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HISTORY OF DERMATOLOGY

Historical Perspective on the Classification of Vasculitis

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Introduction

Vasculitis—for which the diagnosis is no more specific than that of pneumonitis or nephritis—represents something of a clinical umbrella term, encompassing some groups of diseases that can be considered among the most difficult and interesting in medicine.[1,2] It still attracts the attention of clinicians and pathologists through the intellectual challenge presented by its unresolved etiological complexities[3] and the enigmas they hide, sparking the curiosity of physicians and researchers alike.[4] Why resort to considering its historical roots? Because old discoveries can be the starting point for new research and, in particular, because the current classifications of vasculitis can be better understood in the light of their nosological antecedents.[5]

Concept and Definition of Vasculitis

Vasculitis is characterized by inflammation of the blood vessels.[6,7] It constitutes a syndrome encompassing a group of diseases that have a poorly understood etiology but that are generally the result of an immunological process that targets the vascular endothelium. The clinical manifestations are highly variable and are related to distal ischemia or bleeding of the affected organs or territories. The extent and severity ranges from a self-limiting cutaneous condition to a potentially fatal multiorgan disease. Vasculitis can be primary or associated with connective tissue, infectious, or neoplastic disease.[8]

Difficulties in the Classification of Vasculitis

Vasculitis is one of the fields of medicine most resistant to logical ordering.[1,9] The classification of the vasculitides has presented serious problems since the first description of periarteritis nodosa by Kussmaul and Maier in the 19th century.[3]

In our opinion, the following factors account for the difficulties in classification: (1) confusion in the nomenclature; (2) lack of understanding of the etiology and pathogenesis; (3) the multisystemic and variable nature of the symptoms; (4) the heterogeneity of the vasculitic conditions; (5) nonspecific patterns of vascular inflammation; (6) overlap between different entities, with recourse to the use of overlap, intermediate, mixed, or nonspecific syndromes; (7) the difficult and imprecise determination of the extent of vasculitis in practice; and (8) an excess of classifications that may be complex or simple but are always changeable and often contradictory.

The classifications of vasculitis are therefore by necessity provisional and require regular meetings of experts. As stated by Stone,[5] "all of the classifications of vasculitis can be considered unfinished."

Is a Classification of Vasculitis Necessary in Clinical Practice?

Despite the nosological difficulties, the classification of vasculitis is not a mere academic necessity, it is of value because not all types of vasculitis have the same prognosis or merit the same treatment. Early diagnosis and precise classification of vasculitis has the following therapeutic implications[3,10,11]: (1) early treatment of the most severe types of vasculitis with immunosuppressant drugs to prevent the progression of irreversible structural damage; (2) the option to use antiviral treatment in vasculitis associated with viruses (hepatitis B virus [HBV] and hepatitis C virus [HCV]); and (3) avoiding the use of cytotoxic drugs in entities with a benign course or in cases in which they do not have demonstrated efficacy.

Historical Perspective on Vasculitis

The Tree of the Vasculitides: Evolution of the Polyarteritis Nodosa Trunk

Although numerous general classifications were attempted during the second half of the 20th century,[12] none was

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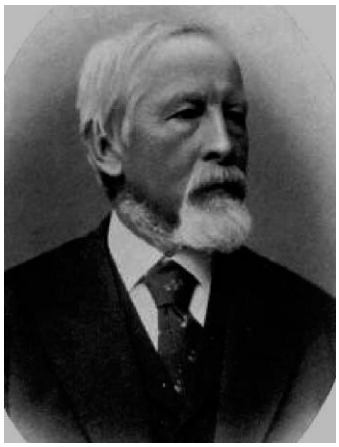

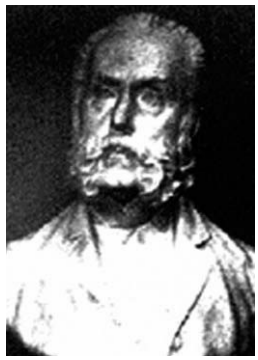

Figure 1. Kussmaul (left) and Maier (right).

completely satisfactory.[5] However, the first modern-day case of systemic vasculitis was described 140 years ago by Adolf Kussmaul and Rudolf Maier (Figure 1) as periarteritis nodosa. Figure 2 shows a tree diagram of the historical evolution of classic polyarteritis nodosa (PAN) of Kussmaul (1866), the reference for all types of vasculitis.[13,14]

The separation of other forms of vasculitis from the PAN trunk has occurred following the comparative study of the different characteristics of classic PAN, such as general restriction to the medium vessels; almost exclusively arterial disease; the tendency to present microaneurysms; the absence of pulmonary involvement, granulomatous disease, and antineutrophil cytoplasmic antibodies (ANCA); and the frequent association with HBV.[5]

