Paraneoplastic Vasculitis in Patients with Solid Tumors: Report of 15 Cases

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ABSTRACT. ***Objective.*** To review all cases of concurrent vasculitis and solid tumors diagnosed at our Department over a 15-year period and explore evidence that would support the notion of vasculitis being a true paraneoplastic syndrome.

Methods. We reviewed the records of all patients diagnosed with vasculitis and solid tumors within 12 months of each other and prospectively followed until death or our report. We analyzed the main features and outcome of vasculitis in this setting. We also reviewed all cases published in the French-English literature.

Results. Fifteen patients (9 men and 6 women) in whom both vasculitis and solid tumor occurred within the same 12 months were identified. Mean age was 72.5 years (range 58-84). In 7 cases the diagnosis of vasculitis antedated that of cancer, in 6 both processes were synchronously diagnosed, and in 2 vasculitis appeared after cancer diagnosis. The most common vasculitis was cutaneous leukocytoclastic vasculitis (n = 9). Other vasculitides included Henoch-Shönlein purpura (n = 2), polyarteritis nodosa (n = 1), and giant cell arteritis (n = 3). The commonest malignancies were carcinomas of urinary organs (40%), lung (26.7%), and gastrointestinal tract (26.7%). The median followup was 28.4 months (range 1–96). Thirteen of the 15 patients demonstrated concordance of disease activity and treatment response for both cancer and vasculitis. Vasculitis flared heralding tumor recurrence or progression in 7 (46.6%) cases.

Conclusion. In our patients, resolution of vasculitis following effective treatment of the putatively linked malignancy, and recurrence of vasculitis heralding tumor recurrence or progression, provide strong evidence for vasculitis being a true paraneoplastic syndrome. Chronic or persistent vasculitis with poor response to usually effective therapy, especially in elderly patients, should raise questions about underlying malignancy. (First Release Dec 15 2007; J Rheumatol 2008;35:294–304)

Key Indexing Terms:
VASCULITIS TUMORS PARANEOPLASTIC SYNDROMES

Neoplastic or malignant disorders are associated with a large number of vasculopathic syndromes that affect both the venous and the arterial vascular trees[1]. However, coexistence of vasculitis and malignancy is rare, and paraneoplastic vasculitides represent less than 5% of all the vasculitides[2-5], being more frequently associated with hematological malignancies than with solid tumors[1-13]. The temporal relationship of malignancy to vasculitis development is variable. Vasculitis has been reported to occur prior to discovery of the neoplasm[5,6,10,11], concurrently with it (within 1 month before or after)[3,4,6], or after malignancy recognition[5,6]. Vasculitis may also herald a malignancy recurrence[7]. Whether these associations are coincidental or truly represent aberrant immunologic responses linked to malignancy is to date unknown[2-10].

Paraneoplastic vasculitides may be of small, medium, and large-sized vessels, but small vessel vasculitis (leukocytoclastic vasculitis) is the most frequently observed[2-12]. Lung (non-small-cell), prostate, colon, breast and renal carcinoma, are the most common solid malignancies described associated with vasculitis[2-11].

We describe 15 patients with various forms of vasculitis and solid tumors diagnosed at our department over the last 15 years that share temporal relationships and in most cases parallel responses to treatment of malignancy. We have also reviewed all cases published in the French-English literature.

MATERIALS AND METHODS

We analyzed the clinical, laboratory, pathologic features, treatment, and outcome of all patients consecutively diagnosed at our Department from January 1991 to January 2006 as having vasculitis and concurrent solid tumors, and prospectively followed until death or our report. Malignancy and vasculitis were considered to be concurrent when both processes were identified within 12 months of each other. Only patients with biopsy-proven vasculitis and malignancy were included in the study. All patients were screened for medications taken before and during the onset of vasculitis and cancer. Vasculitis

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was considered to be possibly related to malignancy when no known precipitating factors of vasculitis such as infections or medications were present, consistency of the relationship between effective treatment for malignancy and vasculitis was observed, and/or synchronous recurrence of both diseases were documented during the followup. Investigation of cancer was not standardized. Patients with recent history of cancer were more prone to be carefully investigated than patients without. Vasculitides were classified according to the criteria proposed by the American College of Rheumatology[14]. All patients were regularly followed up after diagnosis: monthly for the first 3 months; every 2 months the next 6 months; every 4 months until 2 years; every 6 months until 5 years if no relapse appeared and, yearly subsequently.

