Current Classifications

Thara Larbi, Saloua Hamzaoui, Maya Abdallah, Mourad Ennafaa, Ali Harmel, Kamel Bouslama, Lotfi Hendaoui, and Skander M'rad

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Abstract

The term "vasculitis" covers a wide range of anatomoclinical entities whose histological substratum is an inflammation of the vascular wall. Several classifications have followed each other for half a century, based mainly on the size of the affected vessels. Those used most commonly are the classification criteria of the American College of Rheumatology and the nomenclature of the Chapel Hill Consensus Conference. The aim was to differentiate among the vasculitides and not to create diagnostic criteria on an individual scale. The diversity of the vasculitides, the absence of anatomoclinical specificity, the lack of knowledge of their etiopathogeny, and the existence of overlapping forms explain the difficulties in developing a rational classification.

1 Introduction

The term "vasculitis" or "angiitis" covers a wide range of anatomoclinical entities whose histological substratum is an inflammation of the vascular wall, whether it is arterial, venous, or capillary. Systemic vasculitis encompasses heterogeneous diseases characterized by their etiopathogeny, their clinical expression, and their prognosis. These differences led to several classifications derived from the classification of Zeek (1952) based mainly on the size of the affected vessels. The objective of these classifications is not an academic exercise, but rather to differentiate one vasculitis from another so as to improve their treatment and care. Those most commonly used, even

T. Larbi (✉) · S. Hamzaoui · M. Abdallah · M. Ennafaa · A. Harmel · K. Bouslama · S. M'rad
Medical School of Tunis,
Department of Internal Medicine,
Mongi Slim University Hospital,
La Marsa, 2046 Sidi Daoud, Tunisia
e-mail: l_thara@hotmail.com

L. Hendaoui
Medical School of Tunis,
Department of Medical Imaging
and Imaging Guided Interventions,
Mongi Slim University Hospital,
La Marsa, 2046 Sidi Daoud, Tunisia

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though imperfect, are the classification criteria of the American College of Rheumatology (ACR) (Fries et al. 1990) and the nomenclature of the Chapel Hill Consensus Conference (CHCC) (Jennette et al. 1992). These classifications have not included all the vasculitides. Specific classification criteria are also used, such as the international classification criteria of Behçet's disease (Anonymous 1990).

2 Historical Background

In 1866, Kussmaul and Maier (1866) described the first detailed observation of periarteritis nodosa (PAN). The presence of nodules along the arteries gave this vasculitis its name (Ferrari 1903). The term "periarteritis nodosa" (PAN) covered all the systemic vasculitides for several years.

Vasculitis has been known since antiquity. In Iraq in the eleventh century, Ali Ibn Isa El Kahal made the connection between the inflammation of the temporal artery and blindness, described much later under the term "Horton's temporal arteritis." "…I make an excision and cauterization of the temporal arteries to treat the patients presenting with hot and inflamed temporal muscles which can lead to a loss of vision…" he wrote in his *Tadhkirat al-Kahhalin* ("Memorandum for Oculists") (Hollenhorst et al. 1960; Loddenkemper 2004).

In Zeek (1952) used the term "necrotizing angiitis" and proposed the first classification of vasculitis through a review of the literature. This review concerned five vasculitic syndromes: hypersensitivity angiitis, granulomatous allergic angiitis, rheumatoid arthritis, polyarteritis (periarteritis) nodosa, and temporal arteritis. This was followed by a multitude of classifications (Alargon-Segovia and Brown 1964; De Shazo 1975; Gilliam and Smiley 1976; Fauci 1978; Lie 1994).

In the absence of a clearly established etiopathogenic basis, the main parameters of these classifications were:

- The size of the vessels involved: large, medium-sized, or small vessels.
- The primary or secondary character (in association with an underlying disease, which could be iatrogenic, neoplasic, or connective tissue disease).
- The infectious or noninfectious origin.
- The extension of vasculitis (systemic or localized)
- The histological findings.

3 Main Classifications

3.1 ACR Classification Criteria (1990)

Through a multicentric prospective study (48 centers, 1,020 cases, 807 analyzed cases), the ACR group of experts' mission was to establish the classification criteria for seven primary vasculitic syndromes, namely, Takayasu's arteritis, giant cell arteritis, polyarteritis nodosa, Churg–Strauss syndrome, Wegener's granulomatosis, Henoch–Schönlein purpura, and hypersensitivity vasculitis. These criteria were used to identify a given vasculitis (sensitivity) and to differentiate it from the other vasculitides (specificity) so as to homogenize the groups of patients in epidemiology studies and therapeutic trials (Hunder et al. 1990). Thus, these criteria are not a diagnostic tool for individual cases.

