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Hypersensitivity vasculitis in adults: A benign disease usually limited to skin

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ABSTRACT

Objectives. *To examine the clinical spectrum of hypersensitivity vasculitis (HV) inan unselected population of adults and establish differences between patients with HV limited to the skin and those with systemic involvement.*

Methods. *Retrospective study of adult patients (>20 years) with biopsy-proven cutaneous leukocytoclastic vasculitis diagnosed as having HV, who were seen at the single hospital serving a well defined population between 1984 and 1998. Patients were classified as having HV according to the criteria of Michel et al. (9). To examine outcome and relapses of the disease only those patients with a follow-up of at least 1 year were included in this study.*

Results. *64 patients with a mean follow-up of 4.9 ± 3.5 (range: 1.1 - 13.6) years were studied. Ten (15.6%) had visceral involvement (3 gastrointestinal and 7 renal manifestations) during the course of the disease. The remaining patients had a leukocytoclastic vasculitis limited to the skin. When the study was concluded persistent hematuria and proteinuria was only observed in 1 patient and none developed renal insufficiency. Patients with a history of drug treatment and elevated ESR had more systemic complications but the difference was not statistically significant. The outcome was excellent in both patients with HV limited to the skin and in those with systemic complications during the course of the disease.*

Conclusions. *In unselected adults HV is generally a benign disease confined exclusively to the skin. In those patients with systemic manifestations, visceral involvement is generally mild and transient.*

Introduction

Hypersensitivity vasculitis (HV) is a disease that includes prominent involvement of the skin and frequently appears to be precipitated by the use of medications. Pathologically, the disease tends to involve the small vessels, characterized by leukocytoclastic angiitis (1). Hypersensitivity vasculitis is not uncommon in adults (2). In the most recent studies its outcome has been excellent (3-5). However, an important matter of concern for the clinician who often sees patients with HV is the establishment of clinical features that may be useful in discriminating patients with isolated cutaneous HV from those with systemic involvement. To do so we examined an unselected series of patients with cutaneous vasculitis seen in a single referral hospital.

Patients and methods

A retrospective study was conducted of the case records of all adult patients diagnosed with cutaneous vasculitis in the Hospital Xeral-Calde (Lugo, Spain) from January 1984 through December 1998. The main characteristics of the Lugo population have been reported elsewhere (2,3,5,6). Hospital Xeral-Calde is the single referral center for a mixed rural (60%) and urban population of approximately 250,000 people living in the Lugo region of northwestern Spain.

Patients were included if they had a skin biopsy consistent with cutaneous leukocytoclastic vasculitis. Patients more than 20 years of age were considered as adults (2, 3, 7-9). As described in earlier studies on cutaneous vasculitis (4, 10), the pathologists from Lugo did not routinely perform immunofluorescence-staining studies on the skin biopsies. For this reason, the following classification criteria were used.

Case histories of all biopsy-proven adult patients who fulfilled the American College of Rheumatology (ACR) criteria for HV or Henoch-Schönlein purpura (HSP) were reviewed (1, 8). Then the HV and HSP patients were separated using the criteria proposed by Michel *et al*. (9). According to their format, primary cutaneous vasculitis could be classified as HV if it fulfilled less than 3 of the following criteria: 1) cutaneous palpable purpura, 2) bowel angina, i.e. abdominal pain that worsened after meals or bowel ischemia usually including bloody diarrhea, 3) gastrointestinal bleeding, i.e. melena, hematozechia or a positive test for occult blood in the stool, 4) gross hematuria or micro-hematuria, 5) age at disease onset ≤ 20 years, and 6) absence of medications. Adults with cutaneous leukocytoclastic vasculitides other than HV were excluded. If the Chapel Hill Consensus Conference (CHCC) defini-

tions had been used, a few patients who were classified as HV according to Michel *et al*. would have also fulfilled the CHCC definitions for microscopic polyangiitis (11). However, at the end of this study only one of them had persistent hematuria and proteinuria.

Between December 1999 and February 2000 adults with HV who had less than 1 year's follow-up were asked to attend the hospital for further evaluation (clinical history, focusing particularly on relapses, and laboratory analyses including full blood cell count and routine blood and urine biochemistry tests). Those patients with less than 1 year's follow-up who did not attend the hospital for further evaluation were excluded. Partial information about the adults with HV diagnosed between 1988 and 1997 has recently been reported (2, 3).

