Alicja Siemińska

Department of Allergology and Pneumonology, Medical University of Gdansk, Poland
Head: Prof. E. Jassem, MD, PhD

Churg-Strauss syndrome — a rare disease or a difficult diagnosis?

Zespół Churga-Strauss — rzadka choroba czy trudne rozpoznanie?

Pneumol. Alergol. Pol. 2012; 80, 1: 3–5

According to the Chapel Hill consensus conference definition, Churg-Strauss syndrome (CSS) is a granulomatous and eosinophil-rich inflammation involving the respiratory tract, and necrotising vasculitis affecting small-to medium-sized vessels, and is associated with asthma and eosinophilia [1]. CSS is a rare diagnosis. While its prevalence has been estimated in several studies at 0.5–6.8 per 1 million [2, 3], the actual real-life prevalence figures are likely to differ. Some of the cases diagnosed as CSS may in fact be conditions that merely imitate the syndrome and — conversely — many cases of actual CSS may remain undetected. It is therefore desirable to point out several aspects of the diagnostic difficulties related to CSS.

The current issue of *Polish Pneumonology and Allergology* features a paper by Fijołek et al. [4], who present the principles of diagnosis of CSS based on their own experience with 38 patients and point out the diagnostic difficulties associated with this syndrome. Among other things, the authors remind us that histopathology, which offers the possibility of establishing a definite diagnosis in multiple other conditions, is not pathognomonic in CSS. The triad of histopathological features, first described by Churg and Strauss in 1951 [5], namely necrotising vasculitis, eosinophilic tissue infiltrates, and extravascular granulomas, may also be identified in other conditions in which eosinophilia is seen [6]. In addition, all of these three symptoms are rarely seen together in CSS due to the phasic course of the disease, as described by Lanham et al. [6]. It is this quite characteristic sequence of symptoms making up the natural history of the disease that is helpful in the diagnosis of CSS and is referred to as the Lanham (Hammersmith) criteria. Based on a retrospective evaluation of patients, Lanham et al., and later Guillevin et al. [7], concluded that most cases of CSS start from allergic rhinitis (usually severe and requiring frequent polypectomies), followed by asthma (usually difficult to control and steroid-dependent), followed by peripheral blood eosinophilia (> 1 500/ /μl). After this prodromal phase of the disease vasculitis develops. This sequence is not an absolute rule, as in some patients allergic rhinitis is not present, in others all the phases occur simultaneously, and still in others vasculitis is followed rather than preceded by asthma [7].

Currently the diagnosis of CSS is most commonly based on a combination of specific clinical manifestations that distinguish the syndrome from other primary vasculitides (the 1990 American College of Rheumatology [ACR] criteria) [8]. It should therefore be emphasised that the first step in the diagnostic algorithm for CSS should be to establish the diagnosis of vasculitis, i.e. (1) to demonstrate clinical manifestations indicating vasculitis, (2) to simultaneously demonstrate at least one of the following criteria: histological confirmation of vasculitis and/or formed granulomas, presence of antineutrophil cytoplasmic antibodies (ANCA) to

Address for correspondence: Prof. Alicja Siemińska, MD, PhD, Department of Allergy and Pneumonology, Medical University of Gdansk, Dębinki St. 7, 80–952 Gdańsk, Poland, Tel./Fax: +48 58 349 1625

Manuscript received on: 5 November 2011

ISSN 0867-7077

myeloperoxidase (MPO) or proteinase-3 (PR-3) in the blood, and (3) to rule out other possible diagnoses [9].

The diagnostic difficulty associated with this approach may be a result of the fact that in about 50% of cases clinical manifestations of vasculitis are not present in the initial phase of the disease [7].

The second step in the diagnostic algorithm involves the diagnosis of CSS using the ACR criteria that distinguish it from other vasculitides, such as granulomatosis with polyangiitis (GPA) or microscopic polyangiitis, or using the Lanham criteria [6]. When the ACR criteria are used, the diagnosis may be based on the presence of at least 4 out of the following 6 criteria: (1) asthma, (2) eosinophilia of more than 10% in the peripheral blood, (3) neuropathy, (4) migrating or transient pulmonary infiltrates on X-ray, (5) paranasal sinusitis, and (6) tissue (extravascular) eosinophilia on histopathology.