The criteria established by the ACR group of experts were epidemiological data (age) and clinical, biological, histopathological, and arteriographic findings. The classification criteria of each vasculitis can be found in the corresponding chapters. Their sensitivity and specificity were highly variable, from 71 to 94% and from 84 to 99%, respectively (Fries et al. 1990) (Table 1). About 20 years later, these classification criteria, the first of their kind, are still widely used.

3.2 The Nomenclature of the CHCC (1994)

A panel of multidisciplinary experts (internists, rheumatologists, nephrologists, immunologists, and pathologists) met in Chapel Hill in North Carolina with a double objective:

- To establish a precise and universal nomenclature for ten current vasculitic syndromes (nine systemic and one localized).
- To define these vasculitides.

These definitions were based mainly on histological characteristics, namely:

- The size of the affected vessels.
- The presence of a granuloma and/or fibrinoid necrosis.
- The nature of the inflammatory infiltrate.

Immunological data were taken into consideration for some of these definitions, such as the presence of

Table 1 Sensitivity and specificity of the American College of Rheumatology 1990 classification criteria

Vasculitis	No. of patients	Sensitivity (%)	Specificity (%)
Giant cell arteritis	214	93.5	91.2
Takayasu's arteritis	63	90.5	97.8
Polyarteritis nodosa	118	82.2	86.6
Wegener's granulomatosis	85	88,2	92
Churg–Strauss syndrome	20	85	99.7
Henoch-Schönlein purpura	85	87.1	87.7
Hypersensitivity vasculitis	93	71	83.9

One hundred and twenty-nine patients with unspecified vasculitis were included in the analysis.

immune complexes and deposits of immunoglobulin A or cryoglobulinemia.

These ten vasculitic syndromes were divided into three groups and defined as in the following three sections (Jennette et al. 1992) (the italic style indicates the frequent, but nonessential characteristics for the purpose of definition).

3.2.1 Large Vessel Vasculitis: (Aorta and Its Main Branches)

- Giant cell (temporal) arteritis: granulomatous arteritis of the aorta and its main branches with a predilection for the extracranial branches of the carotid artery.
  The temporal artery is often affected.
  Usually occurs in patients aged over 50 years, often associated with polymyalgia rheumatica.
  The term "temporal" was put in brackets to indicate that it is frequently but not always involved. The temporal artery can also be affected in the course of other vasculitides such as in Wegener's granulomatosis (Nishino et al. 1993).
- Takayasu's arteritis: granulomatous inflammation of the aorta and its main branches.
  Usually occurs in patients younger than 40 years.
  This definition does not refer to the female predominance as stated in the literature.

3.2.2 Vasculitis of Medium-Sized Vessels (Visceral Arteries: Renal, Hepatic, Coronary, and Mesenteric Arteries)

- Polyarteritis nodosa (classic PAN): necrotizing inflammation of the small and medium-sized arteries without glomerulonephritis or vasculitis of the arterioles, capillaries, or venules.
- Kawasaki's disease: arteritis affecting the large, medium-sized, and small arteries and associated with a mucocutaneous lymph node syndrome.
  Coronary arteries are often affected. The aorta and veins may be affected. Usually occurs in children.

3.2.3 Small Vessel Vasculitis: (Venules, Arterioles, Capillaries, and Distal Intraparenchymal Arteries)

- Wegener's granulomatosis [antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis]: granulomatous inflammation of the respiratory tract and necrotizing vasculitis of the small and medium-sized vessels (capillaries, venules, arterioles, and arteries).
  Necrotizing glomerular nephropathy is usually found.
- Churg–Strauss syndrome (ANCA-associated vasculitis): eosinophil-rich granulomatous inflammation of the respiratory tract and necrotizing vasculitis of the small and medium-sized vessels associated with asthma and eosinophilia.
- Microscopic polyangiitis (ANCA-associated vasculitis): necrotizing vasculitis with few or no immune deposits affecting the small vessels (capillaries, venules, and arterioles).
  Necrotizing glomerulonephritis and pulmonary capillaritis are frequent.
- Henoch–Schönlein purpura: vasculitis with immunoglobulin A predominant immune deposits affecting the small vessels (capillaries, venules, and arterioles).
  The skin, gut, glomeruli, and articulations are typically affected.

