Reappraisal of the 1990 American College of Rheumatology criteria for the classification of cutaneous vasculitis: an analysis based on 766 patients

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ABSTRACT

Objective. *The term cutaneous vasculitis (CV) includes a wide and heterogeneous group of entities. The American College of Rheumatology (ACR) established a set of criteria to classify vasculitis in 1990. Our aim was to further investigate into the applicability of these criteria for the classification of patients with primary CV.*

Methods. *We analysed a large and unselected series of patients with CV attended to a university referral centre from January 1976 to December 2011. Patients were classified according to the methodology and criteria proposed by the ACR1990 core data set. Patients were also classified according to the same ACR 1990 database as proposed by Michel et al. in 1992 to differentiate Henoch-Schönlein purpura (HSP) from hypersensitivity vasculitis (HV).*

Results. *We assessed 766 patients (346 women and 420 men) with a mean age of 34 years. Patients with cutaneous lesions in the setting of conditions different from primary CV were excluded. According to the 1990 ACR criteria, 405 (63.1%) of the 642 patients with primary CV were classified as having HSP and 230 (35.8%) as HV. However, 119 (18.5%) patients fulfilled the ACR 1990 criteria for both entities. In addition, 7 (1.1%) did not meet the ACR 1990 criteria for any of them and, therefore, they were considered as non-classified vasculitis. When patients with primary CV were tested for the Michel et al. criteria, 392 (61.1%) were classified as having HSP and 250 (38.9%) as HV. Frequent discordance between the ACR 1990 and the Michel et al criteria was observed. It ranged between 18.4 and 21.7% for HSP and 32.2 to 38% for HV.*

Conclusion. *According to our data, the ACR 1990 criteria are of limited value for the classification of patients with primary CV.*

Vasculitis is a general term for a group of related disorders characterised by blood vessel inflammation leading to tissue or organ injury. Tissue biopsy is the cornerstone of the diagnosis of vasculitis (1). However, in the daily clinical practice it is not exempt of potential limitations as sometimes it provides an incomplete or non-specific pathologic result. In addition, biopsy is not always feasible and it is not routinely performed in typical cases of cutaneous vasculitis (CV), in particular in children.

Classification of vasculitis has been a challenging problem for decades. Diagnosis often relies on a combination of clinical, laboratory and histopathologic findings. For this reason, in 1990, the American College of Rheumatology (ACR) proposed a series of classification criteria based on data comparing clinical features of patients with seven types of primary vasculitis: Giant Cell Arteritis (GCA), Takayasu Arteritis (TA), Wegener's Granulomatosis (WG), Churg-Strauss Syndrome (CSS), Polyarteritis Nodosa (PAN), Hypersensitivity Vasculitis (HV) and Henoch-Schönlein Purpura (HSP) (2).

The term "cutaneous vasculitis" (CV) refers to a wide and heterogeneous group of entities linked by the presence of necrotising inflammatory lesions in the cutaneous blood vessels (3). The clinical spectrum and epidemiology of CV may range from an isolated cutaneous involvement to a life-threatening syndrome (3, 4), including conditions that following definitions proposed

after the publication of the ACR 1990 classification criteria for vasculitis are now included in the category of ANCA-associated vasculitis (5).

According to the ACR 1990 classification criteria, most cases of primary CV fall into two well-defined entities: HSP or HV (6, 7). HSP is the most frequent pediatric vasculitis affecting the skin (8-10). Patients with HSP often have joint and gastrointestinal manifestations and nephritis (11, 12). Nevertheless, precipitating events, usually an upper respiratory tract infection and/or drug intake, are more frequently observed in patients with HV (11, 12).

Based on the same ACR 1990 database of patients, in 1992 Michel *et al*. proposed new criteria to differentiate HSP from HV (13). These criteria emphasized the fact that relevant histological data are not always available and supported the use of clinical and laboratory findings to differentiate HSP from HV (13). Both the ACR1990 criteria and those proposed by Michel *et al*. are summarised in the Table I.

