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L17. What can we expect from the revised Chapel Hill consensus conference nomenclature of vasculitides?

Historical overview of vasculitisc nomenclature

The 2012 Chapel Hill Consensus Conference Nomenclature of Vasculitides [1] is based on observations and discoveries that...
began in the first half of the 19th century. The major clinical and pathologic manifestations of vasculitis were identified before the end of the 20th century. In recent decades, there has been accelerating understanding of etiologies and pathogenic mechanisms. As our understanding of vasculitis has evolved, so have the names we use to identify distinct categories.

In the 19th century, Schönlein [2], Henoch [3,4], Osler [5,6] and others were able to identify a form of purpura that was distinct from purpura caused by bleeding diathesis, insect bites or infectious diseases. This variant often was accompanied by arthralgias, abdominal pain and nephritis. Osler also observed that adults with purpura were prone to develop peripheral neuropathy, pulmonary hemorrhage, iritis and nephritis, including rapidly progressive glomerular disease with every glomerulus “compressed by a crescentic mass” [5,6]. Histologic examination of purpuric lesions demonstrated inflammation of small dermal vessels with extensive leukocytoclasia [7].

Although clinical differences had been noted between what was called Henoch-Schönlein purpura in children versus Henoch-Schönlein purpura in adults, the fact that small vessel vasculitis included multiple etiologically and pathogenetically different categories was not clearly realized until biomarkers were discovered that demonstrated that some small vessel vasculitis had IgA-dominant immune deposits in vessel walls [8], some were associated with circulating cryoglobulins [9] and others with circulating anti-neutrophil cytoplasmic antibodies [10–15]. This set the stage for categorizing vasculitis based on pathobiological parameters rather than clinical and pathological features alone.

In parallel with the identification of vasculitis affecting small vessels, vasculitis affecting medium arteries was being recognized. Although there were earlier reports of systemic necrotizing arteritis, in 1866, the internist Kussmaul and pathologist Maier were first to publish a detailed clinical and pathologic report of a patient with systemic necrotizing arteritis [16]. Their patient presented with fever, muscle weakness, paresthesias, myalgias, abdominal pain and oliguria and was found at autopsy to have inflammatory nodules in medium and small arteries throughout the body. Because the inflammation extended into the perivascular tissue and formed visible

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**Figure 1**

Historical evolution of the nomenclature of necrotizing systemic vasculitis. The upper panel lists investigators who made seminal contributions to the description of specific clinical and pathologic patterns of vasculitis. The middle panel notes the discovery of biomarkers that demonstrate different pathogenetic categories of vasculitis. The bottom two panels provide the diagnostic terms (names) proposed by the 1194 and 2012 Chapel Hill Consensus Conference on the Nomenclature of Vasculitides (CHCC). Note that the 2012 version has fewer eponyms and more reference to pathogenic pathways.
inflammatory nodules, they used the term periarteritis nodosa for this disease process [16]; however, because the initial primary site of inflammation is in fact the vessel wall and not the perivascular tissue, this term has been replaced over time with the more appropriate term polyarteritis nodosa.

As more patients with the pathologic finding of necrotizing arteritis were evaluated, multiple investigators observed that many patients, in fact most patients, with necrotizing arteritis also had clinical and pathologic evidence for vasculitis affecting small vessels, including small (microscopic) arteries, arterioles, venules and capillaries, including glomerular and pulmonary alveolar capillaries [17–25]. Some patients also had necrotizing granulomatous inflammation (granulomatosis) accompanying the vasculitis [22–25]. These patients with arteritis accompanied by small vessel vasculitis and/or granulomatosis were initially considered to be variants of polyarteritis/periarteritis nodosa; however, in a landmark article, Godman and Churg were the first to clearly recognize that microscopic periarteritis/polyarteritis, Wegener’s granulomatosis and allergic angiitis and granulomatosis (Churg-Strauss syndrome) were distinct from periarteritis/polyarteritis nodosa and were likely to be related to one another [23]. This astute conclusion, based primarily on pathologic features, was substantiated later when these three expressions of small vessel vasculitis were all found to be associated with ANCA [10–15] whereas polyarteritis nodosa is not [26,27], further substantiating the categorization of vasculitis on the basis of biomarkers (figure 1).