Table 2 Classification of systemic vasculitis depending on the size of the affected vessels and the primary or secondary character

	Large size	Medium size	Small size
Primary	Giant cell arteritis Takayasu's arteritis	Periarteritis nodosa Kawasaki's disease	Wegener's granulomatosis Churg–Strauss syndrome Microscopic polyangiitis Henoch–Schönlein purpura Goodpasture's syndrome Essential mixed cryoglobulinemia
		Thromboangiitis obliterans	
	Cogan's syndrome		
	Behcet's disease		
Secondary	Aortitis (syphilis, tuberculosis)	PAN-hepatitis B	Infectious
		Iatrogenic (Merkel 2001) Associated with neoplasias: hemopathies, solid cancers (Fain et al. 2007)	
			Secondary cryoglobulinemias Connective tissue diseases
Pseudo Vasculitides (Staud et al. 1996)	Arterial fibrodysplasias Aortic coarctation		Infectious endocarditis Cholesterol emboli Antiphospholipid syndrome Auricular myxoma Angiotropic lymphomas Pheochromocytoma (Saïd et al. 2010)

- Essential cryoglobulinemic vasculitis: vasculitis with cryoglobulin immune deposits affecting the small vessels (capillaries, venules, and arterioles) and associated with a serum cryoglobulin. The skin and glomeruli are often affected.
- Cutaneous leukocytoclastic angiitis: isolated cutaneous leukocytoclastic angiitis without systemic vasculitis.

3.2.4 Summary

This classification has three main advantages: clear and precise definitions have been established, the "ANCA-associated vasculitis" has been individualized among the vasculitides of the small vessels, and finally it has separated microscopic polyangiitis from polyarteritis nodosa, a distinction which is now widely acknowledged.

4 Limitations

The multiplicity of classifications suggests their limitations and inadequacies. The difficulty in establishing a rational classification is mainly due to:

- The multitude of vasculitic syndromes which have been identified: over 20 vasculitides have been enumerated. Several of them have not been included in the present classifications, such as Behçet's disease, Buerger's thromboangiitis obliterans, and other less frequent vasculitides (Goodpasture's syndrome, Cogan's syndrome, McDuffie's hypocomplementemic vasculitis) as well as secondary vasculitis (Table 2).
- The absence of clinical specificity: this is because any vessel has only three main ways of reacting to an injury—by increasing its permeability (purpura is the most typical illustration of this), by giving rise to microaneurysms or macroaneurysms, as in PAN and in Behçet's disease, or it can lead to an intimal proliferation (stenosis, thrombosis and ischemia).
- The absence of histological specificity: the same histological findings can correspond to a multitude of diagnostic possibilities. Leukocytoclastic vasculitis is a good demonstration of this.
- Lack of knowledge about much of their etiopathogeny.
- The presence of overlapping forms.

4.1 Limitations of the ACR Classification Criteria

Even though they represent an important stage in the classification of vasculitis, these criteria have been criticized (Jennette et al. 1992; Rao et al. 1998; Watts 2007; Basu 2010).

Apart from the fact that the criteria included only seven vasculitic syndromes, the main criticisms are as follows:

- The diagnosis had been made on the basis of the experts' judgment (Bloch et al. 1990). No prior definition of the vasculitis studied had been given to the experts; thus, there are possible sources of bias.
- Their low positive predictive value (17–29%) in patients suspected as suffering from a vasculitis (Rao et al. 1998); hence, the impossibility of using them as a diagnostic tool.
- They do not differentiate between microscopic polyangiitis and polyarteritis nodosa.
- Polynuclear neutrophil anti-cytoplasmic antibodies (ANCA), testing for which was not practice in the 1990s, have not been included in these classification criteria.

4.2 Limitations of the CHCC nomenclature

The definitions given by the CHCC are based on histological data. This restriction is a major impediment in using them in practice. The feasibility and reliability of biopsies vary greatly depending on the affected organ and the phase (emerging, active, quiescent, healed) of the disease. At a late stage, histology shows only nonspecific fibrosing lesions.

Even though widely used, the adaptation of the CHCC nomenclature as a diagnostic criterion of primary vasculitis turned out to be irrelevant (Sørensen 2000; Lane 2002). In the absence of histological proof, Sørensen (2000) proposed clinical, biological, and radiological markers which were meant to reflect the granulomatous involvement of the respiratory airways, aortitis, and glomerulonephritis ("surrogate markers"). The CHCC nomenclature, even supplemented with these surrogate markers, fails to act as diagnostic criteria.