We conducted a MEDLINE (National Library of Medicine, Bethesda, MD, USA) search with the subject headings "vasculitis," "leukocytoclastic vasculitism," "Henoch-Shönlein purpura," "polyarteritis nodosa," "Wegener granulomatosis," "ANCA associated vasculitis," "temporal arteritis," and "malignancy," "cancer," or "solid tumors," to identify pertinent literature and case reports of vasculitis in association with cancer, published up to November 2006.

RESULTS

In a series of 596 consecutive patients diagnosed at our Department during the last 15 years as having vasculitis and prospectively followed up to date, 60 malignancies (17 hematological and 43 solid malignancies) were recorded in 56 patients (9.39%). Malignancy was diagnosed before vasculitis in 21 cases, simultaneously in 10 cases, and post vasculitis in 29 cases. We only identified 15 of these 56 patients, in whom vasculitis was concurrent with a solid tumor (within 12 months of each other): 9 in 276 patients (3.2%) with leukocytoclastic vasculitis (LCV); 2 in 31 patients (6.6%) with Henoch-Shönlein purpura (HSP); 1 in 86 patients (1.2%) with polyarteritis nodosa (PAN) or antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis, and 3 in 204 patients (1.5%) with giant cell arteritis (GCA). They represented 2.5% of the total series and 25% of all recorded malignancies. Patient age averaged 72.5 years (range 58-84). Six patients were women and 9 men. In 7 (46.7%) cases, vasculitis antedated malignancy by an average of 4 months (range 2 to 10), and in 6 (40%) cases the diagnoses of both processes were simultaneous. In only 2 cases, vasculitis appeared 2 months after cancer diagnosis. Characteristics of the 15 described patients are summarized in Table 1. Three patients have been previously reported[15].

Presenting features of vasculitis in patients with concurrent malignancy. Nine patients (56.3%) developed LCV, 2 HSP, 1 PAN, and 3 GCA.

The presenting features of vasculitis were similar in patients with and without concurrent malignancy (Table 1). The main finding in patients with LCV was palpable purpura, with lower limb ulcers in 2 cases, cutaneous panniculitis in 1 and arthritis in 4. In 4 of the 9 patients, malignancy was suspected due to the development of severe asthenia and weight loss, associated with digital ischemia in 1 case. In 3 patients, vasculitis and malignancy were diagnosed at the same time. In one case, an advanced lung carcinoma with liver metastases was discovered due to an hemoptysis; in another case, iron deficiency anemia revealed a colon neoplasm. Finally, bilateral digital ischemia raised the suspicion of a hidden malignancy in one patient who had a locally advanced lung cancer. LCV appeared 2 months after malignancy diagnosis in 2 cases.

Patients who developed HSP and malignancy presented with severe complaints (scattered necrotizing purpuric lesions, polyarthritis, abdominal pain, renal failure, and pulmonary hemorrhage in 1 case) and no apparent precipitating factor (infection or medication). In both cases, the diagnosis of vasculitis and malignancy were synchronous. In one patient (case 10), malignancy was discovered due to severe rectal bleeding. In another (case 11), a chest radiograph showed a nodule 2 cm in diameter with segmental atelectasis in the left upper lobe, confirmed by chest computerized tomography scan. Fine needle biopsy revealed lung adenocarcinoma.

The patient who developed PAN (case 12) suffered several bouts of purpura, abdominal pain, and arthritis in spite of therapy. Colonoscopy revealed a colon adenocarcinoma.

