The Spectrum of Paraneoplastic Cutaneous Vasculitis in a Defined Population

Incidence and Clinical Features

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Abstract: Cutaneous vasculitis may be associated with malignancies, and may behave as a paraneoplastic syndrome. This association has been reported in a variable proportion of patients depending on population selection. We conducted the current study to assess the frequency, clinical features, treatment, and outcome of paraneoplastic vasculitis in a large unselected series of 766 patients with cutaneous vasculitis diagnosed at a single university hospital.

Sixteen patients (10 men and 6 women; mean age ± standard deviation, 67.94 ± 14.20 yr; range, 40–85 yr) presenting with cutaneous vasculitis were ultimately diagnosed as having an underlying malignancy. They constituted 3.80% of the 421 adult patients. There were 9 hematologic and 7 solid underlying malignancies. Skin lesions were the initial clinical presentation in all of them, and the median interval from the onset of cutaneous vasculitis to the diagnosis of the malignancy was 17 days (range, 8–50 d). The most frequent skin lesions were palpable purpura (15 patients). Other clinical manifestations included constitutional syndrome (10 patients) and arthralgia and/or arthritis (4 cases). Hematologic cytopenias (11 cases) as well as immature peripheral blood cells (6 cases) were frequently observed in the full blood cell count, especially in those with vasculitis associated with hematologic malignancies.

Specific treatment for vasculitis was prescribed in 10 patients; nonsteroidal antiinflammatory drugs (4 patients), corticosteroids (3 patients), chloroquine (1 patient), antihistamines (1 patient), and cyclophosphamide (1 patient). Ten patients died due to the malignancy and 6 patients recovered following malignancy therapy. Patients with paraneoplastic vasculitis were older, more frequently had constitutional syndrome, and less frequently had organ damage due to the vasculitis than the remaining patients with cutaneous vasculitis.

In summary, cutaneous paraneoplastic vasculitis is an entity not uncommonly encountered by clinicians. The most common underlying malignancy is generally hematologic. In these cases the presence of cytopenias and immature cells may be red flags for the diagnosis of cancer. In patients with paraneoplastic cutaneous vasculitis, the prognosis depends on the underlying neoplasia.

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Abbreviations: ACR = American College of Rheumatology, ANA = antinuclear antibodies, ANCA = antineutrophil cytoplasmic antibodies, ESR = erythrocyte sedimentation rate, IQR = interquartile range, RF = rheumatoid factor, SD = standard deviation.

INTRODUCTION

The term *cutaneous vasculitis* includes a wide and heterogeneous spectrum of syndromes clinically characterized by predominant involvement of the skin, with histopathologic findings that have in common vascular inflammation and blood vessel damage.[8,13,34,40,50,51,61,92,93,94] Although isolated cutaneous vasculitis is usually a benign process, in some cases it may be the clinical presentation of a systemic necrotizing vasculitis or other entities such as systemic infections or connective tissue diseases. Cutaneous vasculitis may also be associated with malignancy and may behave as a paraneoplastic syndrome.

In 1986, Longley et al[60] suggested that malignant neoplasms might produce antigens and consequently cause paraneoplastic vasculitis. In the same year, McLean[67] established 2 criteria that were required to establish the presence of paraneoplastic vasculitis: first, the simultaneous appearance of both vasculitis and neoplasm; and second, their parallel course. The pathogenetic mechanisms for the development of paraneoplastic vasculitis remain unknown. Furthermore, the stronger association between vasculitis and hematologic malignancies as compared with solid tumors, as well as the different tendency for each hematologic disorder to develop vasculitis, is poorly understood.[99] Most studies on cutaneous paraneoplastic vasculitis include case reports, or small series of patients.[17,86,91] We previously described 4 cases of paraneoplastic cutaneous vasculitis.[8]

To further investigate the characteristics of cutaneous vasculitis associated with neoplasia, we assessed the frequency, clinical features, treatment, and outcome of all patients diagnosed as having paraneoplastic vasculitis from a large series of unselected patients with cutaneous vasculitis. A literature review was also conducted.

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PATIENTS AND METHODS

Patient Population

We studied the case records of patients from a teaching reference hospital in northern Spain (Hospital Universitario Marqués de Valdecilla, Santander) who were diagnosed as having cutaneous vasculitis from January 1976 to December 2011. Methods were similar to those previously published.[8] Briefly, the diagnosis of cutaneous vasculitis was based on either 1) a skin biopsy showing characteristic histologic findings of vasculitis or 2) the presence of typical non-thrombocytopenic palpable purpura. In the latter case, skin biopsies were not performed because either patients were children with clinically evident cutaneous vasculitis, usually Henoch-Schönlein purpura, or they were adults who in addition to non-thrombocytopenic palpable purpura, also had biopsy-proven necrotizing vasculitis in other systems such as nerve, muscle, lung, or kidney.

The majority of patients with suspected cutaneous vasculitis were sent to the hospital by general practitioners or they self-referred to the emergency unit. In most cases, consultation by dermatology staff physicians was usually requested. Patients with cutaneous vasculitis were screened for medications taken before and during the onset of vasculitis, as well as for other data suggestive of systemic vasculitis or connective tissue disease. Malignancy and vasculitis were considered to be concurrent when both processes were identified within 12 months of each other. Vasculitis was considered to be possibly related to malignancy when 1) no known precipitating factors of vasculitis were present, such as infections, medications, connective tissue diseases, or systemic necrotizing vasculitis; 2) a consistent relationship between malignancy and vasculitis was observed; and/or 3) synchronous recurrences of both diseases were documented during follow-up.