5 Concordance of Classifications

A significant discordance was found between these two classifications. In a prospective cohort of 99 patients with primary systemic vasculitis (57 with Wegener's granulomatosis, 24 with microscopic polyangiitis, 18 with Churg–Strauss syndrome), 38 patients complied with the ACR classification criteria for one vasculitis, 40 patients complied with the criteria for two vasculitic syndromes, and 21 patients complied with the criteria for three vasculitic syndromes at the same time. Sixty of these patients complied with the ACR classification criteria for PAN, thus highlighting their low specificity. Applying the CHCC nomenclature to the same cohort resulted in 37% of unclassified forms (Lane et al. 2005).

Another study of 24 patients revealed a low concordance level (20%) between the two classifications (ACR versus CHCC) (Bruce and Bell 1997).

6 Which Classifications for the Future?

To offset the inadequacy of the present classifications, Watts (2007) and his collaborators proposed an algorithm to classify patients with ANCA-associated vasculitis and PAN. The chosen classification criteria were those of the ACR, the strict definitions of the CHCC and the criteria of Lanham et al. 1984) for Churg–Strauss syndrome. This algorithm included the "surrogate markers" and ANCAs with anti-proteinase 3 or antimyeloperoxidase specificity. These autoantibodies were used only in the classification of Wegener's granulomatosis and microscopic polyangiitis but not for Churg–Strauss syndrome, where the ANCAs are present only in 40% of cases (Sablé-Fourtassou 2005).

Liu et al. (2008) compared this algorithm with the CHCC criteria through a cohort of 550 Chinese patients with ANCA-associated vasculitis and PAN. The advantage of this algorithm was that it limited the overlaps and the unclassified forms. This algorithm, however, needs to be validated on a much broader scale before its utilization can be generalized.

Recently, 39 experts of the European League Against Rheumatism (EULAR) specified the points to be developed in the future definitions and the criteria

for systemic vasculitis (Basu et al. 2010). The main shortcomings of the nomenclature, the present definitions, and the classifications were discussed. Five points were put forth:

1. Nosology: the terms "definitions," "classification criteria," and "diagnostic criteria" should be clarified to avoid confusion. The nomenclature used should reflect, as far as possible, the etiopathogeny of the disease in question for a much more rational approach. The group of experts did not come up with any proposition.
2. Definitions: if age had been included in the definition of some types of vasculitis (giant cell arteritis, Takayasu's arteritis), its discriminatory role should not be overestimated.
3. Necessity of taking biopsies: as the definition is histological, it is recognized that a histological examination is essential for the diagnosis of vasculitis and especially to exclude some of the differential diagnoses. A biopsy of the organs involved is not always possible and whether it is even worthwhile depends on the localization. Particular focus was on the biopsy of the temporal artery in the diagnosis of giant cell arteritis and the frequent presence of immunoglobulin A deposits in Henoch–Schönlein purpura.
4. Laboratory tests: the place of ANCAs in the diagnosis of small vessel vasculitis was highlighted especially for Wegener's granulomatosis and microscopic polyangiitis. The combination of direct immunofluorescence and ELISA improves their diagnostic performance but they should not be used for screening purposes. Their absence tends to support the diagnosis of PAN. However, the detection of ANCAs using the ELISA method is still a nonstandardized method.
5. Radiological diagnosis: vascular imaging has been most helpful in the diagnosis of large vessel vasculitis. Computed tomography angiography and magnetic resonance angiography have replaced conventional angiography in the diagnosis of Takayasu's arteritis. The role of Doppler echography of the temporal arteries and of high resolution MRI was stressed for the diagnosis of giant cell arteritis. *However, we have to keep in mind that 40% of patients with extracranial giant cell arteritis have negative temporal biopsies and the ultrasonography and MRI findings will also be negative.* As for the PET scan, the present data are insufficient to specify its role in the diagnostic strategy for vasculitis.

7 Conclusion

Two "classifications" are widely used, namely, the ACR classification criteria and the CHCC nomenclature. The former established criteria to differentiate one vasculitis from another, (classification criteria) and not a vasculitis from a different disease (diagnosis criteria). The latter provided a universal nomenclature of the main primary vasculitic syndromes and proposed a classification based on the size of the affected vessel. Using these two classifications as diagnostic criteria has turned out to be disappointing. New attempts should be made to develop a classification which is more useful in clinical practice.

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