L47. Single-organ vasculitis: Conceptual and practical considerations

It has long been recognized that a subset of vasculitic conditions remains confined to single organs or organ systems [1,2]. These forms of vasculitis have been known by many different names in the medical literature, including “localized”, “limited”, “isolated” or “non-systemic” vasculitis. More recently, they were termed “single-organ vasculitis (SOV)” [3,4], and this term may establish itself as the standard designation [5]. Accurately separating SOV and systemic vasculitis (SV) is of importance because of prognostic and therapeutic implications. Research into SOV was hampered by the rarity of these conditions, their heterogeneity and the multiplicity of medical specialties that may deal with them. Efforts increased to elaborate a unifying concept for SOV, and the increasing interest in SOV is emphasized by its integration into the 2012 revised Chapel Hill consensus conference (CHCC) definitions for the nomenclature of vasculitis and several recent comprehensive reviews of the topic [3,4,6,7].

Definition and classification

The inclusion of SOV among the vasculitis entities covered by the 2012 revised CHCC definitions met the need for a universally accepted definition (table 1) [5]. Therefore, SOV was defined as a “vasculitis in arteries or veins of any size in a single organ that has no features that indicate that it is a limited expression of a systemic vasculitis”. Most importantly, this definition clearly separates SOV from the localized forms of SV, such as localized granulomatosis with polyangiitis or renal-limited antineutrophil cytoplasm antibody (ANCA)-associated vasculitis, which have at times been amalgamated with SOV entities [4,6,7]. The CHCC definition and other authors [5,7] developed the concept that SOV can be unifocal or diffuse (multifocal). This division highlights that in some organs, such as the nervous system or skin, SOV can result in multiple, topographically remote clinical lesions as opposed to only focal manifestations seen in SOV affecting organs of narrow anatomical boundaries (e.g., genital tract). This distinction has some degree of arbitrariness and may be primarily relevant for treatment decision-making.

Yet, several grey areas remain in the proposed definition of SOV. Concomitant arthralgia and myalgia may be diversely interpreted as associated with systemic inflammation. In such instances, clinicians may diagnose SOV or SV depending on whether the musculoskeletal symptoms are attributed to generalized vasculitis. Along the same line, the “Peripheral Nerve Society” advocated that peripheral-nerve SOV cannot be reconciled with prominent systemic inflammation defined by an erythrocyte sedimentation rate > 100 mm/h [8]; however, consensus is lacking. Furthermore, separating SOV and localized forms of SV is not straightforward. For example, isolated idiopathic aortitis is frequently considered a large-vessel SOV [7,8], although it could also be considered a localized pattern of Takayasu arteritis.

The lingering conceptual question is whether SOV is a standalone nosologic entity or part of a spectrum of phenotypic expressions of SV that overlap to some degree in their key characteristics. Although evidence is accumulating that true SOV infrequently evolves into SV, individual cases diagnosed as SOV may be reclassified as SV or a limited form of SV because of new symptoms, especially during the initial stages of the disease. This situation, combined with the somewhat unclear boundaries of SOV, may favor SOV as being on a vasculitis continuum (figure 1).

Clinical presentation and diagnosis

Most of the available knowledge of SOV relies on relatively small case series published over decades. SOV can affect virtually any organ system, but the skin, central and peripheral nervous system, muscle, gastrointestinal and urogenital tracts, breasts and eyes are the most prominent targets. In contrast, SOV in the heart, liver, lung, joints, ear, nose and throat and kidneys seems rare if not non-existent.

Depending on the entity, SOV manifests as an array of clinical presentations, including purpura, ulcers, livedo, mononeuritis multiplex, stroke, abdominal pain, testicular masses, menstrual bleeding, and visual loss. Within the confines of a specific organ system, comparative studies stressed that the presenting clinical features of SOV are the same as those seen in SV [8–10]. Conversely, SOV is less-often accompanied by constitutional symptoms and increased levels of inflammatory markers than is SV [8–10]. A peculiar presentation is lower-limb-restricted vasculitis, characterized by multi-organ involvement, with skin, peripheral-nerve, muscular, joint and/or periosteal lesions of the legs. Strictly speaking, lower-limb-restricted vasculitis is not a genuine SOV but is commonly included in this group [7] because of its close relationship with the SOV cutaneous polyarteritis nodosa, which has the same characteristic of limited topographic distribution [11,12].

