Drug-associated Cutaneous Vasculitis: Study of 239 Patients from a Single Referral Center

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ABSTRACT. ***Objective.*** The 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides defined drug-associated immune complex vasculitis as a distinct entity included within the category of vasculitis associated with probable etiology. In the present study we assessed the clinical spectrum of patients with drug-associated cutaneous vasculitis (DACV).

Methods. Case records were reviewed of patients with DACV treated at a tertiary referral hospital over a 36-year period. A diagnosis of DACV was considered if the drug was taken within a week before the onset of the disease.

Results. From a series of 773 unselected cutaneous vasculitis cases, 239 patients (30.9%; 133 men and 106 women; mean age 36 yrs) were diagnosed with DACV. Antibiotics (n = 149; 62.3%), mainly β-lactams and nonsteroidal antiinflammatory drugs (NSAID; n = 24; 10%) were the most common drugs. Besides skin lesions (100%), the most common clinical features were joint (51%) and gastrointestinal (38.1%) manifestations, nephropathy (34.7%), and fever (23.8%). The most remarkable laboratory data were increased erythrocyte sedimentation rate (40.2%), presence of serum cryoglobulins (26%), leukocytosis (24.7%), positive antinuclear antibodies (21.1%), anemia (18.8%), and positive rheumatoid factor (17.5%). Despite drug discontinuation and bed rest, 108 patients (45.2%) required medical treatment, mainly corticosteroids (n = 71) or immunosuppressive drugs (n = 7). After a median followup of 5 months, relapses occurred in 18.4% of patients, and persistent microhematuria or renal insufficiency in 3.3% and 5%, respectively.

Conclusion. DACV is generally associated with antibiotics and NSAID. In most cases it has a favorable prognosis, although a small percentage of patients may develop residual renal damage. (J Rheumatol First Release Sept 15 2014; doi:10.3899/jrheum.140390)

Key Indexing Terms:
CUTANEOUS VASCULITIS DRUGS HYPERSENSITIVITY VASCULITIS
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The term "cutaneous vasculitis" (CV) defines a heterogeneous and wide group of conditions characterized by skin small-vessel inflammation and necrosis. Although skin biopsy is the main tool for the diagnosis of CV, it is not routinely done in typical cases of pediatric CV. When performed, the most common histopathologic finding is a leukocytoclastic vasculitis due to immune complex deposition or type III hypersensitivity reactions[1,2,3,4].

CV may be an idiopathic entity or possibly be associated with several factors, such as infections, drugs, neoplasms, or connective tissue disorders[4,5,6,7,8,9,10,11,12,13,14].

The potential role of drugs in the development of CV has generally been discussed in the setting of hypersensitivity vasculitis[13,15,16,17]. Information specifically focused on patients with drug-associated CV (DACV) is scarce[13]. In most cases it is the result of description of single case reports[18] or small series[19,20,21,22,23] that basically described an adverse event related to a certain drug. Nevertheless, in the revised nomenclature of the 2012 International Chapel Hill Consensus Conference, drug-associated immune complex vasculitis was considered a distinct entity included in the group of vasculitides associated with probable etiology[24]. In light of these considerations, in the present

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study we assessed the clinical spectrum of patients with DACV.

MATERIALS AND METHODS

Patients. We reviewed the clinical records of all patients diagnosed with CV between January 1976 and January 2012 at a tertiary referral center for 350,000 people in northern Spain. The diagnosis of CV was based on either a skin biopsy showing characteristic histological findings of vasculitis, or typical nonthrombocytopenic palpable purpura.

Methods were similar to those reported elsewhere[13,25]. Briefly, patients with CV were classified according to the American College of Rheumatology (ACR) criteria[26]. Henoch-Schönlein purpura (HSP) was diagnosed according to the criteria proposed by Michel, *et al*[27]. Patients were excluded if they had vasculitis due to major infections such as endocarditis or pneumonia. DACV was considered present when the patient had been exposed to a new drug within a week prior to the onset of CV[12,13,15].

