] Maloon A, Fritz VU, Kaplan CL. Neurological complications of systemic vasculitis. A report of 2 cases. S Afr Med J 1985;68:603–5.
[15] Chang Y, Kargas SA, Goates JJ, Horoupian DS. Intraventricular and subarachnoid hemorrhage resulting from necrotizing vasculitis of the choroid plexus in a patient with Churg-Strauss syndrome. Clin Neuropathol 1993;12:84–7.
[16] Nishino H, Rubino FA, DeRemee RA, Swanson JW, Parisi JE. Neurological involvement in Wegener's granulomatosis: an analysis of 324 consecutive patients at the Mayo Clinic. Ann Neurol 1993;33:4–9.
[17] Guillevin L, Durand-Gasselin B, Cevallos R, Gayraud M, Lhote F, Callard P, Amouroux J, Casassus P, Jarrousse B. Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. Arthritis Rheum 1999;42:421–30.
[18] Cruz DN, Segal AS. A patient with Wegener's granulomatosis presenting with a subarachnoid hemorrhage: case report and review of CNS disease associated with Wegener's granulomatosis. Am J Nephrol 1997;17:181–6.
[19] Memet B, Rudinskaya A, Krebs T, Oelberg D. Wegener granulomatosis with massive intracerebral hemorrhage: remission of disease in response to rituximab. J Clin Rheumatol 2005;11:314–8.
[20] Seror R, Mahr A, Ramanoelina J, Pagnoux C, Cohen P, Guillevin L. Central nervous system involvement in Wegener granulomatosis. Medicine 2006;85:54–65.

[21] Zhang W, Zhou G, Shi Q, Zhang X, Zeng XF, Zhang FC. Clinical analysis of nervous system involvement in ANCA-associated systemic vasculitides. Clin Exp Rheumatol 2009;27(1 Suppl 52):S65–9.
[22] Pagnoux C, Guilpain P, Guillevin L. Churg-Strauss syndrome. Curr Opin Rheumatol 2007;19:25–32.
[23] Lanham JG, Elkon KB, Pusey CD, Hughes GR. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. Medicine 1984;63:65–81.
[24] Stojanovich L. Autonomic dysfunction in autoimmune rheumatic disease. Autoimmun Rev 2009;8:569–72.
[25] Guillevin L, Lhote F, Gayraud M, Cohen P, Jarrousse B, Lortholary O, Thibult N, Casassus P. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. Medicine 1996;75:17–28.