Clinical definitions

Clinical definitions were the same as those described for patients diagnosed with HV between 1988 and 1997 (3). Briefly, precipitating events were considered to be present if prior to the onset of vasculitis there was a history of drug treatment and/or infection [most of them involving the upper respiratory tract (URT) in which treatment for the infection did not resolve the vasculitis]. To increase the evidence for causality between precipitating events and the development of HV, drugs had to have been taken or the URT infection must have occurred within a week before the onset of HV (3). Fever was considered to be present if the temperature was > 37.7ºC.

Nephritis was defined as previously reported (2,3,12,13): mild nephropathy if hematuria (≥ 5 red blood/hpf) and/or proteinuria (> 300 mg/24 hours) without nephrosis was present; severe nephropathy if nephrotic syndrome (i.e. 1 g/day/m^2 body surface area or > 3.5 g/day proteinuria with plasma albumin ≤ 25 g/l), with or without edema and/or acute nephritic syndrome (i.e. hematuria with at least two of the following: hypertension, raised plasma urea or creatinine and oliguria) was present. Renal insufficiency if the plasma creatinine concentration was above 125% of the upper limit of normal. Joint manifestations if patients complained of well defined arthralgia or if synovitis was observed on examination (3). Gastrointestinal manifestations included bowel angina and gastrointestinal bleeding (3, 9). Anemia: hemoglobin < 11 gm/dl; leukocytosis: white blood cell count > 11,000/ mm^3. Raised erythrocyte sedimentation rate (ESR) (Westergren): values > 15 mm/1st hr in men and 20 mm/1st hr in women. Increased serum IgA: values > 450 mg/dl. Relapse if a patient diagnosed with HV and asymptomatic for at least 1 month presented again a new flare of skin lesions or other systemic complications (3, 12).

Statistical analysis

Continuous data were expressed as the means ± standard deviation (SD), and categorical variables as percentages. Comparisons were made using Student's t-test for continuous variables. To analyze the categorical data we performed the chi square test or Fisher's exact test when the minimum expected value was less than five. Statistical significance was defined as $p \leq 0.05$. Calculations were performed using the statistical package Stata Intercooled, version 6.0 (Stata Corporation, College Station, TX, USA).

Results

Clinical features and etiological factors in HV patients

Between 1984 and 1988 73 patients older than 20 years met the criteria proposed by Michel *et al*. for HV and 33 for HSP. Patients with HSP were not considered in this study. Among the group of patients with HV, 9 of them had less than a 12-month follow-up and, due to this, they were also excluded from the study.

The main epidemiological features of the 64 patients with HV and a follow-up of at least 12 months are shown in Table I. Men outnumbered women and the median onset of HV was 61 years. No seasonal pattern was observed. A history of drug treatment prior to the onset of HV was found in almost 50% of the cases. As expected, skin lesions were the most frequent clinical manifestation at disease onset. Joint manifestations were not uncommon. However, at the onset of the disease gastrointestinal and renal manifestations were only observed in 3 and 6 patients, respectively (Table II). The limited inflammatory response in most patients was correlated with the presence of normal ESR in 40% of the patients. Although complete data on anti-neutrophil cytoplasmic antibodies (ANCA) were not available, because some cases

Table I. Epidemiological data and etiological factors in 64 biopsy proven adults (> 20 years) with hypersensitivity vasculitis and a follow-up of at least 12 months.

Age (years)	
Mean age ± SD	57.5 ± 17.6
range	21-83
median	61
Sex (men/women)	40/24
proportion of men	62.5
Seasonal pattern	
summer	15 (23.4)
fall	15 (23.4)
winter	20 (31.3)
spring	14 (21.9)
Etiological factors	
Unknown	32 (50.0)
Upper respiratory tract infection	11 (17.2)
Drugs	31 (48.4)

( ): Data expressed in percentages.

Table II. Initial manifestations (at the onset of the disease) and routine laboratory data at the time of diagnosis in 64 adults (> 20 years) with hypersensitivity vasculitis and a follow-up of at least 12 months.

Skin lesions	64 (100.0)
Joint manifestations	19 (29.7)
Fever	6 (9.4)
GI manifestations	
bowel angina	3 (4.7)
G-I bleeding	0 (0.0)
Renal manifestations*	
hematuria	4 (6.3)
proteinuria	2 (3.1)
renal insufficiency	0 (0.0)
Leukocytosis	7 (10.9)
Anemia	4 (6.3)
Increased ESR	38 (59.4)
Increased serum IgA	12/49 (24.5)
Positive RF	4/59 (6.8)
Positive ANA	0/55 (0.0)
Cryoglobulins	0/43 (0.0)
Low C3	0/49 (0.0)
Low C4	3/49 (6.1)

*Hematuria (≥ 5 red blood/hpf) and/or proteinuria (> 300 mg/24 hours). Renal insufficiency: plasma creatinine concentration above 125% upper limit of normal (2, 3, 12, 13).
no. positive/no. tested. ( ):Data expressed in percentages.