Of note is the fact that this algorithm also takes into account the presence and type of ANCA, which have only recently become a classification criterion for vasculitides — already after the introduction of the ACR criteria [10, 11]. It should, however, be underlined that ANCA are not specific for vasculitides and their determination cannot be used as a screening tool. On the other hand, in patients with clinically suspected systemic vasculitis, determination of ANCA by indirect immunofluorescence and by ELISA detecting antibodies to MPO (pANCA) and PR-3 (cANCA) should be ordered, even if no clinically overt vasculitis is present [12]. It should also be borne in mind that the prevalence of ANCA in CSS has not exceeded 40% in most studies and is therefore much lower in CSS than in GPA (73%) [2]. In most cases they are pANCA and much less frequently cANCA [13] CSS accompanied by the presence of ANCA (the so-called ANCA-positive CSS), which is characterised by a higher risk of renal involvement (glomerulonephritis), neuropathy and skin involvement.

ANCA-negative CSS is characterised by higher risk of heart involvement and eosinophilic pneumonia [11, 14]. Many authors believe that these are two separate phenotypes of the disease [2]. Histopathology most commonly reveals eosinophil-rich necrotising vasculitis affecting small vessels in patients with ANCA-positive CSS and perivascular and/or tissue eosinophilic infiltrates without vasculitis in patients with ANCA-negative CSS [2].

The imperfections of disease definitions, diagnostic criteria, and classification criteria considerably hinder the diagnosis of CSS and other vasculitides [15]. The clinicopathologic definition of CSS adopted at the Chapel Hill consensus conference (which allows the distinction of patients from other members of the population) and the ACR classification criteria (which allow the distinction of CSS from other vasculitides, e.g. GPA) are, for instance, commonly used interchangeably. However, in the absence of a histological and/or clinical confirmation of vasculitis they are of little value in the diagnosis of CSS (due to their low sensitivity and specificity) and should not be used for this purpose [15, 16].

The authors of the analysis presented in the current issue of *Polish Pneumonology and Allergology* [4] have proposed a diagnostic model in which the presence of asthma, eosinophilia, paranasal sinusitis, and extrapulmonary clinical manifestations suggestive of vasculitis form the basis for the diagnosis of CSS. Biopsy confirmed vasculitis only in 34% of the subjects and the absence of 4 out of the 6 ACR diagnostic criteria for CSS in several patients did not rule out the diagnosis.

According to the current recommendations of the European League Against Rheumatism (EULAR), patients in whom there are uncertainties regarding diagnosis of CSS should be tested for ANCA and encouraged to undergo biopsy [15]. It should be stressed that if the biopsy material is obtained, the correct interpretation of the microscopic picture is essential for the diagnosis and this requires extensive knowledge on the part of the pathologist and the provision of accurate details by the clinician regarding the stage of the disease and its clinical manifestations.

Churg points out that tissue eosinophilia, an important pathologic criterion of the early phase of CSS, may persist despite normalisation of peripheral blood eosinophil counts in, for instance, chronic eosinophilic pneumonia (CEP) in the course of this syndrome [12]. The author suggests that many cases of undiagnosed CSS may be mimicked by CEP. In the clinical material related to CEP, more than half of the patients' CEP co-existed with asthma, and in some cases tissue biopsies revealed histopathological signs of vasculitis, while in other cases vasculitis was suggested by the course of the disease [17–19].

The presence of extravascular eosinophilia is, according to Churg, insufficiently treated as a strong pathologic criterion for CSS, while unnecessary emphasis is placed on the requirement to establish signs of vasculitis, which — by definition — is absent in the prodromal phase [12]. On the other hand, the vasculitis (in the subsequent phase of the disease) often shows no features of necrotising vasculitis in the biopsy material, there-

fore the author postulates reconsidering the widespread attachment to the term 'necrotising vasculitis'. What is more, the absence of granulomas in the biopsy material does not rule out the diagnosis of CSS as — in contrast to the original material investigated by Churg and Strauss [5] originating from autopsies — organ biopsies provide much less tissue, so the chances of finding granulomas are smaller. On the other other hand, the formation of granulomas is often suppressed by the treatment [12].

Finally, it should be added that despite the numerous difficulties related to the diagnosis of CSS the number of new cases is increasing due to the changes in the management of asthma. It is currently believed that the prevalence of this rare syndrome may be much higher than suggested by the available data [2, 3] and may reach as much as 60 per 1 million [20, 21]. The use of antileukotrienes or omalizumab, which modify the course of asthma and make it possible to lower doses of glucocorticosteroids or completely discontinue them, may hypothetically cause progression from the so-called formes frustes to a full-blown syndrome with eosinophilia and vasculitis [22, 23]. Other authors suggest a direct contribution of these drugs to the pathogenesis of CSS [24, 25].

The emerging analyses of clinical material related to patients with CSS, including the invaluable paper by Fijołek et al. [4], allow us to better understand this rare syndrome and might, in the future, contribute to the development of strong diagnostic criteria. Only then will it be possible to determine the actual prevalence of this syndrome.