Another variant of necrotizing arteritis was recognized in very young children with mucocutaneous lymph node syndrome [28,29]. Although the term infantile periarteritis nodosa was used in some early publications [30,31], Kawasaki disease quickly became the favored name worldwide, and this variant of vasculitis was clearly distinct from polyarteritis nodosa.

Arteritis discussed thus far is characterized in the acute phase by extensive necrosis and by a predilection for medium arteries. Another category of vasculitis is characterized by indolent chronic inflammation, often with giant cells, and a predilection for the aorta and its major branches. The first variant of large vessel vasculitis (LVV) that was recognized occurred in older patients and frequently involved the temporal arteries [32,33].

### Table I

**Names for vasculitides adopted by the 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides. Names in italics are new or have been changed substantially compared to CHCC 1994**

<table>
<thead>
<tr>
<th>Large vessel vasculitis (LVV)</th>
<th>Takayasu arteritis (TAK)</th>
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</thead>
<tbody>
<tr>
<td>Giant cell arteritis (GCA)</td>
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<tr>
<td>Medium vessel vasculitis (MVV)</td>
<td>Polyarteritis nodosa (PAN)</td>
</tr>
<tr>
<td>Small vessel vasculitis (SVV)</td>
<td>Kawasaki disease (KD)</td>
</tr>
<tr>
<td>Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)</td>
<td>Microscopic polyangiitis (MPA)</td>
</tr>
<tr>
<td>Granulomatosis with polyangiitis (Wegener’s) (GPA)</td>
<td>Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)</td>
</tr>
<tr>
<td>Immune complex SVV</td>
<td>Anti-glomerular basement membrane (anti-GBM) disease</td>
</tr>
<tr>
<td>Cryoglobulinemic vasculitis (CV)</td>
<td>IgA vasculitis (Henoch-Schonlein) (IgAV)</td>
</tr>
<tr>
<td>Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q) vasculitis</td>
<td>Variable vessel vasculitis (VVV)</td>
</tr>
<tr>
<td>Behcet’s disease (BD)</td>
<td>Cogan’s syndrome (CS)</td>
</tr>
<tr>
<td>Single-organ vasculitis (SOV)</td>
<td>Cutaneous leukocytoclastic angitis</td>
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<tr>
<td>Cutaneous arteritis</td>
<td>Primary central nervous system vasculitis</td>
</tr>
<tr>
<td>Isolated aortitis</td>
<td>Others</td>
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<tr>
<td>Vasculitis associated with systemic disease</td>
<td>Lupus vasculitis</td>
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<tr>
<td>Rheumatoid vasculitis</td>
<td>Sarcoid vasculitis</td>
</tr>
<tr>
<td>Others</td>
<td>Vasculitis associated with probable etiology</td>
</tr>
<tr>
<td>Hepatitis C virus–associated cryoglobulinemic vasculitis</td>
<td>Hepatitis B virus–associated vasculitis</td>
</tr>
</tbody>
</table>

**Table I (Continued)**

| Syphilis-associated aortitis |
| Drug-associated immune complex vasculitis |
| Drug-associated ANCA-associated vasculitis |
| Cancer-associated vasculitis |
| Others |

Revised from reference [1] with permission.
thus leading to the misleading term temporal arteritis. As more patients were studied, it became clear that not all patients have temporal artery involvement and that arteries throughout the body can be affected [34]. The more appropriate term giant cell arteritis progressively supplanted temporal arteritis. Another variant of LVV with pathologic features that resemble giant cell arteritis was found in younger patients [35,36]. Resultant variant of LVV with pathologic features that resemble giant cell arteritis progressively supplanted temporal arteritis. Another