Finally, 3 patients developed GCA concurrent with malignancy. Their main symptom was polymyalgia rheumatica associated with persistent headache, scalp tenderness, or sudden visual loss. In 2 patients, relapse of headache and polymyalgic symptoms after 4 and 5 months of therapy, with recurrent inflammatory response and a mild to severe asthenia and weight loss, raised the suspicion of an underlying malignancy. In one case (patient 13) a persistent cholostasis led to the discovery of a cholangiocarcinoma. In another case (patient 14) an acute hematuria disclosed a renal neoplasm. In the remaining patient, diagnosis of GCA and malignancy were synchronous.

Presenting features of malignancy in patients with concurrent vasculitis. Solid tumors of urinary organs, lungs, and the gastrointestinal system were the most common observed. Six of the 15 patients (40%) developed urinary tract cancers: 3 urinary bladder carcinoma (2 transitional-cell and 1 squamous-cell carcinoma), 2 prostate adenocarcinoma, and 1 renal cell carcinoma. Four (26.7%) patients developed lung cancer (3 adenocarcinoma and 1 squamous cell carcinoma), and 4 (26.7%) gastrointestinal tract tumors (3 colon adenocarcinoma and 1 cholangiocarcinoma). Finally, one (6.7%) patient had an infiltrating ductal breast carcinoma. In 9 patients malignancy was surgically removed. In the remaining patients, malignancy was discovered at a complicated stage, being locally advanced or with distant metastases.

Laboratory findings in patients with concurrent vasculitis and malignancy. Laboratory findings were nonspecific and included normocytic normochromic anemia in 12 (80%) patients, marked increase of erythrocyte sedimentation rate (ESR) (> 80 mm Hg) in 8 (53%), elevated fibrinogen levels in 14 (93.3%), and proteinuria (2 to 4 gr/l) in both patients who developed HSP. Serological tests for cytomegalovirus, Epstein-Barr virus, parvovirus, mycoplasma, Q fever, HIV, and hepatitis virus B and C were negative in all cases. Antinuclear antibodies (ANA) were detected in 8 (53%) patients, with titers ranging from 1:80 to 1:640 and speckled immunofluorescence pattern. Rheumatoid factor (RF) was positive in 3 (20%) cases.

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Table 1. Characteristics of patients with vasculitis and solid tumors.

Case	Age/Sex	Type of Vasculitis	Presenting Features of Vasculitis	Type of Neoplasia	Occurrence of Vasculitis/Neoplasia
1	84 F	LCV	Purpura, arthritis, microhematuria	Urinary bladder transitional carcinoma	6 mo before
2	74 M	LCV	Purpura, arthritis, microhematuria	Urinary bladder carcinoma	3 mo before
3	83 F	LCV	Purpura, arthritis, microhematuria	Urinary bladder carcinoma	2 mo after
4	72 M	LCV	Purpura, arthritis, digital ischemia, limb ulcers	Prostate adenocarcinoma	4 mo before
5	69 M	LCV	Purpura, arthritis, weight loss	Prostate adenocarcinoma	2 mo after
6	80 M	LCV	Purpura	Lung squamous carcinoma	3 mo before
7	69 M	LCV	Purpura, digital ischemia	Lung adenocarcinoma	synchronous
8	67 M	LCV	Purpura, limb ulcers	Colon adenocarcinoma	synchronous
9	73 F	LCV	Purpura, arthritis, limb ulcers	Colon adenocarcinoma	synchronous
10	68 M	HSP	Purpura, arthritis, renal failure, pulmonary hemorrhage, abdominal pain, rectorrhage	Colon adenocarcinoma	synchronous
11	58 M	HSP	Purpura, arthritis, abdominal pain, renal failure	Lung adenocarcinoma	synchronous
12	69 M	PAN	Purpura, arthritis, chondritis, panniculitis, eyelid edema, myalgia, limb paresthesis	Colon adenocarcinoma	10 mo before
13	83 F	GCA	Cephalgia, scalp tenderness	Cholangiocarcinoma	6 mo before
14	61 F	GCA	Cephalgia, fever, polymyalgia rheumatica	Renal cell carcinoma	4 mo before
15	77 F	GCA	Scalp tenderness, monocular amaurosis, polymyalgia rheumatica	Breast carcinoma	synchronous

LCV: leukocytoclastic vasculitis; HSP: Henoch-Shönlein purpura; PAN: polyarteritis nodosa; GCA: giant cell arteritis.