Clinical and laboratory definitions. Patients older than 20 years were considered adults. This cutoff age was already chosen as a criterion for HSP by the ACR committee[28] because this age allowed discriminating HSP from hypersensitivity vasculitis in previous studies[27]. In our study, the cutoff point of 20 years of age was chosen to differentiate subgroups of patients, defining them as children or adults following the ACR 1990 classification criteria[26], because HSP in adults appears to be a more severe disease with a higher risk of renal sequelae than in younger individuals[29,30,31]. Therefore, patients with CV fulfilling criteria for HSP were not excluded from the present study. Fever was defined as an axillary temperature > 37.7ºC. Constitutional symptoms included asthenia and/or anorexia, and weight loss of at least 4 kg. Joint symptoms included arthralgia and/or joint effusion. Gastrointestinal (GI) manifestations included bowel angina (diffuse abdominal pain worsening after meals), GI bleeding (melena, hematochezia, or positive stool guaiac test), nausea, and vomiting. Nephropathy was categorized as mild or severe. Mild nephropathy was defined by the presence of microhematuria (≥ 5 red cell/hpf) without fulfilling the criteria for nephritic syndrome, and/or nonnephrotic proteinuria. Severe nephropathy was defined by the presence of nephrotic syndrome (plasma albumin levels ≤ 25 g/l and either 1 g of proteinuria/day/m^2 of body surface area in children, or > 3.5 g/day in adults), or nephritic syndrome (hematuria with at least 2 of the following: hypertension, increased plasma urea or creatinine levels, and oliguria). Renal insufficiency was defined as a serum creatinine level above 125% of the upper limit of normal. Anemia was defined as a hemoglobin level ≤ 11 g/dl, leukocytosis if the white blood cell count was ≥ 11,000/mm^3, and leukopenia if it was < 3000/mm^3. Erythrocyte sedimentation rate (ESR) was considered elevated when it was higher than 15 or 20 mm/h for men or women, respectively. Pharmacological treatment was started in case of persistent skin lesions or visceral involvement, including severe abdominal pain, GI bleeding, or nephropathy. Relapse was defined as a new flare of cutaneous lesions in a patient asymptomatic for at least 1 month.

Data collection and literature review. Besides epidemiologic and clinical features, laboratory studies, including complete blood cell count, coagulation tests, liver and renal function tests, ESR, and urinalysis were performed at the time of diagnosis in most adults. Also, an immunological profile was performed in most adults but in only a minority of children. It included rheumatoid factor, antinuclear antibodies, serum levels of C3 and C4 complement fractions, and serum cryoglobulins. Antineutrophil cytoplasmic antibodies (ANCA) were measured only in patients studied since 1990. Other tests were performed only when indicated, based on the judgment of the attending physician, such as anti-nDNA antibodies, blood cultures, stool guaiac test, bone marrow biopsy, hepatitis B or C serology, human immunodeficiency virus infection serology, and chest radiograph.

Data on clinical, laboratory, and histopathologic features, etiology, treatment, and outcome were obtained from the clinical charts according to a prespecified protocol, and then stored in a computerized database. To minimize entry error, all data were double-checked and reviewed for diagnosis confirmation.

A comparative study between the group of patients with DACV and those with other CV unrelated to drugs was also performed. Moreover, a literature review of all case series on DACV published in English between 1984 and 2012 was conducted using the MEDLINE database (US National Library of Medicine).

Statistical analysis. Normal distributed variables were expressed as mean ± SD, and those not normally distributed as median and interquartile range (IQR). Continuous variables were compared by the 2-tailed Student's t-test or Mann-Whitney U test as appropriate. Dichotomous variables were analyzed by means of chi-squared test or Fisher's exact test. A p value < 0.05 was considered statistically significant. Analysis was performed with the STATISTICA software package (Statsoft Inc.).

RESULTS

Between January 1976 and January 2012, 773 patients (422 men and 351 women; mean age 34 ± 27 yrs) were diagnosed with CV. Among them, 239 (30.9%; 133 men and 106 women; mean age 36 ± 28 yrs) fulfilled definitions for DACV. Of the 239 CV cases related to drugs, 101 (42.3%) were children (age ≤ 20 yrs) and 138 (57.7%) were adults (age > 20 yrs).