Table I

<table>
<thead>
<tr>
<th>SOV entities</th>
<th>Alternative name</th>
<th>Commonly involved structures or clinical features</th>
<th>Predominantly involved vessel size</th>
<th>Relevant references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse SOV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cutaneous polyarteritis nodosa</td>
<td>Medium-vessel cutaneous SOV</td>
<td>Nodules, livedo, ulcers</td>
<td>Medium</td>
<td>[11,12,26,27]</td>
</tr>
<tr>
<td>Cutaneous leukocytoclastic angiitis</td>
<td>Small-vessel cutaneous SOV</td>
<td>Purpura, urticaria</td>
<td>Small</td>
<td>[21]</td>
</tr>
<tr>
<td>Primary angitis of the central-nervous system</td>
<td>Central-nervous-system SOV</td>
<td>Headache, focal neurological signs, seizure, confusion</td>
<td>Medium, small</td>
<td>[17,18,23,28,29]</td>
</tr>
<tr>
<td>Isolated peripheral-nervous-system vasculitis</td>
<td>Peripheral-nervous-system SOV</td>
<td>Mononeuritis multiplex, symmetric polyneuropathy</td>
<td>Small</td>
<td>[13,25,30]</td>
</tr>
<tr>
<td>Focal SOV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized vasculitis of the aorta</td>
<td>Aortic SOV</td>
<td>Aortitis, aneurysm</td>
<td>Large</td>
<td>[31–33]</td>
</tr>
<tr>
<td>Vasculitis of the gastrointestinal tract</td>
<td>Gastrointestinal SOV</td>
<td>Intestine, gallbladder, appendix, pancreas</td>
<td>Medium, small</td>
<td>[15,22,24]</td>
</tr>
<tr>
<td>Vasculitis of the urogenital tract</td>
<td>Urogenital SOV</td>
<td>Testis, cervix, uterus, ovaries</td>
<td>Medium, small</td>
<td>[8–10,34–36]</td>
</tr>
<tr>
<td>Vasculitis of the breast</td>
<td>Breast SOV</td>
<td>Breast lesion or mass</td>
<td>Medium, small</td>
<td>[8]</td>
</tr>
<tr>
<td>Retinal vasculitis</td>
<td>Eye (retinal) SOV</td>
<td>Visual loss</td>
<td>Small</td>
<td>[37]</td>
</tr>
<tr>
<td>Muscular vasculitis</td>
<td>Muscular SOV</td>
<td>Myalgia, myositis</td>
<td>Medium, small</td>
<td>[38,39]</td>
</tr>
<tr>
<td>Lower-limb-restricted polyarteritis nodosa</td>
<td>Lower-limb-restricted polyarteritis nodosa</td>
<td>Skin, joints, peripheral nerve, muscle, periost</td>
<td>Medium</td>
<td>[40]</td>
</tr>
</tbody>
</table>

Adapted from reference [7].
The demonstration of vessel inflammation by histology or vascular imaging is the mainstay of SOV diagnosis. In addition, SOV is a diagnosis of exclusion, established only after ruling out SV. Because vasculitis confined to a single organ may be the initial manifestation of a newly-occurring SV, a diagnosis of SOV might be ascertained only after a minimum of 6 months without progression to systemic disease [14]. The difficulty in defining such a time frame is highlighted by the recommendation of other authors that SOV should be closely monitored over 5 years for progression to SV [15]. Diagnostic work-up must also rule out the presence of ANCAs and mixed cryoglobulinemia [13,16] (table II).

**Pathology findings**

Data from pathology suggest that SOV embraces large-, medium- and small-vessel disease; occasionally, the vessel wall inflammation is granulomatous in nature [6,14]. Interestingly, medium-vessel involvement appears to be frequently reported in SOV and this observation is at variance with the relative uncommonness of its systemic peer polyarteritis nodosa. In contrast to SV, for which the predominantly affected vessel size and additional pathology findings are pivotal in classification and diagnosis, detailed histological criteria do not yet play a major role in SOV. An exception to this rule is cutaneous SOV, in which the affected vessel type delineates the two major subpatterns – cutaneous polyarteritis nodosa and leukocytoclastic angiitis – reflecting medium- and small-vessel disease, respectively [16] (figures 2 and 3). Similarly, central-nervous-system SOV may be split into small- and medium-vessel entities, which have distinct patterns in terms of therapy response and relapse risk [17] or into granulomatous and...
lymphocytic variants [18]. Further study is warranted to clarify whether such a refined pathology-based subcategorization has clinical relevance for other SOV entities. Whether pathology evidence of immunoglobulin A deposits can be seen in cutaneous SOV or should unequivocally lead to a diagnosis of IgA vasculitis (Henoch–Schönlein) is unresolved and a potential source of heterogeneous classification [16,19,20].