To the best of our knowledge, these criteria have not been validated in unselected patients with CV. Therefore, in the present study we aimed to investigate into the applicability of the ACR 1990 criteria for the classification of primary CV. For this purpose we took advantage of a large series of patients with CV from a single referral centre.

Patients and methods

This was a retrospective study of unselected patients diagnosed as having CV at a teaching tertiary-care hospital in Santander (Northern Spain), from January 1976 to December 2011. The diagnosis of CV was based on either *a*) a skin biopsy showing histological findings of vasculitis (neutrophilic infiltration, leukocytoclasia, fibrinoid necrosis or erythrocyte extravasation into the vessel wall) or *b*) the presence of typical non-thrombocytopenic palpable purpura. Patients were classified according to the ACR 1990 methodology and criteria. A comparative study between the ACR 1990 classification criteria (6, 7) and the criteria proposed by Michel *et al*. was performed (13).

Data were extracted from the clinical charts according to a predefined protocol and then stored in a computerised database. To minimise entry error, all data were double checked and reviewed for diagnosis confirmation. Statistical analysis was conducted using the STATISTICA software package (Statsoft Inc. Tulsa, OK, USA).

Results

Seven hundred and sixty-six patients (420 men and 346 women, mean age: 34 years) diagnosed with CV were included in the study.

Patients with cutaneous lesions in the setting of conditions different from primary CV were excluded. Due to this, CV associated with connective tissue diseases (n=35), bacterial infections (n=27), malignancies (n=16), essential mixed cryoglobulinaemia (n=13), granulomatosis with polyangiitis (Wegener granulomatosis) (n=3), eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (n=3), urticarial vasculitis (n=21) and polyarteritis nodosa (n=7) we not assessed in the present study. Of note, a patient with urticarial vasculitis was associated with an underlying malignancy and it

Table I. Criteria proposed by the American College of Rheumatology in 1990 (ACR 1990) for the classification of Henoch-Schönlein purpura (HSP) and Hypersensitivity Vasculitis (HV), and those by Michel *et al*. to differentiate both entities.

Criterion Definition		
ACR 1990 (6, 7)		Michel *et al*. 1992 (13)
HSP	*HV*	*HSP or HV*
1. Age <20 years: Onset of the first symptoms at the age of 20 or less.	1. Age >16 years: Onset of the first symptoms at the age of 16 or more	1. Age at onset ≤ 20 years: Development of first symptoms at age 20 or less.
2. Palpable purpura: Slightly elevated purpuric rash over one or more areas of the skin not related to thrombocytopenia.	2 Palpable purpura: Slightly elevated purpuric rash over one or more areas of the skin not related to thrombocytopenia.	2. Palpable purpura: Slightly elevated purpuric rash over one or more areas of the skin not related to thrombocytopenia.
3. Skin biopsy: Granulocytes inside arteriolar or venular wall.	3. Skin biopsy: Granulocytes in a periarteriolar, extraarteriolar o venular location.	3. Gastrointestinal bleeding: Gastrointestinal bleeding, including melena, haematochezia or positive test for occult blood in the stool.
4. Bowel angina: Diffuse abdominal pain that worsens with meals.	4. Maculo-papular rash: Raised plates of various sizes.	4. Bowel angina: Diffuse abdominal pain worse after meals or bowel ischaemia usually including bloody diarrhoea.
	5. Drugs at onset: Presence of medication that may cause the syndrome.	5. No medications: Absence of any medications at onset of disease which may have been a precipitating factor.
		6. Haematuria: Gross haematuria or microhaematuria.
Classification criteria		
The presence of any 2 or more criteria classifies the patient as HSP with a sensitivity of 87.1% and a specificity of 87.7%.	The presence of 3 or more criteria classifies the patient as HV with a sensitivity of 71% and a specificity of 83.9%	The presence of any 3 or more criteria yields a correct classification of HSP in 87.1% of cases. The presence of 2 or less criteria yields a correct classification of HV in 74.2% of cases.

was included in both groups. The remaining 642 patients with primary CV were classified using the ACR 1990 criteria as HSP or HV.

