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 unsel ected 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 cytopneas (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; non-steroidal 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, and 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 cytopenas 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.

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. 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. suggested that malignant neoplasms might produce antigens and consequently cause paraneoplastic vasculitis. In the same year, McLean 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. Most studies on cutaneous paraneoplastic vasculitis include case reports, or small series of patients. We previously described 4 cases of paraneoplastic cutaneous vasculitis.

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 selected patients with cutaneous vasculitis. A literature review was also conducted.
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. 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) and because this age best discriminated Henoch-Schönlein purpura from hypersensitivity vasculitis in previous studies. 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 anemia (diffuse abdominal pain worsening after meals), gastrointestinal bleeding (melaena, 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 ≥11 × 10⁹/L, and leukopenia was defined as a leukocyte count <3 × 10⁹/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 Hеп-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 value ≤ 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,
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. 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 cutaneous 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 polynuropathy. 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.](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 had positive ANA (by immunofluorescence 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 cytophenias (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).

**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 Su15 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 al86 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 al86 had vasculitis involving the intestine leading to acute abdomen. In the series reported by Castro et al,17 1 patient with paraneo-

![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].]
Histologic features in our patients with paraneoplastic vasculitis were consistent with typical small-vessel leukocytoclastic vasculitis. However, larger skin blood vessel involvement has also been reported. In this regard, in the series by Sánchez-Guerrero et al 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. Information on previously reported cases of cutaneous vasculitis occurring in the setting of an underlying hematologic neoplasm is summarized in Table 3. Castro et al 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.

Less commonly, cutaneous paraneoplastic vasculitis is related to the presence of an underlying solid tumor. 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. Solans-Laquè et al 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. It is noteworthy that, in 2009, Nozawa et al 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 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 10⁹/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 x 10⁹/L; anemia as hemoglobin <110 g/L (see Methods section).
†Values are number positive/total number tested (%).
| 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 |
| 79        | 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         | IgG multiple myeloma | 3 mo before | NA |
| 14        | 71/W         | IgG multiple myeloma | 7 yr after | Improved |
| 48        | 53/M         | IgG 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 thrombocytemia | 3 mo after | NA |

Abbreviation: NA = not available.
| 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                |
| 32        | 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.
‡Remission of vasculitis heralding tumor recurrence.
§Remission of vasculitis with prednisone with/without immunosuppressive agents.

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 al16 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 vise versa 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,64 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.31,56 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
| 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 after | 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 after prednisone with/without immunosuppressive agents.
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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