Clinical and Laboratory Definitions

We used the following definitions: 1) Patients aged older than 20 years were considered adults. The cutoff age of 20 years was chosen because this age was proposed as a criterion for Henoch-Schönlein purpura by the American College of Rheumatology (ACR)[72] and because this age best discriminated Henoch-Schönlein purpura from hypersensitivity vasculitis in previous studies.[71] 2) Fever was defined as an axillary temperature >37.7°C. 3) Constitutional syndrome was defined as asthenia and/or anorexia, and weight loss of at least 4 kg. 4) Joint symptoms included arthralgia and/or joint effusion. 5) Gastrointestinal manifestations: bowel angina (diffuse abdominal pain worsening after meals), gastrointestinal bleeding (melena, hematochezia, or positive stool Guaiac test), nausea, and/or vomiting. 6) The nephropathy was categorized as mild or severe. Mild nephropathy included those patients with microhematuria (≥5 red cells/high-power field) without reaching nephritic syndrome and/or proteinuria that did not reach the nephrotic range. 7) Relapse was considered when a patient previously diagnosed as having cutaneous vasculitis and asymptomatic for at least 1 month, presented again with a new flare of cutaneous lesions. 8) Anemia was defined as a hemoglobin level ≤110 g/L. 9) Leukocytosis was defined as a white cell count $\geq 11 \times 10^9$/L, and leukopenia was defined as a leukocyte count $< 3 \times 10^9$/L. 10) The Westergren erythrocyte sedimentation rate (ESR) was considered elevated when it was >15 or >20 mm/h for men or women, respectively.

Clinical Study

In most patients presenting with cutaneous vasculitis, routine laboratory studies, including complete blood cell count, coagulation studies, and liver and renal function tests, were performed at the time of diagnosis. ESR, routine urinalysis, and chest radiograph were also performed.

Most adults (but only a minority of children) had an immunologic profile including rheumatoid factor (RF), performed initially by quantitative latex agglutination test, and later by nephelometry; antinuclear antibodies (ANA), by indirect immunofluorescence using until the late 1980s rodent tissues as substrate and since then Hep-2 cells; serum levels of C3 and C4, first by radial immunodiffusion and more recently by nephelometry; and cryoglobulins. The composition of the cryoprecipitate was determined by double immunodiffusion with specific antibodies. Antineutrophil cytoplasmic antibodies (ANCA) were tested by indirect immunofluorescence on alcohol-fixed neutrophils, and, later, by ELISA with purified proteinase-3 and myeloperoxidase. ANCA were measured only in patients studied since 1990. Other tests, such as anti-nDNA antibodies (by immunofluorescence with *Crithidia luciliae* as substrate); blood cultures; Guaiac test for occult blood; bone marrow biopsy; and serology for hepatitis B, C, or human immunodeficiency virus infection, were performed only when indicated.

Data Collection, Statistical Analysis, and Literature Review

Data were first reviewed and then analyzed to compare the etiologic, clinical, laboratory, and histopathologic features, as well as treatment and prognosis. Data were extracted from the clinical records according to a specifically designed protocol, reviewed for confirmation of the diagnosis, and stored in a computerized file. To minimize entry error all data were double checked. A comparative study between patients with paraneoplastic cutaneous vasculitis and the remaining patients diagnosed with cutaneous vasculitis in adults was performed.

The statistical analysis was performed with the STATISTICA software package (Statsoft Inc. Tulsa, OK). Results are expressed as mean ± standard deviation (SD) or as median, range, and/or interquartile range (25th, 75th) (IQR). Continuous variables (normally and not normally distributed) were compared with the 2-tailed Student t test or the Mann-Whitney U test, respectively. The chi-square test or the Fisher exact test was used for the dichotomous variables. Statistical significance was considered as $p \text{ value} \leq 0.05$.

We conducted a review of the literature, selecting studies on paraneoplastic vasculitis published in English between 1990 and 2011. A PubMed database search (National Library of Medicine, Bethesda, MD) was performed.

RESULTS

We assessed the medical records of a series of 766 patients (346 female/420 male) diagnosed as having cutaneous vasculitis from a university hospital in Santander, northern Spain. The mean age of the entire series was 34.00 ± 27.49 years (range, 1–95 yr).

Frequency and Demographic Data Relating to Paraneoplastic Vasculitis

Of the 766 patients, 421 (178 women/243 men) were older than 20 years, with a mean age of 55.60 ± 17.52 years (range, 24–95 yr). In the current series there were no children with paraneoplastic cutaneous vasculitis. Sixteen patients (10 men and 6 women; mean age, 67.94 ± 14.20 yr; range, 40–85; IQR,

TABLE 1. Main Clinical Features of 16 Patients Presenting With Cutaneous Vasculitis, Confirmed by a Skin Biopsy Showing Leukocytoclastic Vasculitis, Who Were Finally Diagnosed as Having a Malignancy

Patient	Age/Sex (yr)	Main Clinical Feature	Peripheral Blood Smear	Neoplasia
1	83/M	Palpable purpura, necrotic ulcer, constitutional symptoms	Anemia, leukopenia	Myelodysplastic syndrome
2	52/W	Palpable purpura, constitutional symptoms	Pancytopenia, immature cells	Myelodysplastic syndrome
3	56/M	Palpable purpura, constitutional symptoms, fever	Anemia, leukopenia, immature cells	Myelodysplastic syndrome
4	70/M	Palpable purpura, constitutional symptoms, polyarthritis	Anemia, leukopenia, immature cells	Non-Hodgkin lymphoma
5	78/M	Palpable purpura, constitutional symptoms, fever, arthralgia, abdominal pain	Anemia	Waldestrom macroglobulinemia
6	61/W	Palpable purpura, hematuria, polyneuropathy	Anemia	Waldestrom macroglobulinemia
7	76/M	Palpable purpura, urticarial lesions, constitutional symptoms, fever	Pancytopenia, immature cells	Hairy cell leukemia
8	81/W	Palpable purpura, erythema, constitutional symptoms, fever	Anemia, immature cells	Mantle cell lymphoma
9	40/W	Urticarial lesions, fever, polyarthritis	Anemia, immature cells	Megakaryocytic leukemia
10	49/W	Palpable purpura, constitutional symptoms, fever	Anemia	Infiltrating breast carcinoma
11	80/M	Palpable purpura, constitutional symptoms	Anemia	Lung adenocarcinoma
12	85/W	Palpable purpura, ulcers	Normal	Breast carcinoma
13	53/M	Palpable purpura, arthralgia	Normal	Pyriform sinus squamous cell carcinoma
14	71/M	Palpable purpura, constitutional symptoms	Normal	Bladder carcinoma
15	70/M	Palpable purpura	Normal	Glottic squamous cell carcinoma
16	82/M	Palpable purpura, abdominal pain, fecal occult blood, hematuria	Normal	Oropharyngeal squamous cell carcinoma

54.50–80.50 yr) presenting with cutaneous vasculitis were finally diagnosed as having an underlying malignancy (Table 1). They constituted 3.80% of the 421 adult patients.