References

1. Jennette J.C., Falk R.J., Andrassy K. et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum. 1994; 37: 187–192.
2. Sinico R.A., Bottero P. Churg-Strauss angiitis. Best Pract. & Res. Clin. Rheumatol. 2009; 23: 355–366.
3. Pagnoux Ch., Guillevin L. Churg-Strauss syndrome: evidence for disease subtypes? Curr. Opin. Rheumatol. 2010; 22: 21–28.
4. Fijołek J., Wiatr E., Gawryluk D. et al. Pneum. Alerg. Pol. 2012; 80: 20–28.
5. Churg J., Strauss L. Allergic granulomatosis, allergic angiitis and periarteritis nodosa. Am. J. Pathol. 1951; 27: 277–301.
6. Lanham J.G., Elkon K.B., Pusey C.D., Hughes G.R.V. Systemic vasculitis with asthma and eosinophilia: A clinical approach to the Churg-Strauss syndrome. Medicine (Baltimore) 1984; 63: 65–81.
7. 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 (Baltimore)1999; 78: 26–37.
8. Masi A.T., Hunder G.G., Lie J.T. et al. The American College of Rheumatology 1990 criteria for the classification of Churg--Strauss syndrome. Arthritis Rheum. 1990; 33: 1094–1100.
9. Watts R., Lane S., Hanslik T. et al. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiology studies. Ann. Rheum. Dis. 2007; 66: 222–227.
10. Guillevin L., Lhote F., Amouroux J. et al. Antineutrophil cytoplasmic antibodies,abnormal angiograms and pathological findings in polyarteritis nodosa and Churg-Strauss syndrome: indications for the classification of vasculitides of the Polyarteritis Nodosa Group. Br. J. Rheumatol. 1996; 35: 958–964.
11. Sinico R.A., Di Toma L., Maggiore U. et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss Syndrome. Arthritis Rheum. 2005; 52: 2926––2936.
12. Churg A. Recent advances in the diagnosis of Churg-Strauss Syndrome. Mod. Pathol. 2001; 14: 1284–1293.
13. Hoffman G.S., Specks U. Antineutrophil cytoplasmic antibodies. Arthritis Rheum. 1998; 41: 1521–1537.
14. Sable-Fourtassou R., Cohen P., Mahr A. et al. Antineutriphil cytoplasmic antibodies and the Churg-Strauss syndrome. Ann. Intern. Med. 2005; 143: 632–638.
15. Basu N., Watts R., Bajema I. et al. EULAR points to consider in the development of classification and diagnostic criteria in systemic vasculitis. Ann. Rheum. Dis. 2010; 69: 1744–1750.
16. Conron M., Beynon H.L. Churg-Strauss syndrome. Thorax 2000; 55: 870–877.
17. Fox B., Seed W.A. Chronic eosinophilic pneumonia. Thorax 1980; 5: 570–580.
18. Marchand E., Reynaud-Gaubert M., Lauque D., Duriew J., Tonnel A.B., Cordier J.F. Idiopathic chronic eosinophilic pneumonia. Medicine (Baltimore) 1998; 77: 299–312.
19. Carrington C.B., Addington W.W., Goff A.M. et al. Chronic eosinophilic pneumonia. N. Engl. J. Med. 1969; 280: 787–798.
20. Wechlers M.E., Pauwels R., Drazen J.M. Leukotriene modifiers and Churg Straus syndrome: adverse effect or response to corticosteroid withdrawal? Drug Saf. 1999; 21: 241–251.
21. Martin R.M., Wilton L.V., Mann R.D. Prevalence of Churg-Strauss syndrome, vasculitis, eosinophilia and associated conditions: retrospective analysis of 58 prescription-event monitoring cohort studies. Pharmacoepidemiol. Drug Saf. 1999; 8: 179–189.
22. Ruppert A.M., Averous G., Stanciu D. et al. Development of Churg-Strauss syndrome with controlled asthma during omalizumab treatment. J. Allergy Clin. Immunol. 2008, 121: 253–254.
23. Churg A., Brallas M., Cronin S.R., Churg J. Formes frustes of Churg-Strauss syndrome. Chest 1995; 108: 320–323.
24. Puechal X., Riverau P., Vinchon F. Churg-Strauss syndrome associated with omalizumab. Eur J. Intern. Med. 2008; 19: 364–366.
25. Weller P.F., Plaut M., Taggart V. et al. The relationship of asthma therapy and Churg-Strauss syndrome. NIH workshop summary report. J. Allergy Clin. Immunol. 2001; 108: 175–183.