According to the ACR 1990 criteria, 405 (63.1%) of the 642 patients with primary CV were classified as having HSP and 230 (35.8%) as HV. However, 119 (18.5%) patients fulfilled the ACR 1990 criteria for both entities. In addition, 7 (1.1%) did not meet the ACR 1990 criteria for any of them and, therefore, they were considered as non-classified vasculitis.

When patients with primary CV were tested for the Michel *et al*. criteria 392 (61.1%) were classified as having HSP and 250 (38.9%) as HV.

Figure 1 showed the flow chart for the study, including the classification of CV patients according to the ACR 1990 criteria (6, 7), and those proposed by Michel *et al*. (13).

Regrettably, frequent discordance between the ACR 1990 classification criteria and those put forward by Michel *et al*. was observed. In this regard, 88 of the 405 (21.7%) patients who fulfilled the ACR 1990 criteria for HSP did not meet the Michel *et al*. criteria for HSP. Conversely, 72 of 392 (18.4%) patients classified as having HSP according to the Michel *et al*. criteria did not fulfill the ACR1990 classification criteria for HSP.

It was also the case when HV patients were assessed. In this regard, 74 (32.2%) of 230 patients who met the ACR 1990 criteria for HV did not fulfill Michel *et al*. criteria for this condition. Also, 95 (38%) of 250 patients classified as having HV according to Michel *et al*. criteria did not meet the ACR 1990 classification criteria for this entity.

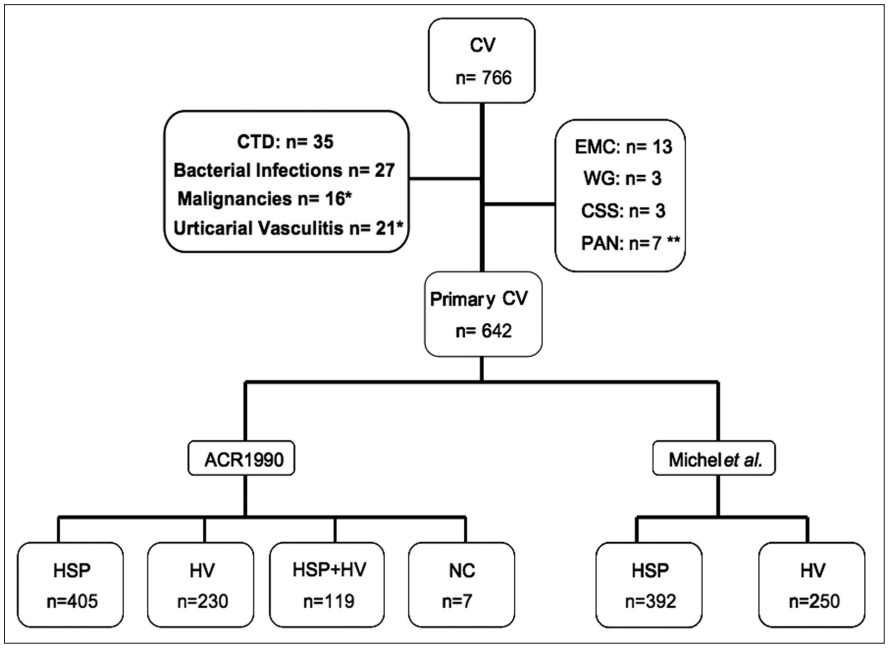

Fig. 1. Flow chart of 766 patients diagnosed with Cutaneous Vasculitis from a single centre.
CV: Cutaneous vasculitis; CTD: Connective Tissue Diseases; EMC: Essential Mixed Cryoglobulinaemia; WG: Wegener Granulomatosis; CSS: Churg-Strauss Syndrome; PAN: Panarteritis nodosa; ACR: American College of Rheumatology; HSP: Henoch-Schönlein Purpura; HV: Hypersensitivity Vasculitis; NC: Not Classified.
*A patient presented with urticarial vasculitis associated with an underlying malignancy and it was included in both groups.
**4 patients with Microscopic Polyangiitis were included in the group of Panarteritis Nodosa following ACR-1990 criteria.

