Etiology of cutaneous vasculitis: utility of a systemic approach

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Abstract

Cutaneous vasculitis (CV) represents a diagnostic challenge, occurs as primary cutaneous disorder or as a manifestation of other entities. **Objective:** To search the cause of CV. **Methods:** Patients with CV were prospectively evaluated. In all patients, skin biopsies were drawn, and direct immunofluorescence was done in most of the patients. American College of Rheumatology (ACR) and Chapel Hill Consensus Conference Criteria (CHCC) were used for classification. **Results:** 32 patients were studied. There was female predominance (71.8%). Children presented drug-associated CV or Schönlein-Henoch purpura (SHP). Adults presented more frequently SHP, systemic lupus erythematosus or paraneoplastic vasculitis, other diagnosis as polyarteritis nodosa, microscopic polyangiitis, thrombotic vasculitis (post-puerperal), antiphospholipid syndrome, Churg-Strauss syndrome, and drug-associated CV were presented. Using the ACR and CHCC criteria, 50% of cases were classified. **Discussion:** In our institution, during this work the etiologic diagnostic of CV increased more than twice. However, in the case of HSV and SHP none of the proposed criteria had high specificity; other parameters were used to discern between both. Six patients remained as not classified. In our view, cryoglobulins and hepatitis serology do not seem useful unless patient's history supports they need to be done. Unclassified patients were followed-up closely for 2 years.

KEY WORDS: Cutaneous vasculitis. Vasculitis. Purpura. Lupus. Rheumatic disease.

Introduction

Vasculitis is a clinicopathological process characterized by blood vessel inflammation and necrosis, which entails their occlusion and causes tissue ischemia^{1,2}. Cutaneous vasculitis (CV) etiologic diagnosis constitutes a challenge, since it can be primary or early manifestations of different systemic diseases such as systemic necrotizing vasculitis, connective tissue diseases (systemic lupus erythematosus [SLE], systemic infections or neoplasms³⁻⁵. The skin offers an opportunity for diagnosis, since it is an accessible source for anatomopathological study⁶.

CVs are classified based on clinical and histological data using the American College of Rheumatology (ACR) criteria since 1990⁷ and the Chapel Hill Consensus Conference (CHCC) criteria issued in 1992 (revised in 2012)⁸; although these classifications are not entirely satisfactory, they continue to be used in clinical practice⁹. Vasculitides are grouped according to the affected vessel size as: a) large vessel vasculitis, which includes giant cell arteritis and Takayasu arteritis¹⁰; b) medium vessel vasculitis, such as polyarteritis nodosa (PAN), cutaneous PAN and Kawasaki's disease¹¹; and c) small vessel vasculitis, which can be granulomatous such as granulomatosis with

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polyangiitis, formerly known as Wegener granulomatosis¹², and eosinophilia with polyangiitis, also known as Churg-Strauss Syndrome (SCS)¹³; and non-granulomatous, which include microscopic polyangiitis (MPA)¹⁴, Schönlein-Henoch purpura (SHP)¹⁵, cutaneous leukocytoclastic vasculitis (LCV)¹⁶ and essential cryoglobulinemia¹⁷.

Vasculitis etiologic factors are diverse and include infectious agents (15-20%), inflammatory conditions (15-20%), medications (10-15%) and neoplasms (5%), with 45-55% of cases not having an etiologic diagnosis^{5,18-20}. In tertiary care referral centers, SLE-associated vasculitides occur more often in adult patients²¹. Vasculitis clinical diagnosis must be confirmed by anatomopathological study, where loss of vascular architecture is observed, caused by wall infiltration by neutrophils, lymphocytes or histiocytes; the presence of fibrinoid necrosis is characteristic²². Direct immunofluorescence can be positive in blood vessels in specific etiologies the direct immunofluorescence can be positive in blood vessels and is useful to classify and confirm the presence of vasculitis and to identify the type of immunoglobulin (Ig) deposited on the vascular wall²³; for example, the presence of IgA is associated with SHP, while IgM can be observed in cryoglobulinemic vasculitis.