There were 9 hematologic and 7 solid malignancies. Drugs and infections are known to play an important role in the development of cutaneous vasculitis, especially in cases of hypersensitivity vasculitis.[11] However, no history of drug intake or infections before the onset of the cutaneous vasculitis was recorded in these 16 patients with paraneoplastic cutaneous vasculitis.

Main Clinical Features

Skin lesions were the first clinical manifestation in the 16 patients with paraneoplastic vasculitis. The median interval from the onset of cutaneous vasculitis to the diagnosis of the malignancy was 17 days (IQR, 12–27 d; range, 8–50 d). The most frequent skin lesions were palpable purpura (15 patients) (Figure 1), legs ulcers (2 patients), urticaria (2 patients), and macular erythema (1 patient). In most cases the cutaneous lesions were located in the lower extremities and had mean ± SD duration of 14.19 ± 4.52 days. Other clinical manifestations were constitutional syndrome (10 patients) and arthralgia and/or arthritis (4 cases). Two patients had abdominal pain and another 2 patients had hematuria. In addition, 1 patient had polyneuropathy. Other systemic manifestations that may be seen in the setting of systemic vasculitis, such as eye, testicular, upper or lower respiratory tract involvement, were not observed.

Laboratory and Pathology Findings

Hematologic cytopenias were frequently observed in the full blood cell count (11 cases) as well as immature peripheral blood cells (6 cases), especially in those with vasculitis associated with hematologic malignancies. Isolated anemia was

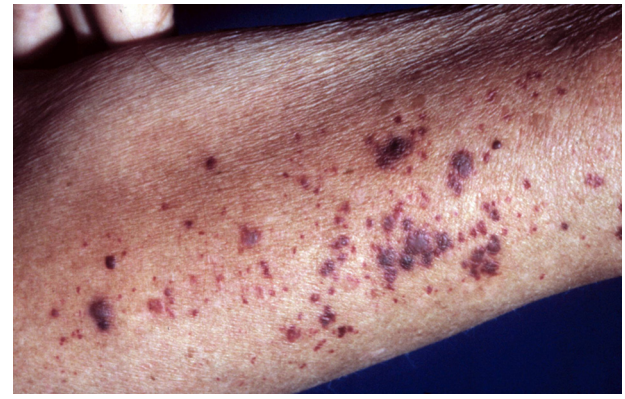

FIGURE 1. Typical non-thrombocytopenic palpable purpura in the lower extremities of a patient presenting with cutaneous vasculitis associated with neoplasia. [This figure can be viewed in color online at http://www.md-journal.com].

present in 6 cases, bicytopenia (anemia and leukopenia) in 3 cases, and pancytopenia in 2 cases.

The median hemoglobin value was 9.65 g/dL (IQR, 9.0–12.5; range, 7.3–16.5); the median ESR was 88 mm/h (IQR, 30–96; range, 17–110). Mild microhematuria was observed in 2 patients.

Two patients had positive RF and 3 had cryoglobulins. In these cases they were at low titer and other diseases such as rheumatoid arthritis or cryoglobulinemia were excluded. A patient with paraneoplastic cutaneous vasculitis in the setting of megakaryocytic leukemia had positive ANA (by immunofluorescence at 1/640). C3, C4, and ANCA were negative or within the normal range in all 16 cases.

Skin punch biopsy was performed in all 16 cases. The characteristic histologic findings, such as neutrophilic infiltration; leukocytoclasia; and fibrinoid necrosis into the vessel wall of arterioles, capillaries, and postcapillary venules, were observed in all of them (Figure 2).

Treatment and Outcome

Specific therapy for vasculitis was required in 10 patients: nonsteroidal antiinflammatory drugs (4 patients), corticosteroids (3 patients), chloroquine (1 patient), antihistamines (1 patient), and cyclophosphamide (1 patient). On follow-up, 10 patients died due to the malignancy and 6 patients recovered following malignancy-specific therapy.

Differences Between Paraneoplastic Vasculitis and Other Cutaneous Vasculitis in Adults

A comparative study between patients with paraneoplastic cutaneous vasculitis and the remaining 405 adult patients with cutaneous vasculitis was performed (Table 2). Patients with paraneoplastic vasculitis were older than those with cutaneous vasculitis ($p < 0.01$). None of the patients with paraneoplastic vasculitis had the typical precipitating events reported in individuals with cutaneous vasculitis, such as infections or drug intake. However, skin lesions lasted longer in those with paraneoplastic vasculitis ($p = 0.03$), and constitutional syndrome occurred more commonly than in the patients with cutaneous vasculitis unrelated to malignancy ($p < 0.01$). Patients with cutaneous vasculitis associated with malignancy less commonly had gastrointestinal manifestations or nephritis, but the difference did not achieve statistical significance. Also, patients with paraneoplastic cutaneous vasculitis more frequently had cytopenias ($p < 0.01$) and/or immature peripheral cells ($p < 0.01$). In addition, these patients more commonly had anemia ($p < 0.01$) and higher ESR values than the remaining patients with cutaneous vasculitis ($p = 0.03$).