By the early 1990s, although new understanding of systemic vasculitides had emerged, there was tremendous disagreement about how to apply this to the categorization of vasculitides, and an even more fundamental problem with lack of consensus about what names to use for various types of vasculitides. There were multiple examples of the same name being used for multiple types of vasculitis, and examples of a distinct type of vasculitis having multiple names. For example, the category of vasculitis that today is widely called microscopic polyangiitis was variously known as microscopic periarteritis nodosa, microscopic polyarteritis or hypersensitivity angiitis, or merely grouped with periarteritis/polyarteritis nodosa and considered one end of a continuum ranging from predominantly small to predominantly medium vessel involvement. Because of this lack of consensus, an ad hoc group of clinicians and pathologists from six countries and multiple medical disciplines convened in Chapel Hill, North Carolina, to attempt to bring more order to the nomenclature of vasculitis.

Outcome of CHCC 1994
The stated goals of the conference were to reach consensus on the names for some of the most common forms of systemic vasculitis and to construct definitions for these vasculitides [37]. An effort was made to adopt names and definitions that are already widely accepted. The resulting article [37] has been cited over 2000 times in the medical literature, and most if not all of the recommendations of the consensus group have become the standard approach to the nomenclature of vasculitis worldwide. The figure 2 illustrates a particularly dramatic change in usage that was probably influenced by CHCC 1994. Prior to 1994, systemic small vessel vasculitis that is now called microscopic polyangiitis had no standardized name. One of the more commonly used terms was microscopic polyarteritis, which was clearly inappropriate in the many patients who had purpura, glomerulonephritis and pulmonary hemorrhage but no arteritis. The graph shows that there was a profound shift in nomenclature beginning in 1994 [38].

Since publication of the first CHCC recommendation in 1994, there have been advances in our understanding of vasculitis and emerging trend in nomenclature that warranted revisions in the CHCC 1994 names and definition. In addition, CHCC 1994 did not include recommendations about how to name a number of important categories of vasculitis, including vasculitis that is secondary to a systemic disease or a known etiology. Because of this, another International Chapel Hill Consensus Conference (CHCC 2012) was convened to improve the CHCC1994 nomenclature [1].

Expected outcome for CHCC 2012
The goals of CHCC 2012 were to make any appropriate changes in CHCC 1994 names and definitions and add important categories of vasculitis that were not included in CHCC 1994, with an emphasis on making changes only when justified [1]. Table I lists the CHCC 2012 revised nomenclature. Major changes are:

- division of small vessel vasculitis (SVV) into immune complex and ANCA-associated categories;
- replacing Wegener’s granulomatosis with granulomatosis with polyangiitis (GPA);
- replacing Churg-Strauss syndrome with eosinophilic granulomatosis with polyangiitis (EGPA);
- addition of anti-GBM disease;
- replacing Henoch-Schönlein purpura with IgA vasculitis;
- adding hypocomplementemic urticarial vasculitis;
- adding a category of variable vessel vasculitis (VVV) to include Behcet’s disease and Cogan’s syndrome;
- adding a category for single-organ vasculitis (SOV);
- adding a category for vasculitis associated with systemic disease;
- adding a category for vasculitis associated with a probable etiology;
- proposing standard abbreviations for each category;
- modifying and adding many vasculitis definitions.