CVs account for 0.13% of outpatient consultations at Dermatology department of General Hospital "Dr. Manuel Gea González". However, there was no diagnostic protocol for these patients focused on determining the etiology. In previous years, etiology was diagnosed in 25% of cases. Therefore, the purpose of this work was to define CV etiologic diagnosis in a general hospital during a 2-year period, and to increase the percentage of etiologic diagnosis. In this study, both previously-mentioned classifications were applied (Table 1)^{24,25}.

Method

Children and adults with clinical and anatomopathological diagnosis of CV, who attend to dermatology department of General Hospital "Dr. Manuel Gea González" during a 2-year period were included. To be incorporated in the study, patients or their legal guardians signed an informed consent form. The study protocol was approved by the institutional ethics and research committee, and for the performance of biopsy and sample taking, the principles of the Declaration of Helsinki were followed. Patients were prospectively studied, with assessment including a detailed clinical

Figure 1. Palpable purpura in an adult patient diagnosed with Schönlein-Henoch purpura.

evaluation and physical examination. Two samples of the skin lesions were obtained by means of a 4-mm punch biopsy technique, one for staining with hematoxylin and eosin and another for direct immunofluorescence (DIF). Complementary tests were requested, including: blood count, erythrocyte sedimentation rate, blood chemistry, general urine test, fecal occult blood (stool guaiac test), serum creatinine, coagulation times, total immunoglobulin (IgA, IgG, IgM), rheumatoid factor, anti-nuclear auto-antibodies (ANA), anti-neutrophil cytoplasm antibodies (ANCA), anti-myeloperoxidase (MPO) and anti-proteinase 3 (PR-3), cryoglobulins, anti-phospholipids, IgG, IgA, IgM, C3 and C4 complement, as well as serology for hepatitis B and C. The ACR and CHCC criteria were used to define etiologic diagnosis. Final operational diagnosis was established by consensus between observers at the conclusion of the diagnostic protocol.

Forty-four patients with clinical diagnosis of CV were initially included in the protocol, out of which 12 were eliminated: in 8 patients, vasculitis was not found by histopathologic study, two pediatric patients were diagnosed with thrombocytopenic purpura, other patient had systemic large vessel vasculitis without CV and, finally, one patient refused to participate in the protocol.

Results

Of a total of 44 patients with clinical diagnosis of vasculitis, 5 children and 27 adults were included. Predominance was observed in the female gender (71.8% vs. 28.2%). The mean age at diagnosis was 37.75 years (range: 6-73 years). Children were 6, 8, 13 (2 patients) and 17 years' old. Clinical manifestations predominated in the lower limbs (69%) and the trunk, with varied morphology, and with palpable purpura (69%) and erythematopurpuric maculae (60%) being more common (Fig. 1). Some patients had ulcers (16%) and nodosities (6%).

Table 1. Vasculitis name and definition adopted by the CHCC and the ACR (modified from Carlson *et al.* 2005)