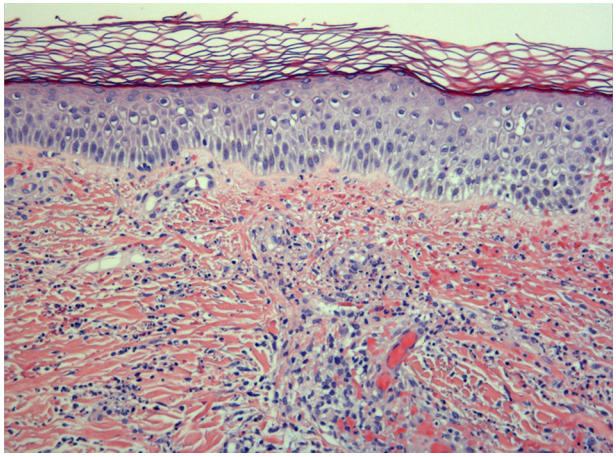

FIGURE 2. Skin biopsy of a patient with neoplasia presenting with palpable purpura. Typical histologic findings consistent with leukocytoclastic vasculitis. Neutrophilic infiltration, leukocytoclasia, fibrinoid necrosis, and erythrocyte extravasation into the vessel wall of arterioles, capillaries, and postcapillary venules from dermis are visible. [This figure can be viewed in color online at http://www.md-journal.com].

DISCUSSION

Cutaneous vasculitis may behave as a paraneoplastic syndrome. However, the actual proportion of malignancy in patients with cutaneous vasculitis remains unknown. Current information on paraneoplastic vasculitis has been generally retrieved from data of relatively small series or from case reports based on a few patients.[17,47,86,89] Gibson and Su[35] reported a frequency of associated malignancy of 8% of patients from a series of individuals with cutaneous vasculitis. Most patients from their series had leukocytoclastic vasculitis confirmed histologically. In the current series there were no children with paraneoplastic cutaneous vasculitis, and the frequency of paraneoplastic vasculitis in adults with cutaneous vasculitis was 3.80%.

The absence of previous selection of patients in the current series and the inclusion of both biopsy-proven cases and cases with typical vasculitic skin lesions that were not biopsied may, somehow, explain the lower frequency of paraneoplastic vasculitis found in our study when compared with previous reports. In this regard, in a series of 222 patients with vasculitis, Sánchez-Guerrero et al[86] reported a frequency of 4.95% paraneoplastic vasculitis. Eleven of the 222 patients had a malignancy. Nine of them had cutaneous vasculitis specifically.

Several possible mechanisms for the development of paraneoplastic vasculitis have previously been suggested:[11,35] 1) impaired clearance of normally produced immune complexes, 2) abnormal production of immunoglobulins that would react either to vascular antigens causing formation of in situ immune complexes or to a circulating antigen forming circulating immune complexes that then deposit in the vessel walls, and finally, 3) production of immunoglobulins directed to not only the abnormal tumor cells but also the normal endothelium.

Cutaneous vasculitis may antedate the discovery of the malignancy, coincide with it, occur after the malignancy has already been recognized, or provide a clue to a recurrence.[28,70] In most cases, paraneoplastic vasculitis antedates the diagnosis of malignancy.[70,86] However, paraneoplastic vasculitis may occur after the diagnosis of malignancy such as in cases of hairy cell leukemia.[70,86] In the current series of 16 patients, the skin lesions occurred before the diagnosis of malignancy. In general, the cutaneous lesions in paraneoplastic vasculitis are similar to those observed in other patients with cutaneous vasculitis.

The main clinical feature in the current series was palpable purpura, and the skin lesions tended to last longer in patients with paraneoplastic vasculitis than in patients with cutaneous vasculitis unrelated to malignancy.

Ten of 16 patients with paraneoplastic vasculitis from the current series had constitutional syndrome, but no severe organ damage due to the vasculitis was seen. In this respect, joint involvement was observed in 4 patients, but only 2 experienced abdominal pain and hematuria, respectively. Nevertheless, 2 of the 11 patients with neoplasia reported by Sánchez-Guerrero et al[86] had vasculitis involving the intestine leading to acute abdomen. In the series reported by Castro et al,[17] 1 patient with paraneoplastic vasculitis had oral ulcers, 1 bursitis, 1 pericarditis, 3 patients had polyneuropathy, and 4 patients had polyarthritis.

TABLE 2. Comparative Study of Paraneoplastic Vasculitis and the Remaining Cutaneous Vasculitis in Adults

Feature*	Paraneoplastic Vasculitis (n=16)	Cutaneous Vasculitis Without Neoplasia in Adult Patients (>20 yr) (n=405)	P
Demographic data			
Age, yr, mean±SD	67.94±14.20	55.60±17.52	<0.01
Sex n (%)			
Men	10 (62.5%)	235 (58.02%)	0.72
Women	6 (37.5%)	170 (41.98%)	
Precipitating events			
Infection	0 (0%)	122 (30.12%)	<0.01
Drug intake	0 (0%)	127 (31.36%)	<0.01
Skin lesions			
Palpable purpura	15 (93.75%)	364 (89.88%)	0.61
Other skin lesions	5 (31.25%)	102 (25.18%)	0.58
Duration, d, mean±SD	14.19±4.52	12.32±5.42	0.03
Constitutional syndrome	10 (62.5%)	27 (6.67%)	<0.01
Joint involvement	4 (25%)	172 (42.47%)	0.20
Gastrointestinal involvement	2 (12.5%)	98 (24.20%)	0.38
Nephropathy	2 (12.5%)	154 (38.02%)	0.06
Analytical findings			
Hemoglobin (g/L), median (IQR)	9.65 (8.9–10.9)	11.80 (9.7–13.2)	0.05
Leukocyte (x 10^9/L), median (IQR)	15,750 (14,400–17,100)	13,400 (12,100–15,500)	0.44
ESR mm/h, median (IQR)	88 (36–106)	42.50 (29–69)	0.03
Abnormal urinalysis, no. (%)	2 (12.5%)	178 (43.95%)	0.02
Any cytopenia, no. (%)	11 (68.75%)	78 (19.26%)	<0.01
Anemia	11 (68.75%)	78 (19.26%)	<0.01
Leukopenia	5 (31.25%)	10 (2.47%)	<0.01
Thrombocytopenia	2 (12.5%)	4 (0.99 %)	0.02
Immature cells in peripheral blood smear, no. (%)	6 (37.5%)	2 (0.49%)	<0.01
Positive ANA†	1/11 tested (9.09%)	79/304 tested (25.99%)	0.47
Positive RF†	2/12 tested (16.67%)	67/310 tested (21.61%)	1.00
Low C3 and/or C4†	0/11 tested (0%)	55/330 tested (16.67%)	0.22
Cryoglobulin†	3/8 tested (37.5%)	88/301 tested (29.23%)	0.44

Abbreviations: C3 and C4 = fractions of complement.