Table III. Clinical features in 64 adults (> 20 years) with hypersensitivity vasculitis during the clinical course of the disease.

Predominant skin lesion	
palpable purpura	50 (78.1)
maculo-papular rash	11 (17.2)
urticarial rash	3 (4.7)
Location of skin lesions	
upper extremities	18 (28.1)
trunk	11 (17.2)
lower extremities	64 (100.0)
Joint manifestations	19 (29.7)
arthralgia without arthritis	12 (18.8)
monoarthritis	2 (3.1)
oligoarthritis	5 (7.8)
Gastrointestinal manifestations	3 (4.7)
bowel angina	3 (4.7)
Gastrointestinal bleeding	0 (0.0)
Renal involvement	
0 None	57 (89.1)
1 Mild #	6 (9.4)
2 Severe §	1 (1.6)
3 Renal insufficiency*	0 (0.0)

Mild nephropathy: hematuria (≥ 5 red blood/hpf) and/or proteinuria (>300 mg/24 hours) without nephrotic range.
§ Severe nephropathy: nephrotic syndrome (i.e. 1g/day/m^2 body surface area or >3.5 g/day proteinuria with plasma albumin ≤ 25 g/l), with or without edema and/or acute nephritic syndrome (i.e. hematuria with at least two of the following: hypertension, raised plasma urea or creatinine and oliguria).
* Renal insufficiency: plasma creatinine concentration above 125% upper limit of normal (2,3,12,13). ( )= Data expressed in percentages.

Table IV. Outcome of biopsy-proven adults with hypersensitivity vasculitis and a follow-up of at least 12 months.

Follow-up (years)	
Mean ± SD	4.9 ± 3.5
range	(1.1-13.6)
Relapses	
Number of patients	8 (12.5)
Median of relapses#	2.0
Mean ± SD#	1.75 ± 0.71
range#	1-3
Complete recovery	63 (98.4)
Persistent hematuria and proteinuria	1 (1.6)
Renal insufficiency	0 (0.0)

Based on the patients who suffered at least one relapse. ( ): Data expressed in percentages.

were diagnosed before the ANCA test was routinely available and also because the methodology has changed during the course of the study period, ANCA (indirect immunofluorescence on alcohol fixed neutrophils) were negative in the 9 patients in whom they were tested. Antinuclear antibodies were negative in the cases on whom they were tested. Also, although in a small number of cases rheumatoid factor was positive and C4 serum levels were decreased, none of these patients had positive cryoglobulins (Table II).

Clinical features during the course of the disease are summarized in Table III. All patients developed skin lesion in the lower extremities. In most patients palpable purpura was the predominant cutaneous manifestation. However, predominant maculo-papular or, less commonly, urticarial rash were observed in 22% of the patients. Systemic manifestations were only observed in 10 patients (15.6%). Gastrointestinal manifestations presented as bowel angina occurred early in the course of the disease in 3 of the 64 patients. Also, during the course of the disease, mild renal disease was found in 9% of patients and 1 of the 64 developed severe renal involvement but none of them progressed to renal insufficiency.

Outcome of adult HV patients

Adults with HV had a benign disease. With respect to this, after a mean follow-up of 4.9 years only 8 (12.5%) patients had suffered relapses (Table IV). Such relapses were mainly characterized by the presence of new flares of cutaneous lesions. Drug treatment was associated with relapses in 3 of the 8 patients. When this study was concluded, persistent hematuria and proteinuria was only observed in one patient, in whom a renal biopsy showed glomerulonephritis with IgG and IgM immunofluorescence staining deposits in the mesangium.

Table V. Epidemiological differences between biopsy-proven adult HV adult patients (> 20 years) with and without systemic manifestations after a follow-up of at least 1 year.

	With systemic manifestsations	Without	p
Number of patients	10/64 (15.6%)	54/64 (84.4%)	
Mean age ± SD	58.9 ± 14.4	57.3 ± 18.3	0.39
Sex (men/women)	8/2	32/22	0.21
Proportion of men	80.0	59.3	
Seasonal pattern			
Summer	2 (20.0)	13 (24.1)	0.78
Fall	3 (30.0)	12 (22.2)	0.59
Winter	3 (30.0)	17 (31.5)	0.93
Spring	2 (20.0)	12 (22.2)	0.83
Etiological factors			
URT* infection	1 (10.0)	10 (15.6)	0.51
Drugs	7 (70.0)	24 (44.4)	0.14

URT*= upper respiratory tract. ( ): Data expressed in percentages.