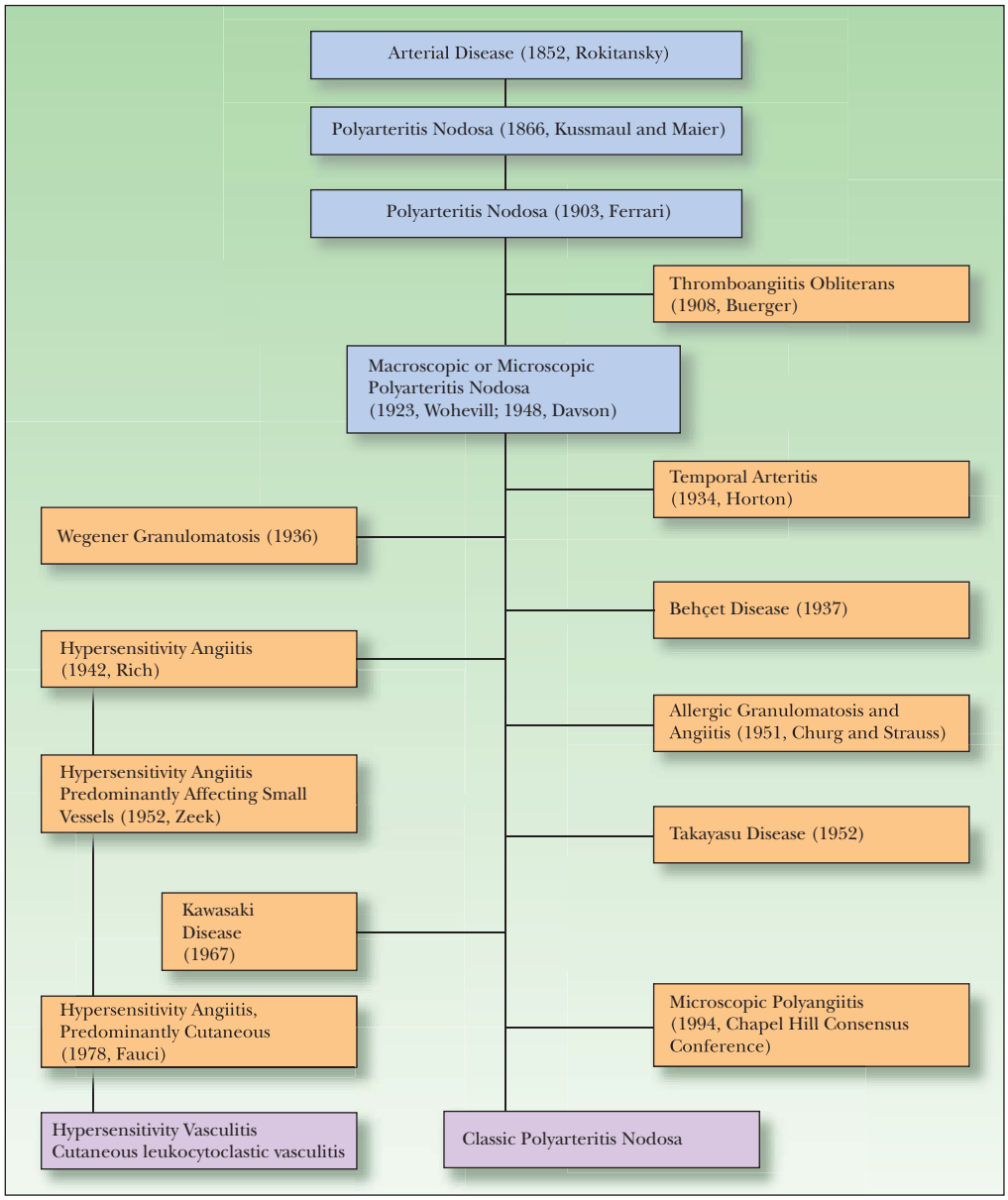

Figure 2. The tree of vasculitic knowledge.

Imitating Baroja,[15] when faced with the tree of vasculitic knowledge (Figure 2), 3 historical periods can be considered.[1,7] The first period, from 1866 to 1900, referred to most forms of vasculitis as periarteritis nodosa. In the second period, from 1900 to 1930, efforts were made to link the origin of vasculitis with toxic or infectious causes (bacteria, toxins, sulfonamides, serum sickness, etc). In the third period, from 1930-40 to date, most of the major systemic vasculitides broke away from the original unifying trunk.

Brief Description of the Origin of Each of the Main Forms of Vasculitis

History of Classic Polyarteritis Nodosa

PAN is correctly considered the "grandfather of the vasculitides."[16] It is very likely that already in the 18th century Matani and subsequently Michaelis, and then in the 19th century Pelletian each discovered cases of this disease.[17] However, most notably, it was K von Rokitansky (1804-1878), referred to by Virchow as the "Linnaeus of pathology," from the Viennese school of thought,[18] who in 1852 described the clinical and autopsy findings of this new entity in the blood vessels.[19] Virchow (1821-1902) went on to describe a case of "endarteritis obliterans" in 1863. In 1866, Adolf Kussmaul (1822-1902), a resident who was a student of Virchow, and Maier, a pathologist, described the case of a 27-year-old man, the tailor Carl Seufert.[20] They were the first to recognize the constellation of symptoms (fever, general malaise, weight loss, productive cough, muscle weakness, abdominal pain, mononeuritis multiplex, and nephropathy with proteinuria) and autopsy findings (inflammation of the perivascular sheath and nodules following the trajectory of medium-caliber arteries) as a novel entity, which they christened periarteritis nodosa.

The death of the tailor was described in moving words: "…on June 2nd he was extremely weak. He could hardly speak, he was struck down with intense and persistent abdominal and muscular pain, with opisthotonos, whilst he groaned and begged the doctors not to abandon him. He died at 2 in the morning on the 3rd of June."[16]

In 1903, upon observing that the inflammatory lesions were not limited to the superficial layer of the arteries but instead affected the whole arterial wall, with formation of aneurysms, Ferrari[21] suggested the more appropriate name of polyarteritis nodosa. This observation was confirmed by Dickson.[22]

Churg-Strauss Vasculitis

In 1951, while at Mount Sinai Hospital in New York, Jacob Churg and Lotte Strauss (Figures 3 and 4) discovered the disease that carries their name.[23] The disease is characterized by the presence of bronchial asthma, tissue eosinophilia and peripheral eosinophilia, and vasculitis of small and medium vessels, with intravascular and extravascular granulomatous inflammation, and with the lungs as the main target organ.[24]

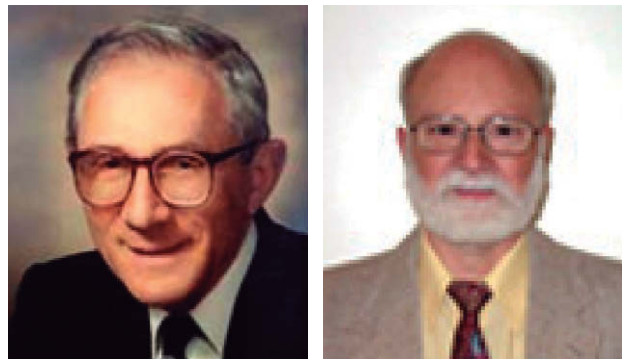

Figure 3. Churg (father [left] and son [right]).