Total complement and complement fractions were decreased in 2 (13.3%) patients (cases 10 and 12). The serum immunoglobulin A level was only increased in patients who developed HSP. ANCA were negative in all cases.

Outcome and followup. The outcomes for the 15 patients varied (Table 2). All patients with LCV received treatment with prednisone (0.5 to 1 mg/kg/day) but skin lesions showed a chronic and relapsing course in all but 1 patient. Seven of the 9 (77.8%) patients had a complete resolution of vasculitis after tumor removal (3 cases) and/or after successful cytotoxic therapy for the underlying malignancy (4 cases). In 5(55.6%) patients, a flare of vasculitis heralded a tumor recurrence. In one patient (case 1), vasculitis flared 3 times heralding 3 tumor recurrences. Two patients with LCV only received palliative therapy for the neoplasm. Digital ischemia improved after treatment of cancer.

Patients who developed HSP received prednisone (1 mg/kg/day), and intravenous gammaglobulins (25 g/day). One patient also required intravenous cyclophosphamide (0.7 mg/m^2) and plasma exchange. In one case (patient 11), vasculitis waned after tumor removal and flared heralding a tumor recurrence. In another case, vasculitis and malignancy did not improve after treatment with prednisone and cytotoxic therapy, and the patient died in a short period of time.

The patient who developed PAN showed a relapsing course of the illness in spite of treatment with oral prednisone (60 mg/day) and cyclophosphamide (150 mg/day), but vasculitis subsided after tumor removal.

Patients with GCA were initially treated with prednisone (1 mg/kg/day) but 2 of them (cases 13 and 14) showed a poor response to treatment, and one (case 14) required the addition of azathioprine to be symptom free. In both cases, GCA complaints completely disappeared after tumor removal, and prednisone was progressively tapered and discontinued over 2 months. In one case (patient 13), headache and polymyalgia rheumatica relapsed 7 months later, heralding a tumor recurrence. The other patient has been symptom free to date. In the remaining patient (case 15), the tumor was completely removed with no recurrence to date, and GCA was treated with tapering doses of prednisone during 2 years with no relapses.

All patients were followed up until death or our report. The median followup was of 28.4 months (range 1 to 96). Ten of the 15 (66.7%) patients died in a mean period of 11 months (range 1 to 24): 9 of them as a direct result of progression of their malignancy and one (case 12) due to a sepsis.

Case Reports

Case 1. An 84-year-old woman with generalized purpura and

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Table 2. Summary of the treatment and outcome of patients with vasculitis and solid organ tumors.

Case	Vasculitis	Malignancy AJCC Staging System	Vasculitis Therapy	Malignancy Therapy	Response to Treatment		Outcome (mo)
					Vasculitis	Malignancy	
1	LCV	Urinary bladder (T1, N0, M0)	PDN	Endoscopic resection	Remission*, 1R**	1 recurrence	Free of disease (36)
2	LCV	Urinary bladder (T3, N2, M0)	PDN	Surgical resection, chemotherapy, radiotherapy	Remission†	Resolution	Deceased (24)
3	LCV	Urinary bladder (T1, N0, M0)	PDN	Endoscopic resection	Remission*, 3R**	3 recurrences	Free of disease (48)
4	LCV	Prostate (T3, N1, M0)	PDN	Chemotherapy	Remission†, 1R**	Lung metastases	Deceased (18)
5	LCV	Prostate (T4, N1, M0)	PDN	Chemotherapy	Remission†, 3R	Bone metastases	Deceased (12)
6	LCV	Lung (T4, N3, M0)	PDN	Palliative therapy	Remission	Progression	Deceased (4)
7	LCV	Lung (T3, N2, M0)	PDN	Chemotherapy	Remission†, 1R**	Liver metastases	Deceased (8)
8	LCV	Lung (T3, N3, M1)	PDN	Palliative therapy	Partial remission	Cerebral metastases	Deceased (1)
9	LCV	Colon (T3, N0, M0)	PDN	Surgical resection	Remission*	Resolution	Free of disease (60)
10	HSP	Colon (T3, N1, M0)	PDN, CF, IGG, PE	Chemotherapy	No response	No response	Deceased (1)
11	HSP	Lung (T2, N2, M0)	PDN + IGG	Surgical resection	Remission*, 1R	Liver metastases	Deceased (8)
12	PAN	Colon (T2, N1, M0)	PDN + CF	Surgical resection	Remission*	Resolution	Deceased (18)
13	GCA	Biliary tract (T3, N1, M0)	PDN	Surgical resection	Remission*, 1R**	Liver metastases	Deceased (16)
14	GCA	Kidney (T1, N0, M0)	PDN, AZT	Surgical resection	Remission*	Resolution	Free of disease (36)
15	GCA	Breast (T1, N0, M0)	PDN	Surgical resection + tamoxifen	Remission*	Resolution	Free of disease (96)