As shown in Table 1, the most common drugs associated

Table 1. Main drugs associated with cutaneous vasculitis.

Drug	n (%)
Antibiotics	149 (62.3)
β-lactams	109 (45.6)
Penicillins	92 (38.4)
Cephalosporins	17 (7.1)
Quinolones	15 (6.2)
Macrolides	10 (4.2)
Carbapenems	4 (1.7)
Sulfamides	4 (1.7)
Cotrimoxazole	3 (1.2)
Tetracyclines	2 (0.8)
Aminoglycosides	1 (0.4)
Glycopeptides	1 (0.4)
NSAID	24 (10.0)
Acetylsalicylic acid	7 (2.9)
Diclofenac	4 (1.7)
Ibuprofen	3 (1.2)
Salazopyrin	1 (0.4)
Ketoprofen	1 (0.4)
Aceclofenac	1 (0.4)
Piroxicam	1 (0.4)
Not specified	6 (3.8)
Paracetamol	9 (3.8)
Allopurinol	5 (2.1)
Anticonvulsants	5 (2.1)
Antihypertensives	4 (1.7)
Diuretics	4 (1.7)
Immunosuppressive agents	4 (1.7)
Other drugs*	35 (14.6)

*Anti-flu medication (n = 10), expectorants (n = 3), anticoagulants (n = 3), proton pump inhibitors (n = 3), antithyroid drugs (n = 3), antihistamines (n = 3), statins (n = 2), gastrointestinal prokinetics (n = 2), famciclovir (n = 1), triamcinolone (n = 1), disulfiram (n = 1), diazepam (n = 1), tetanus vaccine (n = 1), hidrosmine (n = 1). NSAID: nonsteroidal antiinflammatory drugs.

with CV were antibiotics (n = 149; 62.3%), mainly β-lactams (n = 109; 45.6%) and quinolones (n = 15; 6.2%). Other agents involved were nonsteroidal antiinflammatory drugs (NSAID; n = 24; 10%) and paracetamol (n = 9; 3.8%). Twelve patients were taking more than 1 drug.

As expected, patients with a history of antibiotic exposure before the onset of the vasculitis had fever more commonly than those who were not receiving these drugs (p = 0.02). Patients taking NSAID had joint manifestations more frequently (p = 0.03). No other differences were observed among the different subgroups of DACV regarding other clinical and laboratory features, need for treatment, and relapses (data not shown).

Clinical manifestations, laboratory, and histological findings of DACV. The main clinical features of patients with DACV at the onset of the disease and when it was fully established are shown in Figure 1. Skin involvement occurred in all the cases during the course of DACV. The main types of cutaneous lesions were palpable purpura (83.7%), bullous (3.3%), erythema (2.9%), urticaria (2.9%), and ulcers (2.1%). Fever was observed in nearly one-quarter of the patients and constitutional symptoms in 6%. Ninety-one patients (38.1%) had GI manifestations, including abdominal pain (34.7%), nausea, and vomiting (12.1%), and GI bleeding (melena, hematochezia, or positive stool guaiac test; 15.1%). Joint manifestations were present in half of the cases. Nephropathy was diagnosed in up to one-third of patients with DACV, and nephrotic or nephritic syndrome were developed in 17 (7.1%) and 6 cases (2.5%), respectively. Renal insufficiency was documented in 29 patients (12.1%).

Table 2 summarizes the main laboratory results in patients with DACV. ESR was increased in 40.2% of cases, leukocytosis was observed in 24.7%, and anemia in 18.8%. Serum immunological tests were positive in some patients, ranging from 5% (ANCA) to 26% (serum cryoglobulins) of those in whom they were tested.

Skin biopsy was performed in 106 patients with DACV (45.7%). In most children (97 cases) and in some adults (44 cases) with typical nonthrombocytopenic symmetric palpable purpura, skin biopsy was not done. When performed, it disclosed a neutrophilic vasculitis of small vessels with fibrinoid necrosis and leukocytoclasia.