**Etiology**

The etiopathogenesis of SOV is poorly understood. However, as is true for SV [5], there are indications that SOV may be related to cancer, infection or connective tissue disease or a medication-related adverse event. Although such a distinction is yet not entirely defined for SOV, primary and secondary SOV should be separated in terms of the need for screening and treatment of an underlying identifiable cause. Notably, for small-vessel cutaneous SOV, associated conditions are commonly identified and the subset of secondary cases may be even greater in SOV than SV. In a series of 69 cases of cutaneous leucocytoclastic vasculitis, ~75% were found to have an underlying infection, malignancy or connective tissue disease, or drug allergy [21]. Another study found that disease of more than 50% of 70 patients with so-called hypersensitivity vasculitis was related to drug intake or infection [20]. The link between SOV other than cutaneous SOV and underlying diseases or triggers is less clear.

The decision to extensively trace an underlying condition or cause should take into account the specific SOV entity, the mode of disease onset and the presence of SOV-unrelated clinical signs. For cutaneous SOV, the likelihood of an associated disease is greater in adults than children [20]. Screening for secondary SOV should include a thorough medication history, testing for antinuclear antibodies and common viral serologies, blood cultures, and imaging studies according to the clinical context.

The mechanisms accounting for the tropism of SOV for selected organ systems are mysterious but hold potentially critical clues to the etiopathogenesis of vasculitis as a whole. In general, SOV suggests the intervention of organ system-specific vascular factors, whereas lower-limb-restricted SOV points to mechanical factors because the disease develops exclusively in an area of localized increase in hydrostatic pressure.

**Treatment and prognosis**

We lack randomized, placebo-controlled trials to provide guidance on treatment of SOV, but some evidence has emerged from analysis of retrospective case series. Because of the heterogeneous clinical and etiological features of SOV, no universal therapy exists for SOV, and treatment decisions must take into account the distribution of the lesions, underlying etiological factors and disease severity. A unified algorithm for SOV therapy principles is shown in figure 4.
For SOV secondary to an underlying condition, withdrawal of the causative medication or therapy of the associated condition is crucial and might be sufficient to obtain cure. One of the interesting characteristics of SOV therapy is that surgical excision is a widely accepted curative means to treat focal SOV. In such instances, SOV is often an incidental finding after appendectomy [22], cholecystectomy [22], orchiectomy [9] or hysterectomy [10] for suspected common appendicitis, cholecystitis or tumors. Post-surgery outcomes were reportedly good despite no additional therapy [7,14]. Conversely, most instances of diffuse SOV require general immunosuppressive therapy, and the choice of drug regimen relies on the severity of the SOV. In SOV cases not threatening the prognosis, such as cutaneous SOV, generally less aggressive therapy is recommended, with non-steroidal anti-inflammatory drugs, colchicine, topical glucocorticoids, dapsone, pentoxyfilline and other agents [12,19]. Spontaneous recovery may occur even without pharmacological intervention [19]. More intensive therapies must be considered if focal SOV is unresponsive to first-line agents, if vital organs are affected (e.g., central-nervous system, gastrointestinal tract), with risk of permanent damage (e.g., peripheral neuropathy) or with severely painful disease. In such cases, use of medium- to high-dose glucocorticoids and sometimes first-line combination therapy with cyclophosphamide, azathioprine, methotrexate or other immunosuppressive medications are common [12,13,18,19,23]. Most case series strongly support a benign prognosis for SOV, which is suggested as a major distinctive feature of SOV and SV (table II). This general precept likely has to be balanced against the focal or diffuse nature of SOV and the organ system involved. SOV does not necessarily feature an uncomplicated course, as indicated by a study suggesting that survival was lower with gastrointestinal SOV than in a matched general population [24]. In particular, for central or peripheral-nerve SOV, a substantial subset of patients shows severely debilitating organ damage [23,25]. Moreover, high relapse rates have been reported for cutaneous [12] and peripheral-nerve SOV [25], with difficulties in achieving long-term remission even under highly active immunosuppressive therapy. Data widely suggest that SOV infrequently evolves into SV [6,7,11,14,22,25], but the proportion of SV that initially presents as SOV is not well known. However, in general, secondary generalization is considered improbable with increasing time after disease onset.
Perspectives
The most recent endeavors to reunite SOV entities under one umbrella have opened opportunities to enhance our understanding of these diseases and uncovered areas where more progress is needed. The SOV definition and classification criteria require additional refinement to more accurately delineate SOV and SV and limited forms of SV. Further SOV subcategorization based on pathology, etiology or other, yet to be identified characteristics may help individualize homogeneous subgroups in terms of clinical presentation, diagnosis, prognosis and improved patient care.