Figure 4. Lotte Strauss

Thromboangiitis Obliterans

In 1908, Leo Buerger, a surgeon and pathologist from New York, published a detailed study of the arteries and veins of 11 amputated limbs and suggested the name thromboangiitis obliterans.[25] According to Portela,[26] the denomination of Buerger did not designate a new disease but rather a new pathogenic concept in a disease that had been recognized for many years and was well described by Félix von Winiwarter in 1879.

Giant Cell Arteritis

Jonathan Hutchinson[27] was the first to provide a clinical description of temporal arteritis in 1890 while at the London

Figure 5. Schönlein (left) and Henoch (right).

Hospital. In 1932, Horton[28] recognized the existence of a granulomatous arteritis in this disease and extended the clinical syndrome. The observation of the paleopathologist Domingo Campillo[29] is particularly interesting: "numerous mummies displayed signs of arteritis, arterial calcification, and thrombosis of the extrathoracic vessels. The pharaoh Ramses II had temporal arteritis."

Behçet Disease

In 1931, the Greek ophthalmologist Adamantiades described a patient with aphthosis, hypopyon, and anterior uveitis, along with phlebitis and arthritis.[30] However, it was the Turkish dermatologist Hulusi Behçet whose name was given to this disease in 1937 when he stated that is was a nosological entity and recognized the classic triad (mouth and genital aphthous ulcers with uveitis).[30]

Takayasu Arteritis

Takayasu arteritis is characterized by inflammation and stenosis of the large and intermediate arteries, often affecting the aortic arch and its branches. It commonly affects women and its cause is unknown. However, it took half a century to arrive at this definition. At a conference in 1905, Nikito Takayasu, an ophthalmologist from Tokyo in Japan, described the case of a 21-year-old woman with abnormalities of the central retinal vessels. During the ensuing discussion, 2 other ophthalmologists, Onishi and Kagoshima, reported similar findings in 2 patients in whom "radial pulses were not palpable," leading to the designation "pulseless women's disease."[31] It was in the middle of the 20th century when it was considered that the pathology of this process was located in the aortic arch or its branches.[31] Takayasu arteritis has up to 24 synonyms, including Martorell syndrome, described in 1954.[32]

Wegener Granulomatosis

The first case of Wegener granulomatosis was described in 1931 by Heinz Klinger[33] in Germany as a variant of PAN and designated "a limited form of periarteritis nodosa."[34] Although 2 new cases were reported by Hoffman in 1932 and Rössle in 1933, it was the pathologist Frederick Wegener, colleague and close friend of Klinger, who, based on 3 cases, established the disease as a defined entity with a characteristic triad[35]: granulomatous inflammation affecting the respiratory tract, granulomatous necrotizing vasculitis, and glomerulonephritis.

In an intriguing article, Wegener affirmed that he was "sure of having discovered something new," while earlier authors "could not recognize that a new disease had been born."[35]

Schönlein-Henoch Purpura

Johann Schönlein (1793-1864) (Figure 5) was the first to discover in 1837 the association of arthralgia with purpura ("peliosis rheumatica").[36] In 1894, his onetime student, Eduard Henoch (Figure 5), completed the description, recognizing the gastrointestinal symptoms (colic and bleeding in the digestive tract).[36]

Support and Criticism of the Classifications

The classification of the vasculitides has been undertaken based on 5 parameters:

1. Histopathology findings, such as the type and size of the affected vessel and the inflammatory process (necrotizing, granulomatous, giant cell, leukocytoclastic, lymphocytic, or eosinophilic vasculitis)
2. Clinical syndromes: primary, idiopathic, or secondary
3. Potential pathogenic mechanisms, such as infections (HBV, HCV) and immunological abnormalities: formation or deposition of immunocomplexes, ANCA, antiendothelial cell antibodies, pathogenic T-cell response, formation of granulomas
4. Clinical and anatomical basis and pathological processes with therapeutic implications
5. Topography of the organ or system, in other words, localized vasculitides.

However, the histopathological findings do not always clearly correspond to a given clinical entity, and the same histological lesion may occur in various types of vasculitis. Vessels of differing size can be affected in the same vasculitis, and different types of vasculitis can involve vessels of the same size.[37]

Table 1. Types of Classifications of Vasculitis

Historical	Perla Zeek (1952)
	Anthony Fauci (1978)
Principal	Fauci, over time (1978-2005)
	American College of Rheumatology (1990)
	Chapel Hill Consensus Conference (1994)
	Derivatives (Lie, 1991; Watts and Scott, 1997; Segovia, 2001)
Minor (isolated, rhetorical, local)	
Recent additions	Vasculitis associated with ANCA
	Microscopic polyangiitis, a new entity?
	Small-vessel vasculitis surrounding temporal arteritis (Solans)
	Others

Abbreviation: ANCA, antineutrophil cytoplasmic antibodies.

For these reasons, when faced with the specific situation of an individual patient, the inflexibility of the descriptions sometimes makes it difficult to include that patient within the official classification.[24]

Types of Classification

We have dared to classify the classifications, as shown in Table 1.

In 1952, Dr Perla Zeek (Figure 6) proposed the first classification of the vasculitides and included 5 subgroups that had previously been described in isolation[11,37,38]: hypersensitivity angiitis, allergic angiitis, granulomatous angiitis (Churg-Strauss), rheumatic arteritis, and temporal arteritis. The merit of Zeek's classification lies in it being the first effort to systematize the vasculitides and the starting point for subsequent classifications. However, certain drawbacks have been noted: the absence of Wegener granulomatosis and Takayasu arteritis (perhaps because those entities were not published in English) and the predominance in the classification of morphological pattern over clinical factors and pathogenic mechanisms that were hardly outlined at the time.[7]

The Classification of Anthony Fauci Over Time

The best accepted classification of the vasculitides and the most used by clinicians and pathologists for decades was

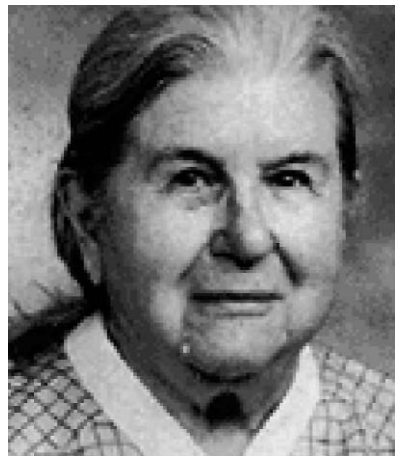

Figure 6. Perla Zeek.