Treatment and outcome of DACV. Vasculitis completely resolved after drug withdrawal and bed rest in 131 cases (54.8%). In the remaining patients, different pharmacological therapies were used, mainly corticosteroids (n = 71; 29.7%) or immunosuppressive drugs (n = 7; 2.9%); specifically cyclophosphamide (n = 5), methotrexate (n = 1), and azathioprine (n = 1). The median duration of corticosteroid therapy was 1.3 months (IQR 0.1–43). At last followup we observed renal damage manifested by chronic persistent microhematuria and/or proteinuria in 3.3% and persistent renal insufficiency in 5% (mild nephropathy in 2.9% and severe renal disease needing dialysis or kidney transplantation in 2.1%).

After a median followup of 5 months (IQR 0.1–211), relapses were observed in 44 (18.4%) of 239 patients with

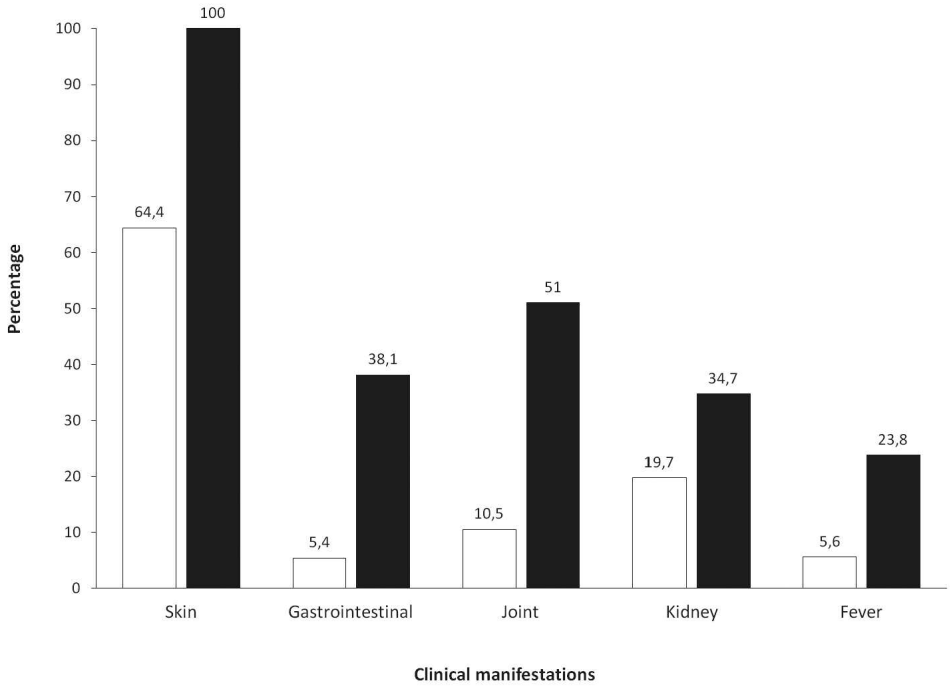

Figure 1. Main clinical features of 239 patients diagnosed with drug-associated cutaneous vasculitis, at the onset of the disease (white bars) and when the cutaneous vasculitis was fully established (black bars).

Table 2. Comparative study between drug-associated cutaneous vasculitis (DACV) and the remaining cutaneous vasculitis (CV).

