Churg-Strauss syndrome — a rare disease or a difficult diagnosis?
Zespół Churga-Strauss — rzadka choroba czy trudne rozpoznanie?

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

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myeloperoxidase (MPO) or proteinase-3 (PR-3) in
the blood, and (3) to rule out other possible dia-
gnoises [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 crite-
ria that distinguish it from other vasculitides, such
as granulomatosis with polyangiitis (GPA) or mi-
croscopic polyangiitis, or using the Lanham crite-
ria [6]. When the ACR criteria are used, the dia-
gnosis may be based on the presence of at least 4
out of the following 6 criteria: (1) asthma, (2) eosi-
nophilia of more than 10% in the peripheral blo-
od, (3) neuropathy, (4) migrating or transient pul-
monary infiltrates on X-ray, (5) paranasal sinusit-
is, and (6) tissue (extravascular) eosinophilia on
histopathology.

Of note is the fact that this algorithm also ta-
takes into account the presence and type of ANCA,
which have only recently become a classification
criterion for vasculitides — already after the intro-
duction of the ACR criteria [10, 11]. It should, ho-
ever, 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 vascu-
litis, determination of ANCA by indirect immuno-
fluorescence and by ELISA detecting antibodies to
MPO (pANCA) and PR-3 (cANCA) should be or-
dered, even if no clinically overt vasculitis is pre-
sent [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 pAN-
CA and much less frequently cANCA [13] CSS ac-
companied by the presence of ANCA (the so-cal-
ded ANCA-positive CSS), which is characterised by
a higher risk of renal involvement (glomerulone-
phritis), neuropathy and skin involvement.

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

The imperfections of disease definitions, dia-
gnostic criteria, and classification criteria consid-
erably hinder the diagnosis of CSS and other vascu-
litides [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 classifi-
cation criteria (which allow the distinction of CSS
from other vasculitides, e.g. GPA) are, for instan-
ce, commonly used interchangeably. However, in
the absence of a histological and/or clinical con-
firmation 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 purpo-
se [15, 16].

The authors of the analysis presented in the
current issue of Polish Pneumonology and Allergo-
logy [4] have proposed a diagnostic model in which
the presence of asthma, eosinophilia, paranasal
sinusitis, and extrapulmonary clinical manifesta-
tions 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 pa-
patients did not rule out the diagnosis.

According to the current recommendations of
the European League Against Rheumatism (EU-
LAR), 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 micro-
scopic 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 per-
ipheral blood eosinophil counts in, for instance,
chronic eosinophilic pneumonia (CEP) in the co-
urse 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 unreal-
essary emphasis is placed on the requirement to es-
ablish signs of vasculitis, which — by definition
— is absent in the prodromal phase [12]. On the
other hand, the vasculitis (in the subsequent pha-
se of the disease) often shows no features of nec-
rotising vasculitis in the biopsy material, there-
before 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 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