Table 2. Classification of Vasculitis (Fauci, 1978)

Polyarteritis Nodosa
Classic form
Allergic granulomatosis
Overlap syndrome
Hypersensitivity Vasculitis
Serum sickness and similar
Schönlein-Henoch purpura
Essential mixed cryoglobulinemia
Vasculitis associated with malignant tumors
Vasculitis associated with other processes
Wegener Granulomatosis
Lymphomatoid Granulomatosis
Giant Cell Arteritis
Temporal arteritis
Takayasu arteritis
Buerger Disease
Kawasaki Disease
Various Vasculitides

that proposed by Fauci; that classification evolved from 1978 (Table 2) to 2002 (Table 3). The Fauci classification has important implications for prognosis and treatment, since it differentiates between predominantly systemic vasculitic syndromes, hypersensitivity vasculitis limited in particular to the skin, and polyangiitis overlap syndrome.[11,24,39,40] It is worth describing how the classification of Fauci, reduced to 7 groups of vasculitis (Tables 2 and 3), has evolved: (1) microscopic polyangiitis (MPA) reappears, (2) the overlap syndrome between vasculitides in different groups is recognized, (3) temporal arteritis and Takayasu arteritis are made independent, (4) Schönlein-Henoch purpura leaves the group of hypersensitivity vasculitides, (5) lymphomatoid granulomatosis disappears and is now

Table 3. Classification of Vasculitic Syndromes (Fauci, 2002)

Generalized Necrotizing Vasculitis
– Polyarteritis nodosa (PAN)
• Classic PAN
• Microscopic polyangiitis
– Churg-Strauss vasculitis
– Polyangiitis overlap syndrome
Wegener Granulomatosis
Temporal Arteritis
Takayasu Arteritis
Schönlein-Henoch Purpura
Predominantly Cutaneous Vasculitis (Hypersensitivity Vasculitis)
– With exogenous stimuli
• Drug-induced vasculitis
• Serum sickness and similar reactions
• Vasculitis associated with infectious diseases
– With probable involvement of endogenous antigens
• Vasculitis associated with tumors
• Vasculitis associated with connective-tissue diseases
• Vasculitis associated with other underlying diseases
• Vasculitis associated with congenital defects in the complement system
Other Vasculitic Syndromes
– Kawasaki disease
– Isolated central nervous system vasculitis
– Thromboangiitis obliterans (Buerger disease)
– Behçet syndrome

Table 4. Vasculitic Syndromes (Fauci, 2005)

Primary
Wegener granulomatosis
Churg-Strauss syndrome
Polyarteritis nodosa
- Microscopic polyangiitis
Giant cell arteritis
Takayasu disease
Schönlein-Henoch purpura
Idiopathic cutaneous vasculitis
Essential mixed cryoglobulinemia
Behçet disease
Isolated CNS vasculitis
Cogan syndrome
Kawasaki disease
Secondary
Drug-induced vasculitis
Serum sickness
Vasculitis associated with other primary diseases (infections, tumors, connective-tissue diseases)

Abbreviation: CNS, central nervous system.

considered to be a T-cell lymphoma, within the spectrum of angiocentric immunoproliferative lesions.[41]

Surprisingly, this changed radically soon after; in 2005, Fauci classified the vasculitides as primary and secondary (Table 4),[6] criteria that had been used for decades. In our opinion, this is a step backwards, although as pointed out by Hughes,[42] it has the virtue of simplicity.

Criteria of the 1990 American College of Rheumatology Classification

The 1990 American College of Rheumatology classification is shown in Table 5. The classification includes only the 7 most common and best characterized vasculitic diseases.[11,43-45] These criteria identify each vasculitis in an attempt to define the disease.[46] Although the criteria served the purpose of classification and were intended for use in epidemiology, their high sensitivity and specificity have meant that they are used by clinicians as diagnostic criteria. The main limitation is that only 7 types of vasculitis are considered, 7 appearing to be a magic number even in the classification of diseases.[47,48] Rao et al[49] have even shown how false vasculitides can meet these criteria.

In our opinion, the American College of Rheumatology classification causes confusion between hypersensitivity vasculitis and Schönlein-Henoch purpura, only recognizing a morphological difference—perivascular or extravascular granulocytosis (arteriolar or venular)—in the first and granulocytosis of the vessel wall in the second.

Chapel Hill Consensus Conference

In 1993, a group of experts met in Chapel Hill in North Carolina, USA, to agree on a classification of the vasculitides, define each entity, and establish an internationally accepted nomenclature (Table 6).[37,45,50] The system they used for classification was based on the size of the vessels and the histopathology findings (well known in the majority of the classifications), to which they added the presence of ANCA.