	DACV, n = 239	Other CV, n = 534	p
Demographic data			
Age, yrs, mean ± SD	36 ± 28	33 ± 27	0.2
Sex, n (%)			
Men	133 (55.6)	289 (54.1)	0.7
Women	106 (44.4)	245 (45.9)	
Other precipitating events, n (%)			
Infection	164 (68.6)	121 (22.7)	< 0.01
Underlying connective diseases	2 (0.8)	36 (6.7)	< 0.01
Clinical manifestations, n (%)			
Skin lesions			
Palpable purpura	200 (83.7)	490 (91.8)	0.01
Other skin lesions*	63 (26.4)	124 (23.2)	0.4
Duration (days), median (IQR)	8 (2–90)	10 (2–240)	0.04
Joint involvement	122 (51)	269 (50.4)	0.9
Gastrointestinal involvement	91 (38.1)	207 (38.7)	0.9
Nephropathy	83 (34.7)	175 (32.8)	0.6
Mild	62 (25.9)	138 (25.8)	0.9
Severe	21 (8.8)	30 (5.6)	0.1
Renal insufficiency	29 (12.1)	38 (7.1)	0.02
Fever	57 (23.8)	125 (23.4)	0.9
Constitutional symptoms	15 (6.3)	32 (6.0)	0.9
Laboratory findings			
Hemoglobin (g/dl), mean ± SD	11.9 ± 2.1	12 ± 2.3	0.8
Leukocytes/mm^3, mean ± SD	14,885 ± 3614	14,254 ± 3418	0.3
ESR mm/h, mean ± SD	49.5 ± 28.1	48.5 ± 28.6	0.7
Abnormal urinalysis, n (%)**	95 (39.7)	209 (39.1)	0.8
Any cytopenia, n (%)	45 (18.8)	68 (12.7)	0.03
Anemia	45 (18.8)	68 (12.7)	0.03
Leukopenia	12 (5)	13 (2.4)	0.06
Thrombocytopenia	3 (1.3)	12 (2.2)	0.5
Positive ANA, n (%)	27/128 tested (21.1)	70/309 tested (22.6)	0.7
Positive RF, n (%)	22/126 tested (17.5)	51/282 tested (18.1)	0.9
Positive ANCA, n (%)	3/65 tested (4.6)	9/109 tested (8.3)	0.4
Low C3 and/or C4 levels, n (%)	11/133 tested (8.3)	38/310 tested (12.2)	0.2
Serum cryoglobulins, n (%)	19/73 tested (26)	56/216 tested (25.9)	0.9

*Other skin lesions were erythema, bullous, ulcers, or edema. ** Abnormal urinalysis refers to the presence of hematuria or proteinuria. IQR: interquartile range; ESR: erythrocyte sedimentation rate, ANA: antinuclear antibodies; RF: rheumatoid factor; ANCA: antineutrophil cytoplasmic antibodies; C3: complement 3; C4: complement 4.

DACV. Thirty-six of these 44 patients achieved complete recovery. Nevertheless, chronic persistent microhematuria was observed in 2 (4.5%), chronic persistent microhematuria and proteinuria in 1, and mild renal insufficiency in 1. One of the patients who experienced relapses was finally diagnosed with systemic lupus erythematosus (SLE; this patient did not show lesions of subacute cutaneous lupus erythematosus but a typical palpable purpura), and 3 died (6.8%) because of upper GI bleeding, respiratory infection, and acute renal failure in the context of chronic renal insufficiency, respectively.

Differences between DACV and other CV unrelated to drugs. Data from a comparative study between patients with DACV (n = 239) and those with other CV (n = 534) are given in Table 2. Patients with DACV had infections more commonly than did the remaining patients with CV ($p < 0.01$). In contrast, underlying connective diseases were more frequent in the group of CV unrelated to drugs ($p < 0.01$). Among the clinical manifestations, patients with DACV had renal insufficiency more frequently ($p = 0.02$). Also, patients with DACV had cytopenias more commonly than did those with CV unrelated to drugs ($p = 0.03$), especially anemia ($p = 0.03$). No differences were observed regarding the need for pharmacological treatment between both groups. Nevertheless, relapses were significantly less common in patients with DACV than in those with other CV ($p < 0.01$).

DISCUSSION

The major issue always facing a study on drug-associated

Table 3. Review of case series of cutaneous vasculitis associated with drugs. Data are percentages unless otherwise indicated.