*Routine laboratory tests were done on all patients at the time of diagnosis. Leukopenia was defined as a leukocyte count <3 × 10^9/L; anemia as hemoglobin <110 g/L (see Methods section).

†Values are number positive/total number tested (%).

Histologic features in our patients with paraneoplastic vasculitis were consistent with typical small-vessel leukocytoclastic vasculitis.[55] However, larger skin blood vessel involvement has also been reported. In this regard, in the series by Sánchez-Guerrero et al[86] vasculitis was limited to small vessels of the skin in 9 of the 11 patients, 1 had involvement of medium-sized vessels only, and 1 had involvement of vessels of both calibers.

Hematologic disorders constitute the most common group of malignancies associated with cutaneous vasculitis.[28,70,86] Information on previously reported cases of cutaneous vasculitis occurring in the setting of an underlying hematologic neoplasia is summarized in Table 3.[5,14,17,27,32,37,48,49,52,58,62,64,68,74,79,84,86,88,90,99] Castro et al[17] reported 7 cases of cutaneous vasculitis, 5 of them with histologically confirmed leukocytoclastic vasculitis, from a series of 162 patients with myelodysplastic syndrome. Most of them had refractory anemia with excess blasts. Cryoglobulinemic vasculitis may also be associated with plasma cell dyscrasias, especially with plasma cell myeloma.[50]

Less commonly, cutaneous paraneoplastic vasculitis is related to the presence of an underlying solid tumor.[41,100] Lung (non-small cell), prostate, colon, renal, breast, head and neck (squamous cell), and endometrial cancer are the most frequent nonhematologic neoplasms associated with cutaneous vasculitis.[10,19,20,27,32,37,52,58,64,68,84,90,99] Solans-Laqué et al[89] reported 15 patients with different forms of vasculitis and solid tumors. Nine patients had leukocytoclastic vasculitis, 2 Henoch-Schönlein purpura, 1 patient developed polyarteritis nodosa, and 3 patients had giant cell arteritis.

Table 4 shows a series of cases of cutaneous vasculitis as a presenting manifestation of an underlying solid malignancy.[1,9,12,15,16,21,23,25,26,30,32,39,42,43,47,53,54,56,57,59,66,69,73–75,77,83,85,86,89,91,96]

It is noteworthy that, in 2009, Nozawa et al[74] described a 63-year-old woman with leukocytoclastic vasculitis in the setting of hypereosinophilic syndrome and mixed cryoglobulinemia who developed simultaneously a malignant B-cell lymphoma and a gastric tubular adenocarcinoma. To our knowledge,

TABLE 3. Cutaneous Leukocytoclastic Vasculitis Due to an Underlying Hematologic Neoplasia, Previous Reports

Reference	Age/Sex (yr)	Neoplasia	Occurrence of Vasculitis in Relation to Neoplasia	Evolution of Vasculitis
32	64/M	Myelodysplastic syndrome	8 d before	NA
8	52/W	Myelodysplastic syndrome	NA	Died
8	56/M	Myelodysplastic syndrome	NA	Resolved
17	58/M	Myelodysplastic syndrome (refractory anemia)	NA	NA
17	59/M	Myelodysplastic syndrome (refractory anemia)	NA	Improved
17	45/M	Myelodysplastic syndrome (refractory anemia with excess of blasts)	NA	Died from Clostr. septicum sepsis
17	35/M	Myelodysplastic syndrome (refractory anemia with excess of blasts)	NA	Died
17	58/M	Myelodysplastic syndrome (refractory anemia with excess of blasts)	NA	Stable/skin improved
17	72/M	Myelodysplastic syndrome (refractory anemia with excess of blasts)	NA	Stable/Skin resolved
17	54/M	Myelodysplastic syndrome (refractory anemia with excess of blasts in transformation)	NA	Skin resolved
88	19/M	Hodgkin disease	2 mo before	Resolved
52	72/M	Hodgkin disease	4 wk after	NA
52	61/M	Hodgkin disease	Simultaneous	NA
32	77/M	Non-Hodgkin lymphoma	2 d before	NA
32	56/W	Non-Hodgkin lymphoma	3 yr before	NA
8	70/M	Non-Hodgkin lymphoma	NA	Resolved
86	64/W	Non-Hodgkin lymphoma	1 yr after	NA
64	62/M	Acute myelogenous leukemia (M4)	Simultaneous	NA
37	70/M	Acute myelogenous leukemia	2.5 yr before	NA
37	31/W	Acute myelogenous leukemia	Simultaneous	NA
49	38/W	Acute myelogenous leukemia	2 mo before	Improved
90	NA	Chronic granulocytic leukemia	4 yr after	NA
86	40/W	Chronic granulocytic leukemia	2 yr after	NA
37	28/M	Myelofibrosis	2.5 yr before	NA
86	79/W	Myelofibrosis, myeloid metaplasia	3 yr after	NA
86	16/M	Myeloblastic leukemia	1 mo after	NA
58	76/M	Diffuse immunoblastic lymphoma	Unknown	NA
84	NA	Immunoblastic sarcoma	Unknown	NA
27	4/M	Lymphoblastic leukemia	4 mo after	NA
37	82/M	IgA myeloma	1 yr before	NA
68	58/W	IgA A myeloma	3 yr after	NA
32	83/W	IgGk multiple myeloma	3 mo before	NA
14	71/W	IgAλ multiple myeloma	7 yr after	Improved
48	53/M	IgGκ multiple myeloma	6 mo before	Improved
79	58/W	Multiple myeloma	NA	Resolved
32	69/W	Polycythemia vera	8 d before	NA
99	50/W	Chronic lymphoid leukemia	3 yr after	NA
62	71/M	Chronic lymphocytic leukemia	NA	Died
8	40/W	Megakaryocytic leukemia	NA	Skin lesions had a chronic course/died
86	53/W	Small-lymphocyte gastric lymphoma	35 yr before	NA
74	63/W	Malignant B-cell lymphoma	1 mo before	Resolved
86	60/M	T-cell lymphoma	Simultaneous	NA
86	67/W	Essential thrombocythemia	3 mo after	NA

Abbreviation: NA = not available.