Only time will tell if CHCC 2012 has a significant influence. Already there has been a perceptible shift in the terminology for ANCA-associated vasculitis with widespread use of MPA, GPA, EGPA terminology, although this received a boost from two earlier publications that advocated the use of GPA [39,40]. Undoubtedly there will be slower adoption of some other nomenclature recommendation, such as the replacement of Henoch-Schönlein purpura with IgA vasculitis; however, if the evidence continues to mount in support of a very specific abnormality in the glycosylation of the hinge region of IgA1 as the cause for both IgA nephropathy and IgA vasculitis, this transition is likely to occur. The addition of anti-GBM disease as a vasculitis is likely to be controversial at first, but given the virtually identical histopathologic pattern of glomerulonephritis shared by anti-GBM disease and AAV, and the clear role for inflammation in injury to alveolar capillaries. If this is not inflammatory injury of vessels, what is it? Hypocomplementemic urticarial vasculitis (HUUV) is rare, but needs to be recognized and diagnosed when it occurs. If the suspected pathogenic link between anti-C1q antibodies and HUV is substantiated, the nomenclature may shift toward anti-C1q vasculitis [41]. The new VVV and SOV categories of vasculitis allow inclusion of variants of vasculitis that were not considered in CHCC 1994, as do the new categories for vasculitis associated with systemic disease and vasculitis associated with a specific etiology. This more comprehensive list will support a greater appreciation of the complete spectrum of inflammatory vascular diseases that should be considered in a patient with signs and symptoms of vasculitis.

With respect to the later point, once again as with CHCC 1994, CHCC 2012 provides only names and definitions for categories of vasculitis, and does not provide specific criteria for classifying patients for clinical trials or for diagnosing patients for clinical management. However, consensus names and standardized definitions will at least establish a firm foundation for the design of studies and the collection of data from large cohorts of well characterized patients that will be required to validate classification criteria and diagnostic criteria for specific variants of vasculitis.

Disclosure of interest: the author declares that he has no conflicts of interest concerning this article.

References

L18. Granuloma formation in granulomatosis with polyangiitis

Extravascular granuloma formation is one of the key features in granulomatosis with polyangiitis (GPA). In most patients, GPA begins in the upper respiratory tract as active, eventually necrotizing extravascular granulomatous disease, with or without local vasculitis. Typically, neutrophilic microabscesses with micronecrosis occur, later bordered by ill-defined granulomas that may proceed to geographic necrosis. In contrast to other types of granulomatous diseases, e.g. sarcoidosis or tuberculosis, the granulomatous inflammation in GPA typically shows very poorly delineated granulomas, or only scattered giant cells, within a dense heterogeneous population of inflammatory bystander cells, mainly lymphocytes, plasma cells, dendritic cells, neutrophils, eosinophils and later fibroblasts (figures 1 and 2). The lymphocytic infiltrate may be organized to form primary and secondary follicles corresponding to ectopic lymphoid tissue. Inflammatory cells, necrosis and fibroblastic proliferation deeply infiltrate the submucous tissues of the upper respiratory tract and may destructively encroach on cartilage and bone with active resorption (figure 2).

Morphological studies of granulomatous lesions in GPA must always take the following into account:
- several different inflammatory cell types constituting “the” granuloma;
- possible differences in activation profiles and mediator expression (e.g. cytokines) between circulating and lesional inflammatory cells;
- comparison of seemingly specific phenomena in GPA with other types of purulent and/or granulomatous inflammation.

Four important components of the extravascular granulomatous inflammation in GPA will be discussed:
- neutrophils and micronecrosis;
- macrophages and giant cells – the granulomatous reaction;
- ectopic lymphoid tissue: potential source of auto-antigen production;
- fibroblast mediated destruction of cartilage and bone.

Neutrophils and micronecrosis

Several studies have shown that in respiratory tract lesions, a purulent neutrophil reaction is an essential feature of GPA [1–3]: small neutrophilic aggregates (microabscesses) around small necrotic areas that contain neutrophilic debris. It has been suggested that micronecrosis with neutrophilic microabscesses constitutes the early phase in the development of the pathomnomic macrophage granuloma in GPA [1]. However, it is not clear how necrotic lesions are induced. Are they solely ANCA-induced and/or do they result from exposure to another initiating injurious agent? Animal models demonstrating PR3-ANCA induced acute pulmonary and renal vascular injury