	Chapel Hill Consensus Conference	American College of Rheumatology
Large vessel vasculitis		
Temporal arteritis	Granulomatous arteritis of the aorta or its major branches (intracranial) Often involves the temporal artery Patients older than 50 years	50 years Headache Abnormal temporal artery on physical Elevated erythrocyte sedimentation Temporal biopsy shows vasculitis
Takayasu arteritis	Granulomatous inflammation of aorta or its major branches Usually in patients younger than 50 years	Patients younger than 40 years Claudication Arterial pulse decrease Blood pressure difference >10 mmHg between arms Abnormal arteriogram
Medium vessel vasculitis		
Polyarteritis nodosa	Necrotizing inflammation of the medium and small vessels without glomerulonephritis	Weight loss larger than 4 kg Livedo reticularis Testicular pain or hypersensitivity Myalgia, myopathy Neuropathy Hypertension (diastolic >90 mmHg) Kidney involvement Abnormal arteriography Neutrophils observed in biopsy
Kawasaki disease	Arteritis that affects large, medium and small vessels Associated with the mucocutaneous lymph node syndrome	
Small vessel vasculitis		
Polyangiitis with granulomatosis (Wegener granulomatosis)	Granulomatous lesions can affect the respiratory tract, granulomatous vasculitis that affects medium and small caliber vessels	Nasal or oral inflammation, presence of nodules, infiltrate or cavitations in chest X-ray Microscopic hematuria Granulomatous inflammation in biopsy
Churg-Strauss syndrome	Eosinophil-rich granulomatous inflammation that affects the respiratory tract Necrotizing vasculitis that affects small and medium vessels and is associated with eosinophilia and asthma	Asthma Eosinophils >10% Neuropathy Pulmonary infiltrates Extravascular eosinophils in biopsy
Microscopic polyangiitis	Necrotizing vasculitis with few or no immune deposits that affects small vessels (capillaries, venules and arterioles) Glomerulonephritis Lung involvement	
Schönlein-Henoch purpura	Vasculitis with immune deposits, predominantly IgA, affecting small vessels (capillaries, venules and arterioles). Often affects the skin, intestine, glomerulus and can be associated with arthralgia or arthritis	Palpable purpura Patients younger than 20 years Intestinal angina Neutrophils on vascular wall observed in biopsy
Cryoglobulinemic vasculitis	Vasculitis with immune cryoglobulin deposits affecting small vessels and that is associated with the presence of serum cryoglobulins Skin and glomeruli are often involved	
Cutaneous leukocytoclastic vasculitis (hypersensitivity-associated vasculitis)	Isolated cutaneous angiitis in the absence of systemic vasculitis or glomerulonephritis	Patients older than 16 years Associated with medications Palpable purpura Rash Positive biopsy

ACR: American College of Rheumatology; CHCC: Chapel Hill Consensus Conference.

SHP was diagnosed in 4 patients, 3 adults and one child (13%), CV associated with connective tissue diseases occurred in 2 adult patients who were diagnosed with SLE (6%), whereas vasculitis secondary to medication ingestion or hypersensitivity vasculitis (HSV) occurred in one adult and two children (9%); 2 cases were associated with neoplasms, which were diagnosed after vasculitis onset. For each one of the next conditions PAN, MPA, anti-phospholipid syndrome (APS), SCS and thrombotic vasculitis) post-puerperal) one patient was diagnosis. Using ACR vasculitis criteria, 44% of patients were classified and 2 more using ACR criteria for SLE; therefore in 50% of patients, etiologic diagnosis was identified. The rest did not meet the criteria or there were no criteria for their condition. We found overlapping of SHP and HSV criteria in 12 cases, with other parameters being used to discern between these diagnoses in case of doubt. Of these, 50% had one or the other pathology, the rest were false positives (5 could not be classified, other was diagnosed as paraneoplastic syndrome during follow-up). Applying CHCC criteria, 50% of patients were classified without diagnostic overlapping; of the 12 patients with LCV initial diagnosis, in 3 of them was the diagnosis confirmed, with the rest being false positives (one paraneoplasm, 2 SHP and 6 patients could not be classified). No patient had cryoglobulinemia or hepatitis-positive serology for. Finally, 18 patients (57%) were classified with the CHCC criteria during the 2-year follow-up.

Discussion

In our institution, 12.4 patients are diagnosed with CV per year, which represents 0.13% of outpatient consultation, according to a review of medical records for a 6-year period. Previously, the rate of etiologic diagnosis in CV cases was 25%. In this study, an etiologic diagnosis was established in 57% of CV cases, which is similar to rates reported in other groups (51%)²⁶. On initial examination, 56% of patients were not classified, during de follow up two patients which represents 6%) received an etiologic diagnosis, the follow-up was carried out every 6 months during 2 years, which included laboratory tests and biopsy when it was required, which facilitated for an opportune diagnosis to be established and for systemic complications to be avoided.

CV was more common in females (71.8%), with a mean age of 37.75 years at onset. The most common diagnosis in children was HSV, although SHP is

generally considered the most common cause of vasculitis in children; however, in this case series this finding can be explained, since, in our hospital, children with SHP are referred to the pediatrics department, given that digestive, renal and articular symptoms are usually more severe than cutaneous lesions. In adults, the most common cause of CV was SHP, followed by SLE and cases associated with neoplasms. Previous studies reported a series of 160 cases with LCV where 10% of them were associated with collagen diseases, which was similar to that reported in our patients, while other series report up to 20%. CV occurred as palpable purpura in the lower limbs in 22/32 patients (68.7%); in other reports, 51% of patients with CV show this palpable purpura²⁷. Cutaneous ulcers as sole manifestation were found in 15.6%, including patients with the following diagnoses: PAN, APS and SLE, thus we consider that patients with lower limb ulcers who are not responsive to treatment should be studied in order to rule out CV.