Advantages of the Chapel Hill Consensus Conference (CHCC) classification are as follows: (1) the recognition

Table 5. Criteria for Classification of Vasculitis: American College of Rheumatology (1990)

Schönlein-Henoch Purpura	Age less than 20 years
	Palpable purpura
	Abdominal pain
	Biopsy with granulocytes in the vessels
Wegener Disease	Nasal or oral inflammation
	Chest radiograph with infiltrates, nodules, or cavities
	Microhematuria or red cell casts
	Granulomatous inflammation in the biopsy
Churg-Strauss Syndrome	Bronchial asthma
	Greater than 10% eosinophilia
	Neuropathy
	Transient pulmonary infiltrates
	Paranasal sinus involvement
	Biopsy with extravascular eosinophils
Hypersensitivity Vasculitis	Age at onset > 16 years
	Palpable purpura
	Maculopapular rash
	Positive biopsy: perivascular or extravascular granulocytes (arteriolar or venular)
Polyarteritis Nodosa	Weight loss
	Livedo reticularis
	Testicular pain
	Myalgia or muscle weakness
	Mononeuropathy or polyneuropathy
	Diastolic blood pressure greater than 90 mm Hg
	Elevated blood urea nitrogen or creatinine
	Hepatitis B virus
	Arteriographic anomalies
	Biopsy of a small or medium caliber artery with granulocytes
Giant Cell Arteritis	Age > 50 years
(Temporal Arteritis)	Recent onset or new characteristics of headache
	Hypersensitivity or reduction of pulse in the temporal artery
	ESR > 50 mm/h
	Compatible biopsy: lymphoplasmacytic infiltrates or granulomatous inflammation
Takayasu Arteritis	Age < 40 years
	Claudication of the limbs
	Weak pulses
	Difference of > 10 mm Hg in blood pressure between the arms
	Arterial bruit (subclavian or aortic)
	Abnormal arteriography (stenosis of the aorta or main branches)

Abbreviation: ESR, erythrocyte sedimentation rate.

Table 6. Chapel Hill Consensus Conference Classification, 1994

Small-Vessel Vasculitis	
Wegener granulomatosis[a]	Granulomatous inflammation of the respiratory tract and necrotizing vasculitis in medium and small vessels (capillaries, venules, arterioles, and arteries). Necrotizing glomerulonephritis is common.
Churg-Strauss syndrome[a]	Eosinophilic inflammation of the respiratory tract and necrotizing vasculitis in medium and small vessels associated with asthma and eosinophilia.
Microscopic polyangiitis[a]	Necrotizing vasculitis with little or no immune deposition, affecting the small vessels (capillaries, venules, or arterioles). Necrotizing vasculitis may be present in small or medium arteries. Necrotizing glomerulonephritis is common and pulmonary capillaritis often occurs.
Schönlein-Henoch purpura	Necrotizing vasculitis with deposits predominantly of immunoglobulin A, affecting the small vessels (capillaries, venules, or arterioles). Typically affects the skin, intestine, and renal glomeruli. It is associated with arthralgia or arthritis.
Essential cryoglobulinemic vasculitis	Vasculitis with cryoglobulin deposits, affecting the small vessels (capillaries, venules, or arterioles), and with cryoglobulins present in the serum. The skin and glomeruli are often affected.
Cutaneous leukocytoclastic angiitis	Cutaneous leukocytoclastic angiitis without systemic involvement or glomerulonephritis.
Medium-Vessel Vasculitis	
Classic polyarteritis nodosa	Necrotizing inflammation of the medium and small arteries without glomerulonephritis or vasculitis of the arterioles, capillaries, or venules.
Kawasaki disease	Arteritis of large, medium, and small vessels, associated with mucocutaneous lymph node syndrome. The coronary arteries are often affected. The aorta and veins can also be involved. Usually occurs in children.
Large-Vessel Vasculitis	
Giant cell (temporal) arteritis	Granulomatous arteritis of the aorta and its main branches with a preference for the extracranial branches of the carotid. Often affects the temporal artery in patients older than 50 years and is associated with rheumatic polymyalgia.
Takayasu disease	Granulomatous inflammation of the aorta and its main branches that usually occurs in patients older than 50 years.

[a]Vasculitis associated with antineutrophil cytoplasmic antibodies.

that MPA exists as a distinct entity and its distinction from PAN and Wegener granulomatosis, (2) emphasis on the group of small-vessel vasculitides associated with ANCA (MPA, Churg-Strauss, and Wegener). The disadvantages, summarized by Zea-Mendosa and Balsalobre-Aznar,[10] are as follows: (1) MPA is overemphasized and PAN is relegated to regions in which HBV is endemic; (2) the definition of classic PAN, without glomerulonephritis or small-vessel vasculitis, means that classic PAN with skin involvement, although common, would be reclassified as MPA; (3) it does not consider the clinical finding that an initial MPA can progress to Wegener disease; (4) hypersensitivity vasculitis as defined in the American College of Rheumatology classification (1990) is referred to in the CHCC classification as cutaneous leukocytoclastic angiitis, a source of confusion generated by using a histopathological abnormality as a clinical entity—the CHCC classification eliminated the term hypersensitivity vasculitis because in many cases there is no hypersensitivity, and although it was changed to cutaneous leukocytoclastic angiitis, due to the typical restriction to the skin and the predominant neutrophilic infiltrate, it does not recognize the etiology involving predominantly lymphocytic infiltrates seen in a minority of patients[5]; (5) up to 10% of leukocytoclastic vasculitis can display systemic visceral complications; and (6) the classification is incomplete, as it fails to include secondary vasculitis.

It is noteworthy, in our opinion, that Churg-Strauss syndrome and Wegener disease are classified as small-

vessel vasculitis. It is not very acceptable, even with the CHCC criteria, to consider not the largest vessels but rather those in greater proportion. Finally, the group containing vasculitis associated with ANCA should also include primary pauci-immune crescentic glomerulonephritis, which was not admitted in the CHCC classification and is really a vasculitis of the glomerular capillaries with positive ANCA.[51]

Nevertheless, the CHCC classification was important and represented a valid starting point for new perspectives on the classification of vasculitis.[51]

Other Classifications Derived From the American College of Rheumatology and the Chapel Hill Consensus Conference Classifications

We can only outline the 3 most important later classifications. Alarcón Segovia[52] presented the vasculitides in order of the largest affected vessel, but specified the type and size of the inflamed vessels and distinguished between primary and secondary entities. Lie[53] classified vasculitis as infectious and noninfectious and included an interesting category of pseudovasculitis. Watts and Scott[54] attempted to resolve some of the problems of the CHCC classification and separated MPA, Wegener granulomatosis, and Churg-Strauss vasculitis from the group of small-vessel vasculitides, and distinguished between primary and secondary vasculitis.