AJCC: American Joint Committee on Cancer; LCV: leukocytoclastic vasculitis; HSP: Henoch-Shönlein purpura; PAN: polyarteritis nodosa; GCA: giant cell arteritis; PDN: prednisone; CF: cyclophosphamide; IGG: intravenous immunoglobulins; PE: plasma exchange. * Remission after cancer removal; † remission after cancer treatment and immunosuppressive therapy; R*: relapse of vasculitis heralding tumor recurrence or tumor progression.

oligoarthritis that was not improved with oral prednisone (60 mg/day) was referred to our Department in November 2001. Examination revealed a palpable purpura on the upper and lower limbs and trunk, and knee and ankle arthritis. Laboratory tests showed normocytic normochromic anemia (hemoglobin, 10.5 g/dl), normal white blood cell (WBC) and platelet count, ESR 64 mm, serum creatinine 1.2 mg/dl, and microhematuria with no proteinuria. Serological and immunological tests were negative. Skin biopsy revealed LCV. She had a history of a transitional cell papillary tumor of the urinary bladder completely removed 6 months before. Cystoscopy revealed a local recurrence. After tumor removal, vasculitis subsided completely. Six months later, she experienced a new flare of vasculitis and recurrence of the bladder tumor was confirmed by cystoscopy. The tumor was once more removed and the patient complaints resolved quickly. One year later, in June 2003, purpura and arthritis reappeared again heralding a new recurrence of the bladder tumor, and subsided after tumor removal. Since then, she has experienced no further flares of vasculitis. The last cystoscopy, in November 2006, was normal.

Case 10. A 68-year-old man presented in April 1998 with widespread purpura on the lower and upper extremities, trunk and face, bilateral ankle arthritis, hypertension (200/100 mm Hg), and pitting edema. Laboratory tests showed normocytic normochromic anemia (hemoglobin 11.5 g/dl), normal WBC and platelet count, and raised ESR (68 mm), α-2 globulin percentages, and immunoglobulin A levels (783 mg/dl). Serum creatinine was normal. Urinalysis revealed proteinuria (2.4 g/24 h). Serological tests were negative. RF was positive (1:128) as were ANA (1:80). Total complement and complement fractions were normal. Cryoglobulin and ANCA were negative. Skin biopsy revealed LCV with IgA immune deposits affecting the capillaries and venules. Chest radiograph showed no abnormalities. With the diagnosis of HSP, intravenous pulses of methylprednisolone (1 g/day) and prednisone (1 mg/kg/day) were given but his general condition deteriorated quickly, with progressive renal insufficiency (creatinine, 5.4 g/dl) and respiratory failure that led to orotracheal intubation and mechanical ventilation. Chest radiograph showed diffuse patchy opacities. Bronchoscopy revealed an alveolar hemorrhage. Intravenous cyclophosphamide, immunoglobulins, and plasma exchange were administered, with no improvement of the disease. On the fifteenth hospital day he presented severe rectal bleeding. Colonoscopy revealed an unresectable tumor on the distal colon which biopsy disclosed as an undifferentiated adenocarcinoma (T3, N1, M0, Dukes C). Levels of carcinoembrionic antigen (CEA) were within normal limits. He received chemotherapy but died 1 month later.