In the laboratory tests, serum IgA was elevated in 14 patients; 2 with SHP, one case of drug-associated vasculitis, one with SLE and 10 with other diagnoses. SHP is a systemic vasculitis where IgA plays a preponderant pathophysiologic role and can be found on skin, kidney and intestinal vascular walls^{28,29}. However, serum IgA is not always elevated in these patients (only 22% of cases are positive) and ACR does not consider it to be a diagnostic criterion³⁰. Moreover, the presence of IgA on the vascular wall, detected by DIF, is regarded as a diagnostic criterion for SHP by CHCC.

In patients diagnosed with SLE and CV, ANA and the complement were found within normal limits, which can be explained because patients were receiving immunosuppressive treatment for SLE. However, we consider important for these tests to be performed during follow-up, especially in patients with lymphocytic vasculitis³⁰. ANCA's constitute an important test in the diagnosis of polyangiitis with granulomatosis, MPA and SCS. p-ANCA and MPO association has 99% specificity, with c-ANCA and PR-3 being similarly associated³¹⁻³³. Blanco et al. found that 30% of adult patients with CV had systemic vasculitis or an associated condition (pulmonary or renal involvement or mononeuritis); therefore, it is important for these tests to be carried out searching for the etiology of a CV⁵. With regard to DIF, performing a biopsy of the lesion is considered more appropriate than in perilesional skin, if tissue necrosis is not observed in the lesion²².

Figure 2. Flow diagram. ANA: anti-nuclear antibodies; ANCA: anti-neutrophil cytoplasmic antibodies; APA: antiphospholipid antibodies; BC: blood count; MPO: anti-myeloperoxidase; PR-3: proteinase 3; PT: prothrombin time; PTT: partial thromboplastin time.

The presence of IgA on the vascular wall is not pathognomonic, but it is highly sensitive (82%) and specific (73%) for LCV diagnosis, and it was associated mainly with the presence of SHP^{34,35}. Recently, a series of 8 cases was published where presence of IgA was found in lymphocytic vasculitis cases that were associated or not with SLE³⁶. The presence of IgM or IgG without IgA does not rule out LCV diagnosis, but it doesn't support it³⁴. In our cases we observed IgA on the vascular wall in 4 patients with SHP, while other patients exhibited IgM and C3 or negative DIF. These results may be explained by IgA lability, which rapidly disappears by proteolysis and phagocytosis in necrotic lesions. The presence of IgA on cutaneous vessels is associated with renal damage, but not with its severity^{37,38}.

It is difficult for CV diagnosis to be established by applying the ACR and CHCC criteria, especially in patients with SHP or HSV, as these classifications do not help to differentiate between both these entities. DIF with IgA present on blood vessels can be of help in some cases. This problem is explained because ACR criteria were designed based on series of clinical, laboratory and histopathologic tests that determined the

most sensitive and specific characteristics for the different types of vasculitis, but they are not always helpful to differentiate between two diagnostic possibilities.

Evidence in this case series indicates that in the Mexican population, unlike other populations, cryoglobulins and hepatitis B and C are not useful as initial tests, unless patient medical history suggests so.

Conclusions

ACR criteria are currently not entirely consistent with the definitions of specific conditions and they don't always allow an accurate diagnostic approach. On the other hand, 1994 CHCC provides definitions of the causes of vasculitis and includes the use of some markers when histologic study is not available. CHCC definitions were revised in 2012⁸, with the purpose to incorporate new terminologies; however, CHCC delivered a nomenclature rather than a classification. In this context, we consider that inclusion of tests such as ANCA facilitates the diagnostic approach^{31,32,39}. According to our findings, we propose the study protocol shown in figure 2 for patients with vasculitis.

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