Recent Additions

Marañón[55] stated that "a few carefully studied patients can be the source of new knowledge." As we have seen in the historical roots of vasculitis, a single case or a small group of cases can give rise to or suggest a new entity. Solans and Cid-Xutglá[56] described a 41-year-old man with fever of unknown origin and headache in whom temporal artery biopsy revealed adventitial inflammation and inflammation of the vasa vasorum, along with involvement of the surrounding small vessels, suggesting a distinct or previously undescribed type of vasculitis. Such a possibility would further add to the difficulties of classifying vasculitis.[57]

The Definitive Classification?

John H Stone[5] performed quite a juggling act to generate a classification based essentially on the size of the vessels within the larger categories of primary and secondary vasculitis. This may be artificial, particularly in the inclusion of vasculitis associated with ANCA and small-vessel vasculitis mediated by immunocomplexes (Table 7).[5] Classifications of vasculitis that are of use in clinical practice have recently been developed.[8,45]

Table 7. Classification of Vasculitis (Stone, 2005)

Primary Vasculitis
Vasculitis Predominantly Affecting the Large Vessels
Takayasu arteritis Giant cell arteritis Cogan syndrome Behçet disease
Vasculitis Predominantly Affecting the Medium Vessels
Polyarteritis nodosa Buerger disease Kawasaki disease Primary central nervous system angiitis
Vasculitis Mediated by Immunocomplexes and Predominantly Affecting the Small Vessels
Goodpasture disease Cutaneous leukocytoclastic angiitis Schönlein-Henoch purpura Hypocomplementemic urticarial vasculitis Essential mixed cryoglobulinemia Erythema elevatum diutinum
Vasculitis Associated With ANCA
Wegener granulomatosis *Microscopic polyangiitis* *Churg-Strauss syndrome* *Renal-limited vasculitis*
Secondary Vasculitis
Diverse Causes of Small-Vessel Vasculitis
Connective-tissue diseases Inflammatory bowel diseases Tumors Infections Drug-induced vasculitis: associated with ANCA Others

Abbreviation: ANCA, antineutrophil cytoplasmic antibodies.

Unresolved Problems: Leftover Vasculitides

Polyangiitis Overlap Syndrome

Polyangiitis overlap syndrome is not considered in the classification proposed by Stone.[5] It includes atypical forms of primary vasculitis that do not fit in any of the known vasculitides. We have proposed the types shown in Table 8.[24,58,59]

Table 8. Vasculitic Overlap Syndromes

Polyangiitis
– Intermediate syndromes in the group of PAN-type systemic vasculitis (idiopathic classic PAN and Churg-Strauss angiitis)
– Combinations of major vasculitic syndromes
• PAN or Churg-Strauss syndrome associated with hypersensitivity vasculitis.
• Wegener granulomatosis associated with PAN or Churg-Strauss syndrome
• Giant cell arteritis associated with PAN, Churg-Strauss syndrome, or hypersensitivity vasculitis.
• Others
Undifferentiated or difficult to classify vasculitis

Abbreviation: PAN, Polyarteritis nodosa

Recurrent Vasculitis

Recurrent vasculitis is a relatively unexplored area. The rate of recurrence is highly variable from one type of vasculitis to another and ranges from 25% to 52% of cases.[60] It is noteworthy that in our experience with 16 cases of Churg-Strauss syndrome, none displayed relapse in the vasculitic phase, suggesting that is could be considered a "one-shot" disease.[61,62]

Residual Vasculitis

Vasculitic scars and their possible long-term clinical consequences (coronary, renal, or cerebral arteriosclerosis, hypertension, chronic liver disease, residual neuropathy, organ failure, etc) is a little-studied area that may have repercussions on the morbidity and mortality of vasculitis.[63]

Pseudovasculitis

Pseudovasculitis refers to entities that mimic vasculitis from a clinical, angiographic, or even histological perspective.[6,53,64,65] Failure to recognize these diseases can lead to incorrect and often delayed diagnosis.

Classic Polyarteritis Nodosa: Still More Branches to Come

Most cases of PAN are of unknown etiology. It is likely that the current definition of idiopathic PAN does not correspond to a single entity but rather still includes various different entities.[5]

Cutaneous Vasculitis

Cutaneous forms of vasculitis (leukocytoclastic, lymphocytic, and granulomatous vasculitis, cutaneous vasculitis secondary to vasculitis obliterans, and large-vessel vasculitis) is still the subject of much debate.[66]

The Future

It is worrying that despite many advances in the understanding of the etiology and pathogenesis and in diagnosis based on laboratory findings and imaging studies,[67-69] the classification of vasculitis is still unresolved.[57] There is still no complete or definitive classification of vasculitis. The classification of vasculitis will continue to evolve because, as affirmed by Wagensberg,[70] scientific truth is only the current or provisional truth, and science is a succession of truths.

The ideal classification is based on etiological criteria, and therefore, in the future a more accurate understanding of the causes and treatment of vasculitis will lead to the disappearance of the classifications reviewed here.

Conclusions

1. The classifications of vasculitis remain provisional.
2. There is no universally satisfactory classification.
3. Early and accurate diagnosis is nevertheless genuinely important for the prognosis and treatment of the disease.
4. Regular meetings of experts are required.
5. The complicated classifications of vasculitis will disappear when the etiology and treatment of each entity is understood.

References

1. Barbado Hernández FJ, Vázquez Rodríguez JJ, Ortiz Vázquez J. Perspectiva del concepto y clasificación de las vasculitis necrotizantes sistémicas. An Med Intern (Madrid). 1984;1:394-400.
2. Barbado Hernández FJ. Vasculitis necrotizante sistémica tipo panarteritis nudosa. Estudio de los marcadores pronóstico. Tesis Doctoral. Universidad Autónoma de Madrid. 1984.
3. Ortiz Vázquez J. Vasculitis. An Med Intern (Madr). 1987;4:211-4.
4. Pedro-Pons A, Rozman C, García San Miguel J, Vidal MT, Ciscar F. Patología y clínica de las colagenosis. Barcelona: Ed. Toray; 1967. p. 1-24.
5. Stone JH. Clasificación y epidemiología de las vasculitis sistémicas. In: Kelley. Tratado de Reumatología, 7th edition. Madrid: Ed. Elsevier; 2006. p. 1350-6.
6. Sneller MC, Langford CA, Fauci AS. Síndromes de las vasculitis. In: Harrison Principios de Medicina Interna.