	Ekenstam, USA	Calabrese, USA	Marques, Portugal	Gyselbrecht, Belgium	Watts, UK	Sais, Spain	García-Porrúa, Spain	Gupta, India	Khetan, India	Ortiz-Sanjuán, Spain
Year	1984	1990	1995	1996	1998	1998	1999	2009	2012	2013
Patients with CV, n	82	220	51	63	84	160	138	50	61	773
Skin biopsy	100	ND	100	100	ND	100	100	100	100	45.7
Patients with drug as a precipitating event, n	8	63	28	5	1	15	33	25	12	239
Antibiotics	ND	ND	ND	80	ND	ND	39.4	16	16.7	62.3
β-lactams	ND	ND	ND	40	ND	ND	30.3	ND	ND	38.9
Macrolides	ND	ND	ND	0	ND	ND	6.1	ND	ND	3.8
NSAID	ND	ND	ND	20	ND	ND	33.3	36	41.6	10
Other drugs	ND	ND	ND	0	ND	ND	27.3	48	58.3	27.7
Age, yrs, mean	ND	ND	ND	ND	ND	ND	54	ND	ND	36
Sex, M/F	ND	ND	ND	ND	ND	ND	23/10	ND	ND	133/106
Joint manifestations	ND	ND	ND	ND	ND	ND	24.2	ND	ND	51
GI manifestations	ND	ND	ND	ND	ND	ND	27.3	ND	ND	38.1
Renal involvement	ND	ND	ND	ND	ND	ND	28	ND	ND	34.7
Leukocytosis	ND	ND	ND	ND	ND	ND	3	ND	ND	24.7
Anemia	ND	ND	ND	ND	ND	ND	4	ND	ND	18.8
Increased ESR	ND	ND	ND	ND	ND	ND	22	ND	ND	40.2
Positive RF (tested*)	ND	ND	ND	ND	ND	ND	0 (0/33)	ND	ND	17.5 (22/126)
Positive ANA (tested*)	ND	ND	ND	ND	ND	ND	0 (0/31)	ND	ND	21.1 (27/128)
Low C3 and/or C4 (tested*)	ND	ND	ND	ND	ND	ND	10.7 (3/28)	ND	ND	8.3 (11/133)

* No. positive/total no. tested. CV: cutaneous vasculitis; M: male; F: female; GI: gastrointestinal; ESR: erythrocyte sedimentation rate, RF: rheumatoid factor; ANA: antinuclear antibodies; C3: complement 3; C4: complement 4; NSAID: nonsteroidal antiinflammatory drugs; ND: not described.

disease is that of causality. Evidence for causality might come from large cohort studies, longitudinal data, and the confirmation of a temporal relationship with disease. Such evidence is lacking for most drugs quoted in this and many other studies of vasculitis. It is especially true for the possible association of antibiotics with CV. In these cases it is difficult to determine whether an infection rather than the antibiotic used for the treatment of this infection was the actual trigger of the CV. Virtually all drugs have been considered as potential precipitating agents for vasculitis[32]. However, the level of evidence for this association is often weak. Skin is usually involved, ranging from an isolated cutaneous leukocytoclastic vasculitis to a severe life-threatening syndrome indistinguishable from systemic ANCA-associated vasculitis. Drugs have also been involved as precipitating factors of subacute cutaneous lupus erythematosus (SCLE). Marzano, *et al*[33] reported vasculitic lesions in 45% of patients with drug-induced SCLE. In our series none of the patients had typical SCLE lesions and only 1 patient with palpable purpura was finally diagnosed with SLE.

CV is by far the most common form of drug-associated vasculitis. However, information on this condition is generally the result of small series or single case reports[12,34-38,39-45] (Table 3). In the present study we report the largest series (to the best of our knowledge) of unselected patients with CV who fulfilled definitions for drug-associated vasculitis, which is now considered a specific entity, according to the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides[24].

DACV accounted for almost one-third of 773 unselected patients with CV from our series. Several clinical and laboratory differences were found between DACV and the remaining patients with CV unrelated to drugs. In this regard, infections, renal insufficiency and cytopenias, mainly anemia, were significantly more frequent in patients with DACV, while underlying connective disorders were more common in the group with CV unrelated to drugs.