Discussion

This study highlights the problems associated with the use of classification criteria to make a diagnosis of patients with CV. Certainly, rheumatic diseases often lack of pathognomonic signs, and the vasculitides are not an exception. The shortcomings of the methods for classification, diagnosis and definitions for the vasculitides affect both clinicians and researchers. Therefore, the ACR made great efforts to achieve the characterisation and classification of different vasculitides. Nevertheless, it is worth mentioning that the ACR 1990 criteria were not intended originally to be diagnostic tools. In this context Rao *et al*. (14) reported that patients who did not have vasculitis could, however, fulfill one or more sets of the ACR 1990 classification criteria.

In keeping with these observations, approximately 20% of the patients from our series that fulfilled the ACR 1990 classification criteria for HSP (6) did not met the Michel *et al*. criteria (13) and vice versa. These differences are probably due to the fact that renal involvement was not included in classification criteria for HSP included in the ACR 1990 set (6). In contrast, the criteria proposed by Michel *et al*. are focused on the presence of typical manifestations of HSP such as abdominal manifestations (gastrointestinal bleeding and bowel angina) and renal involvement manifested by haematuria (13). Therefore, we feel that the criteria put forward by Michel *et al*. may more useful in the daily clinical practice (13). Taking into account preexisting classification criteria and considering that skin biopsy is often not performed, in particular in children, the Pediatric Rheumatology European Society (PReS) with the endorsement of the European League against Rheumatism (EULAR) published new criteria for HSP based on a Delphi consensus in 2006 (15). The criterion of age was removed, and the experts reached consensus to define HSP if there was purpura or petechiae not related to thrombocytopenia with lower limb predominance (mandatory criterion), and at least one of the following four manifestations: abdominal pain, arthritis or arthralgia, renal involvement (haematuria and/or proteinuria), and leucocytoclastic vasculitis with predominant IgA deposit in a skin or kidney biopsy.

Differentiating HSP from HV is of clinical relevance due to the frequent systemic manifestations associated with HSP (11, 12, 16). On the other hand, HV is often a disorder usually confined to the skin (17). With respect to this,

the 2012 Revised International Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitides included many patients that would fulfill definitions for HV within the group of "Single organ Cutaneous Small-Vessel Vasculitis" (5). This entity is equivalent to the previously defined in 1994 by the Chapel Hill International Consensus Conference as "cutaneous leukocytoclastic angiitis" (18).

Besides new strategies to better characterise subtypes of patients with CV, it would be desirable to search for novel biomarkers able to distinguish between HSP and HV. With respect to this, there are some genetic data showing differences between HSP and HV. While some polymorphisms, such *MIF* (-173 G/C), do not appear to be genetic risk factors for either HSP or HV (19), others have been found of potential help to discriminate HSP from HV. In this regard, HSP and HV limited to skin (called cutaneous leukocytoclastic angiitis according the 1994 International Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitides (18)) exhibit different *HLA-DRB1* genotype association (20). *HLA-DRB1**01 is increased and *HLA-DRB1**07 reduced in HSP patients compared to controls (21). *HLA-DRB1**15/16 and especially of *HLA-DRB1**07 are increased in patients fulfilling definitions for HV limited to skin when compared to those with HSP (20). A significant association between the carriage of *IL-1 receptor antagonist allele 2* and severe renal involvement, manifested as nephrotic syndrome and/or renal insufficiency, was found in patients with HSP but not in those with HV limited to skin (22). Moreover, in unselected patients with CV, the polymorphism of *IL8* gene was associated with susceptibility to renal involvement in the context of HSP (23).

In summary, our analysis confirms the frequent overlap between the ACR 1990 classification criteria and the criteria proposed by Michel *et al*. in patients with CV.

Further studies are needed to better define the complex group of conditions presenting with CV.

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