16th edition. Barcelona: Mc Graw Hill Edit; 2005. p. 2203-15.
7. Martínez L. de Letona J. Clasificación de las vasculitis. Rev Clin Esp. 1990;186:34-7.
8. Barbado Hernández FJ, Gómez Cerezo J, Vázquez Muñoz E. Protocolo diagnóstico del paciente con sospecha de vasculitis. Medicine. 2005;9:2055-8.
9. Laín Entralgo P. Nosotaxia. In: Patología general. Barcelona: Toray ed; 1971. p. 28-34.
10. Zea Mendoza AC, Balsalobre Aznar J. Vasculitis: ¿hablamos de la misma cosa? Rev Clin Esp. 2000;200:587-4.
11. Cid Xutglá MC, Coll-Vinent Puig B, López-Soto A, Grau Junyent JM. Vasculitis: definición, clasificación y etiopatogenia. Medicine. 1997;7:2583-90.
12. Lie JT. Nomenclatura and classification of vasculitis: plus ça change, plus c'est la meme chose. Arthritis Rheum. 1994;37:181-6.
13. Rosen S, Falk RJ, Jennette JC. Polyarteritis nodosa, including microscopic form and renal vasculitis. In: Churg A, Churg J, editors. Systemic vasculities. New York: Ed. Igaku-Shoin; 1991. p. 57-77.
14. Iglesias Gamarra A, Restrepo Suárez JF, Valle R, Osorio E, Bolaños A, Méndez O, et al. Historia de las vasculitis. Available from: htpp://www.encolombia.com/medicina/reumatologia/reuma9202-historia.htm
15. Baroja P. El árbol de la ciencia. Madrid: Alianza Editorial; 1995.
16. Stone JH. Poliarteritis nudosa. JAMA (ed. esp.). 2003;12: 137-44.
17. Díaz Fernández AJ, Barat Cascante A, Oliva Aldamiz H. Angeítis necrotizantes. Barcelona: Salvat Editores; 1980. p. 11-46.
18. Laín Entralgo P. Historia de la Medicina. Barcelona: Salvat Editores; 1978. p. 464-76.
19. Rokitansky K. Ueber einige der wichtigsten Krankheiten der Arterien. Denkshr. dk. Akad d. Wissensch; 1852;4-49.
20. Kussmaul A, Maier R. Über eine bisher nicht beschriebene eigenthumliche Arterienerkrankung (periarteritis nodosa) die mit Morbos Brightii und rapad fortschreitender allgemeiner Muskellahmung einhergeht. Dtsch Arch Klin Med. 1866;1: 484-516.
21. Ferrari E. Ueber Polyarteritis acuta nodosa (sogenannte Periarteritis nodosa), und ihre Beziehungen zur Polymyositis und Polineuritis acuta. Beitr Pathol Anat. 1903;34:350-86.
22. Dickson W. Polyarteritis acuta nodosa and periarteritis nodosa. J Pathol Bacteriol. 1908;12:31-57.
23. Churg J, Strauss L. Allergic granulomatousis, allergic angeitis and periarteritis nodosa. Am J Pathol. 1951;27:277-301.
24. Barbado Hernández FJ. Vasculitis. Poliarteritis nudosa. Angeítis alérgica de Churg Strauss. Síndrome vasculítico de solapamiento. In: Rodés Teixidor J, Guardia Massó J, editors. Medicina Interna. 2nd edition. Barcelona: Masson; 2004. p. 3153-8.
25. Menéndez Aulló. La medicina del siglo XX. Madrid: Ed. Recoletos; 1994. p. 30.
26. Portela CJ. Tromboangeítis obliterante. Buenos aires: El Ateneo Ed; 1932. p. 19-20.
27. Hutchinson J. On a peculiar form of thrombosis arteritis of the aged wich is sometimes productive of gangrene. Arch Surg. 1980;1:323.
28. Horton BT, Magath TB, Brown GE. An undescribed form of arteritis of the temporal vessels. May Clin Proc. 1932;7: 700-10.
29. Campillo D. Paleopatología. Los primeros vestigios de la enfermedad. Barcelona: Fundación Uriach; 1993. p. 65-7.
30. Bové Boada A, Ramos Casals M, Brito Zerón P, Font Franco J. Semiología clínica general. In: Ramón Casal M, editor. Enfermedades autoinmunes sistémicas y reumatológicas. Barcelona: Ed Masson; 2005. p. 26-44.
31. Piette AM, Blétry O. Maladie de Takayasu, In: Kahn MF, Peltier AP, Meyer O, Piette JC, editors. Maladies et síndromes systemiques. Paris: Flammarich Mèdicine-Sciences; 2000. p. 685-99.
32. Lie JT. Takayasu's arteritis. In: Systemic vasculitides. Churo A, Churg J, editors. New York: Igaku-Shoin Ed; 1991. p. 159-79.
33. Klinger H. Grenzformen der Periarteritis nodosa. Frankfurt Ztschr Path. 1931;42:455-80.
34. Godman GC, Churg J. Wegener's granulomatosis. Pathology and review of the literature. Arch Pathol. 1954;58:533-53.
35. Wegener F. La granulomatosis de Wegener. Contemplaciones y pensamientos de un patólogo. Available from: http://www.sintomed.org.ar/Mains/publicaciones/wegene2.htm
36. Díaz Fernández AJ, Barat Cascante A, Oliva Aldamiz H. Angeítis por hipersensibilidad. In: Angeítis necrotizantes. Barcelona: Salvat Ed;1980. p. 47-66.
37. Zea Mendoza AC, García de la Peña Lefebvre P, Vázquez Galeano CM. Las vasculitis. Granulomatosis de Wegener y enfermedad de Churg-Strauss. Medicine. 2001;8:1643-54.
38. Zeek PM. Periarteritis nodosa: critical review. Am J Clin Path. 1952;22:777-90.
39. Fauci AS, Haynes BF, Katz P. The spectrum of vasculitis. Clinical pathology, immunology and therapeutic considerations. Ann Intern Med. 1978;89:660-76.
40. Fauci AS. Síndrome de las vasculitis. In: Harrison Principios de Medicina Interna. 15th edition. Barcelona: Mc Graw Hill; 2002. p.2288-302.
41. Barbado Hernández FJ, Gómez Román J. Conferencias clínico-patológicas de la SEMI. Rev Clin Esp. 2006;206: 343-52.
42. Hughes GRV. Enfermedades del tejido conectivo. Barcelona: Consulta Ed; 1987. p. 218-38.
43. Hunder GG, Arend WP, Block DA, Calabrese LH, Fauci AS, Fries JF, et al. The American College of Rheumathology 1990 criteria for the classification of vasculitis. Artritis Rheum. 1990; 33:1065-137.
44. Fries JF, Hunder GG, Block DA, Michel BA, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Summary. Arthritis Rheum. 1990;33:1135-6.
45. Valero Expósito M, García de la Peña Lefebvre P, Zea Mendoza AC. Concepto, clasificación y etiopatogenia de las vasculitis. Medicine. 2005;9:2001-9.
46. Alonso Ruiz A, Ruiz Lucea E. Poliarteritis nudosa. Medicine. 1997;7:2591-95.
47. García Gual C. Los siete sabios (y tres más). Madrid: Alianza Editorial; 1989. p. 13-46.
48. Ordóñez J. El fermento presocrático. In: Ordóñez J, Navarro V, Sánchez Ron JM, editors. Historia de la ciencia. Madrid: Espasa Calpe Ed; 2003. p. 57-90.
49. Rao JK, Allen NB, Pincus T. Limitations of the 1990 American College of Rheumatology classification criteria in