TABLE 4. Cutaneous Leukocytoclastic Vasculitis Associated With an Underlying Solid Organ Tumor, Previous Reports

Reference	Age/Sex (yr)	Neoplasia	Occurrence of Vasculitis in Relation to Tumor	Evolution of Vasculitis/Follow-up
12	52/M	Colon carcinoma	3 mo before	Remission*/1R‡
59	69/W	Colon carcinoma	1.5 yr before	Remission/1R‡
56	37/W	Colon carcinoma	11 mo after	Partial remission*/death at 15 mo
39	75/W	Colon carcinoma	Synchronous	Remission*/NA
16	65/W	Colon carcinoma	NA	Remission*/NA
89	67/M	Colon adenocarcinoma	Synchronous	Partial remission
89	73/W	Colon adenocarcinoma	Synchronous	Remission*
43	63/M	Renal carcinoma	Synchronous	No treatment/death at 5 d
1	63/W	Renal carcinoma	Synchronous	Remission*/NA
66	63/M	Renal carcinoma	Synchronous	Partial remission/NA
47	67/W	Renal carcinoma	Synchronous	Remission*/NA
57	75/W	Renal carcinoma	Synchronous	Remission*/18 mo alive
57	77/W	Renal carcinoma	5 mo before	Remission*/2 mo alive
16	75/W	Renal carcinoma	NA	Remission*/NA
15	NA	Renal carcinoma	NA	Remission*/NA
96	NA	Renal carcinoma	NA	Remission*/death
42	76/W	Renal carcinoma	Synchronous	Remission*
23	63/W	Renal carcinoma	Synchronous	Remission*/12 mo alive
32	62/M	Prostate carcinoma	Synchronous	NA/NA
89	72/M	Prostate adenocarcinoma	4 mo before	Remission†, 1R†
89	69/M	Prostate adenocarcinoma	2 mo after	Remission, 3R‡
39	57/M	Lung carcinoma	3 yr before	Remission§/NA
47	70/M	Lung carcinoma	3 mo after	No remission*/death at 24 mo
32	68/M	Lung carcinoma	Synchronous	Remission†/NA
86	79/M	Lung carcinoma	Synchronous	Remission*/NA
83	NA	Lung carcinoma	NA	Remission*/NA
26	69/M	Lung carcinoma	12 mo before	Remission*/death at 13 mo
21	65/M	Lung carcinoma	Synchronous	Remission*/death at 14 mo
89	69/M	Lung carcinoma	Synchronous	Remission†, 1R†
89	80/M	Lung squamous carcinoma	3 mo before	Remission
53	64/M	Lung squamous carcinoma	1 mo before	Remission*
74	63/W	Gastric tubular adenocarcinoma	1 mo before	Remission*
69	72/M	Gastric adenocarcinoma	8 d before	Remission*
47	52/M	Pancreatic carcinoma	Synchronous	NA/death at 2 mo
25	NA	Pancreatic carcinoma	NA	NA/NA
75	62/W	Cholangiocarcinoma	12 mo before	Remission§/NA
30	57/W	Breast carcinoma	Synchronous	Remission†/NA
86	59/W	Breast carcinoma	7 yr after	NA/NA
86	82/W	Breast carcinoma	17 yr after	Remission†/alive at 2 yr
81	80/W	Breast carcinoma	NA	Remission*/NA
97	68/W	Breast carcinoma	NA	NA/NA
97	78/W	Uterus carcinoma	NA	NA/NA
30	32/W	Uterus carcinoma	2 yr before	Remission*/NA
91	53/W	Ovarian cancer	4 mo before	Remission*/NA
54	32/M	Pheochromocytoma	NA	Remission*/NA
77	NA	Pheochromocytoma	NA	Remission*/NA
73	27/M	Pharyngeal carcinoma	NA	Remission*/NA
86	73/M	Vocal cord carcinoma	14 yr after	NA/NA
47	76/W	Pelvic sarcoma	2 mo after	No treatment/death at 12 mo
85	46/M	Hepatocarcinoma	Synchronous	NA/died
9	NA	Hepatocarcinoma	NA	Remission*/1R‡

(Continued on next page)

TABLE 4. *(Continued)*

Reference	Age/Sex (yr)	Neoplasia	Occurrence of Vasculitis in Relation to Tumor	Evolution of Vasculitis/Follow-up
89	84/W	Urinary bladder	6 mo before	Remission*, 1R†
89	74/M	Urinary bladder	3 mo before	Remission‡
89	83/W	Urinary bladder	2 mo after	Remission*, 3R†
16	65/W	NUO	NA	Remission*/NA

Abbreviations: NA = not available, NUO = neoplasia of unknown origin.

*Remission of vasculitis after cancer treatment (surgery or chemotherapy).

†Remission of vasculitis after cancer treatment and immunosuppressive therapy.

R‡: relapse of vasculitis heralding tumor recurrence.