Case 12. A 69-year-old man presented with purpura, myalgia, and paresthesis of the upper and lower limbs in June 1997. Examination revealed generalized necrotic purpura and asymmetric sensory-motor loss in lower limbs, with decreased deep tendon reflexes. Laboratory tests showed normocytic normochromic anemia (hemoglobin, 9 g/dl), leukocytosis (15,000 /mm^3) with 70% of neutrophils, and raised ESR (110 mm/1st h), fibrinogen levels (6.8 g/dl), and serum creatinine (1.37 mg/dl). Proteinuria and hematuria were not detected. Serological tests were negative. ANA were positive (1:160). Anti-DNA, RF, and ANCA were negative. The electromyographic findings were indicative of a moderate distal mixed

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polyneuropathy. Biopsies of muscle and sural nerve disclosed perivascular pleomorphic infiltrate with fibrinoid necrosis and thrombosis of the small and middle-sized arteries consistent with polyarteritis nodosa. Oral prednisone (60 mg/day) and cyclophosphamide (100 mg/day) were given with a marked improvement of his complaints. However, over the next 6 months he experienced several flares of cutaneous vasculitis, arthritis, and abdominal pain despite sustained treatment with cytotoxic agents. In February 1998, a colonoscopy disclosed a stenotic tumor in the distal colon, which biopsy revealed as an adenocarcinoma. CEA was slightly elevated. The tumor (T2, N1, M0, Dukes B) was completely removed. No further flares of vasculitis were evidenced. Treatment with oral prednisone and cyclophosphamide was maintained for 1 year. Repeated colonoscopies showed no abnormalities. In March 2000 he died due to a urinary sepsis.

Case 13. An 83-year-old woman with a history of cholelithiasis and cholangitis was admitted in April 1999 with one-month history of headache, scalp tenderness, and pain and stiffness involving the neck, shoulder, and pelvic girdles. She denied having jaw claudication. On examination the right temporal artery was thickened, and tenderness and decreased range of movement of both shoulders, with no evidence of proximal muscle weakness, was present. The rest of the examination was unremarkable. Laboratory tests revealed normocytic normochromic anemia (hemoglobin, 9 g/dl), raised ESR (110 mm) and fibrinogen (6.8 g/dl), normal serum muscle enzyme activities, transaminase and bilirubin levels, and raised serum alkaline phosphatase levels (216 UI/l, normal value: 40-110). RF was negative. ANA were positive (1:80). An abdominal ultrasound showed gallbladder lithiasis. Temporal artery biopsy was consistent with GCA. Oral prednisone (60 mg/day) was given, with quick resolution of the GCA symptoms. However, 5 months later headache and polymyalgic symptoms relapsed after attempting prednisone reduction to 15 mg daily. Laboratory test showed raised ESR (80 mm) and fibrinogen levels (8 g/dl), and cholestasis with normal transaminase levels. An abdominal ultrasound showed a choledochal obstruction suggestive of lithiasis, with intra- and extrahepatic ductal dilatation. Endoscopic retrograde cholangio-pancreatography was also suggestive of choledochus lithiasis. Laparotomy revealed an extrahepatic biliary tract tumor involving the gallbladder and the adjacent duodenum (T3, N1, M0), which was completely removed. Histological studies showed a well differentiated cholangiocarcinoma arising from the middle third of the bile duct that involved the gallbladder and the adjacent duodenum. Distant metastases were not found. GCA symptoms subsided quickly after tumor excision. Prednisone was progressively tapered and stopped in 4 months. Seven months later, headache and polymyalgic symptoms recurred. A new course of prednisone (30 mg daily) was started, but she developed persistent abdominal pain, anorexia, and progressive weight loss. An abdominal computerized tomographic scan showed 2 liver metastases and ascites. She died 2 months later due to progressive liver failure.