Table VI. Clinical and laboratory differences during the course of the disease between biopsy-proven hypersensitivity adult patients (> 20 years) with and without systemic manifestations after a follow-up of at least 1 year.

	With systemic manifestations	Without	p
Number of patients	10/64 (15.6%)	54/64 (84.4%)	
Arthralgia without arthritis	2 (20.0)	10 (18.5)	0.91
Arthritis	1 (10.0)	6 (11.1)	0.90
Patients with leukocytosis	1 (10.0)	6 (11.1)	0.90
Patients with anemia	0 (0.0)	4 (7.4)	0.37
Increased ESR	8 (80.0)	30 (55.6)	0.21
Relapses	1 (10.0)	7 (13.0)	0.80

Leukocytosis was defined as a leukocyte count ≥ 11,000/mm^3, anemia as hemoglobin < 11 gm/dl, and the erythrocyte sedimentation rate (ESR) was considered to be elevated if values were > 15 mm/1st hour in men and >20 mm/1st hour in women. ( ): Data expressed in percentages.

Differences between patients with and without systemic manifestations

No differences in age at disease onset or gender were found. However, in those patients with systemic manifestations a history of medication prior to the onset of vasculitis was more common. In this respect, 7 of 10 (70%) adults with renal or gastrointestinal complications had taken medication within 1 week prior to the onset of the disease

versus 24 of 54 (44%) with HV limited to skin. However, this difference did not achieve statistical significance (p = 0.14) (Table V). Relapses were not more common in those with systemic manifestations. The ESR was found to be more commonly elevated in those patients who developed renal or gastrointestinal complications but the difference was not statistically significant (8/10 versus 30/54; p=0.21) (Table VI).

Discussion

The present study is an extension of our previous study and confirms that in most cases, based on the criteria of Michel *et al.* (9), HV in adults is a disease limited to skin with few systemic complications and an excellent outcome. Similar results were also observed by Martínez-Taboada *et al.* (4). However, our study has the additional advantage of a longer follow-up and the inclusion of biopsy-proven leukocytoclastic vasculitis patients only. In keeping with Martínez-Taboada *et al.* the proportion of patients from Lugo classified as having HV who developed renal sequelae was negligible. As reported in the ACR series of HV (1, 9), adults from Lugo with HV also had a frequent history of drug treatment shortly before the onset of the vasculitis. In both series, antibiotics were the most frequently taken drugs and palpable purpura was the most common clinical manifestation. However, unlike the ACR series (1, 9), in our patients gastrointestinal manifestations were uncommon and severe manifestations such as macroscopic bleeding or perforation were not observed. Likewise, in the ACR series renal complications were more frequently observed. Explanations for the differences observed in the severity of the vasculitis between the Lugo series and that from the ACR may be due to high physician awareness of these syndromes among the general practitioners in our area, as all patients with suspected CV are sent to the hospital. Also, the singular and special characteristics of our health system in which patients frequently self-refer to the emergency unit of our hospital without a previous visit to their general practitioners may allow us to see patients with mild disease that in most cases fulfill the classification criteria for HV. In addition, the frequency of systemic complications in the ACR group have probably been overestimated due to the bias of referral to tertiary care facilities.

In our unselected series of adults with biopsy-proven HV a history of drug treatment before the onset of the vasculitis was more common in patients with systemic complications. Such a trend has also been observed by Blanco *et al.* in a retrospective series of 133 HV patients (14). However, unlike these authors, in our series the absence of statistical differences related to a previous history of drug treatment between patients with and without systemic complications may be due to our patient selection method, as only adults with biopsy-proven leukocytoclastic vasculitis and a follow-up of at least 1 year were included.

There has been much controversy regarding the classification criteria for the vasculitides (15-17). In this respect, the term hypersensitivity vasculitis is no longer used by the CHCC in the Nomenclature of Systemic Vasculitis (11). Following the recommendations of these authors, the majority of our patients diagnosed as having HV would fall into the category of cutaneous leukocytoclastic angiitis, a vasculitis restricted to the skin without involvement of vessels in any other organ, and a few of them into the group of microscopic polyangiitis. These results support the concept of a benign disease limited to the skin in most cases.

In conclusion, in unselected adults with biopsy-proven HV classified according to the differential criteria proposed by the ACR vasculitis subcommittee, this vasculitic syndrome is usually limited to skin with few systemic complications and a good outcome.

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