§Remission of vasculitis with prednisone with/without immunosuppressive agents.

this was the first report of synchronous malignant B-cell lymphoma and early gastric cancer associated with paraneoplastic vasculitis caused by hypereosinophilic syndrome with mixed cryoglobulinemia. It is also worth mentioning the report of Lulla et al[62] that described a 71-year-old man with leukocytoclastic vasculitis and chronic lymphoid leukemia, who suffered multiple organ failure. Autopsy revealed diffuse leukocytoclastic vasculitis of the stomach, distal ileum, integument and alveoli with petechial hemorrhages, fibrin thrombi, and gangrenous patchy necrosis. To our knowledge, this was the first report of fatal systemic paraneoplastic leukocytoclastic vasculitis from B-cell chronic lymphoid leukemia.

Most hematologic and solid disorders associated with cutaneous vasculitis that have been previously reported might have been classified as hypersensitivity vasculitis according to the ACR classification criteria.[11] However, it is important to keep in mind that patients with neoplasms were specifically excluded when the ACR classification criteria for vasculitis were designed. Nevertheless, some neoplasms associated with cutaneous vasculitis may also fulfill classification criteria for the diagnosis of Henoch-Schönlein purpura. In Table 5 we summarize the cases that were previously reported on the association between Henoch-Schönlein purpura and malignancies.[2–6,10,18,22–24,29,31,33,38,41,44–46,63,65,76,78,80,84,89,95,98,101,102]

As previously described,[7] 1 of our patients with cutaneous vasculitis presenting with urticarial lesions was diagnosed as having urticarial vasculitis associated with a megakaryocytic leukemia. Urticarial vasculitis is a well-defined condition characterized clinically by urticarial skin lesions generally lasting longer than 24 hours, and histologically by leukocytoclastic vasculitis.[87] Its clinical spectrum ranges from isolated cutaneous involvement to a severe systemic disease. Although the etiology is unknown, urticarial vasculitis has been associated with connective tissue diseases, hereditary complement deficiencies, viral infections, serum sickness, drug reactions, sun or cold exposure, and also with malignancies.

Clinicians should be aware of the potential association between cutaneous vasculitis and neoplasm. Gonzalez-Gay et al[36] proposed a workup to exclude a neoplasm in a patient with cutaneous vasculitis (Figure 3). Such a procedure should include the following:

A) Medical history to establish: 1) Duration of symptoms with special attention to previous episodes of palpable purpura. 2) Constitutional symptoms, including severe fatigue, anorexia, and weight loss. 3) Previous history of medication intake that could influence the development of the cutaneous vasculitis. 4) Exclusion of symptoms of systemic vasculitis or connective tissue diseases, mainly systemic lupus erythematosus, Sjögren syndrome, or rheumatoid arthritis. 5) Symptoms that may indicate an infection presenting with cutaneous manifestations.
B) Physical examination: 1) In the presence of fever a systemic infection should be excluded. 2) Enlarged lymph nodes or viscera would require the search for solid tumors or hematologic malignancies.
C) Laboratory tests: including blood biochemistry profile, full blood cell count, immunoglobulins, RF and ANA, and urinalysis. 1) In the presence of severe anemia or bicytopenia, the possibility of an underlying hematologic malignancy should be excluded. In this case consider performing peripheral blood smear and bone marrow biopsy. 2) In the presence of abnormal immunoglobulins in serum or urine, discard multiple myeloma or primary amyloidosis. Consider in these cases light chain assessment in serum and urine. 3) In the presence of hematuria, exclude kidney cancer.
D) Chest radiograph/computed tomography (CT) scan to exclude lung cancer.
E) Age-appropriate cancer screening as a part of the workup for unexplained cutaneous vasculitis.
F) Since most of the associated solid tumors observed in the present study were common malignancies (other than kidney cancer), screening for conditions such as breast cancer, colon cancer, and lung cancer should be considered in the workup for unexplained cutaneous vasculitis.

Treatment and prognosis of paraneoplastic vasculitis is generally related to the underlying neoplasm. In some cases, the vasculitis may also require treatment with glucocorticoids alone or in combination with immunosuppressive agents.[56] In the series described by Sánchez-Guerrero et al,[86] treatment with prednisone was given to only 2 patients with medium-sized arteritis. In the remaining patients of that series, the vasculitis resolved spontaneously.

As expected for a paraneoplastic syndrome, cutaneous lesions usually heal after surgical removal or radiation therapy of the cancer.[41] In case of death, it was due to metastatic or recurrent tumor rather than to vasculitis complications.[41,56] In the current series, 10 patients died due to the malignancy and 6 patients recovered following malignancy therapy.

In conclusion, cutaneous vasculitis presenting as a paraneoplastic syndrome is an entity not uncommonly encountered by clinicians. The current case series of 766 patients, 421 of whom were adults, sheds light on several important characteristics, especially that cutaneous vasculitis in children is virtually never associated with a paraneoplastic etiology, and that the incidence of an associated malignant etiology rises with age. A malignancy