the diagnosis of vasculitis. Ann Intern Med. 1998;129: 345-52.
50. Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WI, et al. Nomenclature of systemic vasculitides: Proposal of an International Consensus Conference. Arthritis Rheum. 1994;37;187-92.
51. Romero Bueno F, Zea Mendoza AC, Álvarez-Mon Soto M. Vasculitis asociadas a ANCA. Medicine. 1997;7:2596-605.
52. Alarcón-Segovia D. Vasculitis. Generalidades. In: Farreras-Rozman Medicina Interna. Madrid: Elsevier Ed; 2004. p. 1109-10.
53. Lie JT. Vasculitis 1815 to 1991: classification and diagnostic specificity. J Rheumatol. 1992;19:83-9.
54. Watts RA, Scott DGI. Classification and epidemiology of the vasculitides. Balliere's Clin Rheumatol. 1997;11:191-217.
55. Marañón G. Veinticinco años de labor. Madrid: Espasa-Calpe; 1935. p. 17-48.
56. Solans R, Cid-Xutglá M. Fiebre y cefalea en un varón de 41 años. Med Clin (Barc). 2001;117:709-15.
57. Barbado Hernández FJ, Gómez Cerezo J, Ríos Blanco JJ, Vázquez Rodríguez JJ. Más dificultades en la clasificación de las vasculitis. Med Clin (Barc). 2002;119:158-9.
58. Barbado Hernández FJ, Vázquez Rodríguez JJ, Mostaza Prieto JM, Fernández Martín J, Peña Sánchez de Rivera JM, Gil Aguado A, et al. Síndrome poliangeítico de solapamiento: ¿un nuevo síndrome o más confusión? An Med Intern (Madrid). 1988;5:603-10.
59. Prados C, Álvarez-Sala R, Barbado Hernández FJ. Vasculitis de Churg- Strauss: recuerdo y actualización. Med Clin (Barc). 1996;107:62-8.
60. Gordon M, Luqmani RA, Achu D, Greaves I, Richards N, Michael J, et al. Relapses in patients with a systemic vasculitis. Q J Med. 1993;86:779-89.
61. Ríos Blanco JJ, Gómez Cerezo J, Suárez García I, Gutiérrez Molina M, Vázquez Rodríguez JJ, Barbado Hernádez FJ. Síndrome de Churg-Strauss. Nuestra experiencia de dos décadas. Rev Clin Esp. 2000;200:597-601.
62. Ríos Blanco JJ, Gómez Cerezo J, Suárez I, Gutiérrez M, Vázquez JJ, Barbado FJ. Churg-Strauss syndrome: outcome and long term follow-up of 32 patients. Comment on the article by Solans et al. Rheumatology. 2002;41:946-7.
63. Barbado FJ, Vázquez JJ, Khamashta M, Hughes GRV. Vasculitis. In: Bellamy N, editor. Prognosis in the rheumatic diseases. Ontario: Keuwer Academic; 1991. p. 251-67.
64. Sack KE. Cuando la vasculitis no es la vasculitis. Hospital Practice (ed. esp.). 1994;9:57-61.
65. Olive A. Síndromes pseudovasculíticos. Med Clin (Barc). 2003;120:272-7.
66. Smoller BR, McNutt NS, Contreras F. The natural history of vasculitis. Arch Dermatol. 1990;126:84-9.
67. Vázquez Muñoz E, Barbado Hernández FJ, Vázquez Rodríguez JJ. Técnicas de imagen en el diagnóstico de las vasculitis. Med Clin (Barc). 2005;124:383-87.
68. Schmidt W. Use of imaging studies in the diagnosis of vasculitis. Curr Rheumatol Rep. 2004;6:203-11.
69. Cid Xutglá MC. Mecanismos patogénicos de las vasculitis sistémicas. Nuevos conceptos. Med Clin (Barc). 1998;110: 587-96.
70. Wagensberg J. Si la naturaleza es la respuesta ¿cuál era la pregunta? Barcelona: Tusquets Ed; 2003. p. 107-12.