Disclosure of interest: the authors declare that they have no conflicts of interest concerning this article.

References
The challenges in assessing Takayasu arteritis

Standardised clinical assessments are central to progress in complex multi-system disease. Clinical improvement in small vessel systemic vasculitis (SVV) has come through more effective drug regimes adapted to disease severity. Methods to quantify disease activity, disease extent and damage, plus functional impairment have been developed and validated. These measurements have played a major role in the development of successful national/international networks which in SVV have provided sufficient patient numbers for RCT’s with secure statistical analysis. The first priority in new vasculitis is assessment of disease activity. Birmingham Vasculitis Activity Score (BVAS), developed as a comprehensive index of active involvement across 10 organ-related systems, has major uses in clinical trials and in standard practice. The BVAS score at presentation provides a quantitative measure of disease severity which can indicate long-term prognosis and direct choice of therapy. High BVAS scores predict increased early mortality and reduced long-term survival. Cumulative development of scars from disease and therapy add to this. Measurement of the Vasculitis Damage Score (VDI) shows that scars develop early, even as activity is brought under control. Damage has a poor prognosis, with both total VDI score and the number of involved organs as risk factors for fatality. This supports the need for aggressive initial treatment to rapidly limit inflammation and scar development before switching to milder maintenance therapy.

The challenge now is to adapt these tools to fit large vessel vasculitis like Takayasu aorto-arteritis (TA) which appears more common in Asia then Europe/US. In TA, the restricted large vessel involvement leads to a focal pattern of cardiovascular disease differing markedly from diffuse SV. Absence of the widespread tissue infarcts associated with SVV limits systemic illness in TA, while large vessel occlusion may be associated with development of collaterals and presents late, with established scars. The management of TA is a decade behind SVV with no real evidence base for therapy in the absence of validated assessments. The numbers of patients in India stimulated the Indian Vasculitis group (IRAVAS) to develop appropriate assessments.

Disease extent

Initial consensus agreed an inclusive organ-based list of the main clinical features. The resultant disease-extent index (DEI.Tak) was used to analyse the disease pattern in two main Indian centres [1] and has since been used to characterise Turkish cases [2]. DEI.Tak has real value as a database in individual clinics and as an epidemiologic tool – but is not an activity index and it was important to develop one.

Disease activity

Analysis of serial DEI.Tak assessments from a single large clinic series allowed the selection of a set of items reflecting recent active disease to form a clinical activity score. The resultant Indian Takayasu Activity Score (ITAS2010) focuses on CVS items, with special emphasis on bruits, pulse loss, and claudication. It has been extensively validated and reproducibility in scoring live patients was excellent, with better inter-rater variability than for physicians global. Serial assessments showed that ITAS both reflects response to therapy and detects flares. All items scored in less than 5% of cases were omitted, so the slimmed down final ITAS2010 format contains 43 items in six organ-based systems [3]. It is convenient for physicians in the clinic and useful in therapy trials [4].

It remains unclear whether control of clinical evidence of activity is sufficient to prevent progression in a relapsing scarring disease like TA. When PGA is used to judge disease activity, it reflects acute phase response as well as clinical features. We therefore developed a further combined index, ITAS.A, to additionally include acute phase values (ESR or CRP) assigned a score of 0 to 3 – and this provides new information. When assessing response to therapy in one large patient series, ITAS.2010 indicated satisfactory suppression of clinical disease activity at 6/12 [3]. However, the combined ITAS.A score, despite showing an early response, indicated continued disease activity. This pattern was confirmed at a second centre using a different immunosuppressive plus steroid regime [5]. The incomplete response to active induction therapy with persistent disease activity despite clinical improvement noted in ITAS.A was seen in two centres. This observation is consistent with the high relapse rate in TA noted on steroid withdrawal [6], the slow clearance of hot areas in PET scans,