TABLE 5. Henoch-Schönlein Purpura Associated With Neoplasia, Previous Reports

Reference	Age/Sex (yr)	Neoplasia	Occurrence of Vasculitis in Relation to Tumor	Evolution of Vasculitis/Follow-up
10	63/M	Lung carcinoma	9 mo before	Partial remission‡/death at 21 mo
10	73/M	Lung carcinoma	3 mo before	Remission VL*/death at 24 mo
65	59/M	Lung carcinoma	3 mo before	Remission VL*/alive after 25 mo
76	NA	Lung carcinoma	Synchronous	NA/NA
23	57/M	Lung carcinoma	22 mo after	Remission*/alive 4 yr after
80	79/M	Lung carcinoma	6 mo before	Death at 17 mo
98	64/M	Lung carcinoma	Synchronous	Remission*/death at 30 mo
5	67/M	Lung carcinoma	Synchronous	Remission
38	78/M	Lung carcinoma	Synchronous	
89	58/M	Lung adenocarcinoma	Synchronous	Remission*, 1R
2	74/M	Squamous cell bronchial carcinoma	NA	Remission*/remission
31	50/M	Epidermoid carcinoma of the lung	6 mo before	Remission‡/NA
26	55/M	Carcinoid tumor and Schwannoma	3 mo before	Death at 6 mo
41	55/M	Carcinoid tumor	1.5 mo before	Death at 1.5 mo
45	25/M	Renal cell carcinoma	3 mo before	NA/NA
78	46/W	Renal carcinoma	Synchronous	Remission*/alive 3 yr after
33	60/M	Prostate carcinoma	Synchronous	Partial remission‡/NA
78	77/M	Prostate carcinoma	Synchronous	Remission*/alive 4 yr after
22	86/M	Prostate carcinoma	Synchronous	Remission/3 mo
82	75/M	Prostate carcinoma	Synchronous	Remission/NA
46	58/W	Breast carcinoma	12 mo before	Death at 0.5 mo
63	60/W	Breast carcinoma	Synchronous	NA/NA
18	67/M	Gastric carcinoma	Synchronous	Death at 1 mo
44	8/W	Nasopharyngeal diffuse large B-cell lymphoma	NA	Resolved*/alive after 2 yr
76	NA	Epiglottic carcinoma	Synchronous	NA/NA
98	59/M	Esophagus carcinoma	Synchronous	Death at 1.5 mo
102	71/M	Prostate carcinoma	Synchronous	Remission/NA
63	86/M	Prostate carcinoma	Synchronous	NA/NA
63	46/W	Anal carcinoma	Synchronous	NA/NA
89	68/M	Colon adenocarcinoma	Synchronous	No response
10	63/M	Large-cell diffuse lymphoma	9 yr before	NA/NA
95	76/M	T-cell lymphoma	Synchronous	NA/NA
20	37/M	Mycosis fungoides	2 yr before	NA/NA
19	41/M	Multiple myeloma	2 wk after	Remission 3 d later‡/alive 2 mo after
3	NA	IgA multiple myeloma	5 yr before	NA/NA
101	50/M	IgA myeloma	NA	NA/NA
4	29/M	Hodgkin disease	Synchronous	Remission*/complete remission after 2 yr
24	66/M	Non-Hodgkin disease	Synchronous	Died
29	57/W	Myelodysplastic syndrome	NA	NA/NA
6	43/M	Myelodysplastic syndrome	2 mo before	Remission‡/alive after 3 mo

Abbreviation: NA = not available.

*Remission of vasculitis after cancer treatment (surgery or chemotherapy).

†Remission of vasculitis after cancer treatment and immunosuppressive therapy.

‡Remission of vasculitis with prednisone with/without immunosuppressive agents.

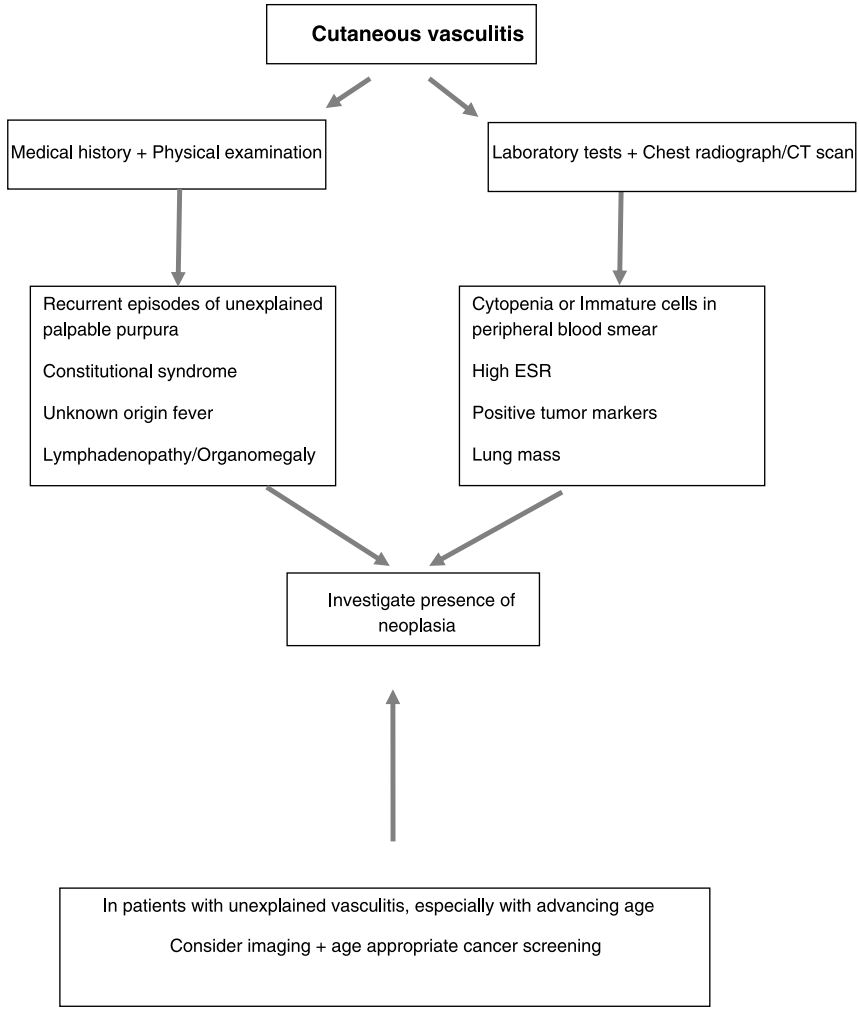

FIGURE 3. Workup in a patient with cutaneous vasculitis to determine the presence of an underlying neoplasm. (Modified from reference 36, Gonzalez-Gay MA, Garcia-Porrua C, Salvarani C, Hunder GG. Cutaneous vasculitis and cancer: a clinical approach. Clin Exp Rheumatol. 2000;18:305–307.)

workup should be considered in patients with unexplained vasculitis, especially patients with advanced age. Hematologic abnormalities in the complete blood count/hemogram are clues to pursue a hematologic malignancy workup, as about half the diagnosed malignancies in our series were of hematologic origin. Most of the associated solid tumors were common malignancies. The prognosis depends on the underlying neoplasia.

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