As discussed, it is possible that in some patients with DACV the clinical manifestations might not be due to the drugs themselves but are the result of an underlying infectious disease. Nevertheless, in clinical practice, it is difficult to determine this. In the present study, patients with vasculitis due to major infections, such as endocarditis or pneumonia, were excluded. In these cases the presence of CV contributed to the diagnosis of the underlying infectious disease, and the onset of antibiotic therapy was posterior to the development of the cutaneous lesions. It was not the case in patients with minor infections, such as urinary or upper respiratory tract infections, in whom it was very difficult to establish the trigger of the CV (either the infection or the antibiotic therapy). On the other hand, many drugs can induce cytopenias or renal function impairment. This may be the case for β-lactams and NSAID, which have been associated with acute interstitial nephritis, probably

mediated by an immune mechanism. In any case, our results highlight an increased risk of renal insufficiency in patients with CV when drugs are involved.

Several case reports have emphasized the potential association between antibiotics and NSAID and CV[38,39,40,41]. In our series, β-lactams were the drugs more commonly associated with DACV. The second pharmacological group was NSAID, which was in accordance with some[15] but not all[12,20,21] the reports on this issue. The reasons for such a discrepancy are unknown. The age of the patients included in the different series may be a plausible explanation because younger individuals may have DACV in the setting of antibiotics used for an upper respiratory infection more commonly than do middle-age or elderly people, who may develop DACV because of NSAID taken for noninfectious diseases.

Besides antibiotics and NSAID, many other drugs have been associated with CV[35,42,43,44,45]. Although a wide spectrum of agents has been involved in the pathogenesis of autoimmune diseases or ANCA-associated vasculitis[46,47], in our series positive ANCA were observed in only 3 of 65 cases tested (4.6%). In addition, none of them developed renal disease during followup.

DACV may be complicated by a variable degree of visceral involvement, including GI, joint, and renal manifestations[48,49,50]. We have observed that about half of the patients with DACV had joint manifestations, and about one-third had GI or renal involvement. These results are often difficult to compare with those from other series because of differences in the age of patients or in the number of individuals with different subtypes of CV. For instance, our series included more patients who fulfilled classification criteria for HSP (33%) than did that published by García-Porrua, *et al* (21%), and this may have contributed to our finding some differences in the clinical spectrum of DACV[12].

Treatment of DACV is mainly based on discontinuation of the drug and bed rest. Corticosteroids are prescribed when persistent skin lesions or visceral involvement are present, such as severe abdominal pain, GI bleeding, or nephropathy. Immunosuppressive agents should be used either as corticosteroid-sparing agents or as an add-on therapy in patients with severe renal disease. In our series, 108 patients (45%) required pharmacological treatment, mainly corticosteroids. The percentage of patients from our series who required medication was similar to that reported by García-Porrua, *et al*[12].

However, in that García-Porrúa, *et al* series, relapses and chronic persistent microhematuria or proteinuria occurred in 7% of patients, but none of them developed renal insufficiency at the end of the followup period[12].

The clinical outcome of our patients with DACV was generally good, with complete resolution of the vasculitis in most cases. Although relapses occurred in 18% of our patients, chronic persistent microhematuria, proteinuria, and/or renal insufficiency were uncommon at last followup.

DACV is a vasculitis triggered by a drug and its evolution is not necessarily linked to new exposures to the drug. In this sense, unlike drug-reaction mediated by IgE in type I hypersensitivity reaction, it is well known that the majority of cutaneous lesions of vasculitis are likely due to immunocomplex deposition/type III hypersensitivity reaction. The mechanisms of this type III hypersensitivity reaction seem to be quite different from those involved in type I hypersensitivity reaction. This may explain why CV relapses can occur after drug discontinuation.

We report on the largest series of DACV cases, to our knowledge. Antibiotics (mainly β-lactams) and NSAID were the most frequent drugs associated with this type of vasculitis. The prognosis of DACV was usually good, although a small percentage of cases developed residual kidney damage.

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