Results of pooled data from the literature review. We found 144 other reports of patients with vasculitis and coexistent solid tumors (Tables 3 to 6). The majority of them were single case reports[11-13,16-68] with only a few series of patients with vasculitis and cancer, most of them dealing with solid and hematological malignancies[2-6,8,10,45,69-71]. The median age at diagnosis was 75.4 years (range 27-86). The most common solid tumors were non-small cell lung cancer (n = 32), renal carcinoma (n = 20), colon adenocarcinoma (n = 18), and breast carcinoma (n = 11). The most common vasculitis was LCV (n = 43)[3-6,8,9,11,12,15-32,72-78]. Other vasculitides were HSP (n = 24)[4,10,33-44,79,80], PAN (n = 22)[5,45-59], MPA (n = 9)[60-63,69], Wegener's granulomatosis (WG) (n = 19)[64-66,70], Churg-Strauss syndrome (CSS) (n = 1)[67], and GCA (n = 30)[68,71,81-89]. In 77% of cases vasculitis appeared before or concurrent with the initial recognition or relapse of the tumor. In some cases[3,67,81,85,88], relationship between cancer and vasculitis was doubtful due to the long interval between the diagnosis of both processes (range from 4 to 17 yrs). Treatment data for the cancer and/or vasculitis were available in only 87 (60.4%) patients. Glucocorticoid therapy alone or with immunosuppressive agents was generally used to treat the vasculitis, and when combined with surgical removal of the cancer, yielded the best results. The followup period was short in several cases, and the outcome of cancer was not specified in 42% of them[3,6,12,13,17,21,25-29,36,46,49,51,55-57,59,60,69,70,72-75,85-89]. In most fully documented cases radical cancer treatment was followed by resolution of the vasculitis and vasculitis recurrences usually occurred with tumor recurrences, suggesting that the vasculitis was a paraneoplastic syndrome[2,3,5,6,9,10,16,19,33,37,58,69,70,78]. In some cases there was a lack of concordance between disease activity and treatment response for both cancer and vasculitis[3,67,71,81,85,88].

DISCUSSION

Our series of patients with vasculitis and concurrent solid tumors is the largest reported to date. In an attempt to achieve a high degree of confidence in observed relationships between vasculitis and cancer, we applied recommended guidelines for vasculitis being a paraneoplastic process: (1) temporal relationship; (2) consistency of the relationship between effective treatment for malignancy and vaculitis; and (3) an unexpected frequency between the 2 conditions[7]. Further, to avoid random events probably included in several cases described[3,46,48,61,72,83,84], only patients diagnosed as having vasculitis and cancer within the same 12 months and followed up until death or our report were considered. Our finding of 6 out of 15 patients with both cancer and vasculitis within the same month (synchronous) suggests that both processes were related and not chance occurrences. A relationship is also supported by the frequent lack of response of vasculitis to glucocorticoid and cytotoxic therapy prior to the initiation of treat-

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Table 3. Reported leukocytoclastic vasculitis associated with solid organ tumors.

Case	Age/Sex	Neoplasia	Occurrence of Vasculitis in Relation to Tumor	Evolution of Vasculitis/Followup	Reference
1	52 M	Colon carcinoma	3 mo before	Remission */1R†	11
1	69 F	Colon carcinoma	1.5 yr before	Remission/1 R†	22
1	37 F	Colon carcinoma	11 mo after	Partial remission*/ death at 15 mo	9
1	75 F	Colon carcinoma	Synchronous	Remission*/NA	74
1	65 F	Colon carcinoma	NA	Remission*/NA	26
1	63 M	Renal carcinoma	Synchronous	No treatment/death at 5 day	23
1	63 F	Renal carcinoma	Synchronous	Remission*/NA	75
1	63 M	Renal carcinoma	Synchronous	Partial remission/NA	18
1	67 F	Renal carcinoma	Synchronous	Remission*/NA	6
1	75 F	Renal carcinoma	Synchronous	Remission*/18 mo alive	16
1	77 F	Renal carcinoma	5 mo before	Remission*/2 mo alive	16
1	75 F	Renal carcinoma	NA	Remission*/NA	26
1	NA	Renal carcinoma	NA	Remission*/NA	29
1	NA	Renal carcinoma	NA	Remission*/death	77
1	76 F	Renal carcinoma	Synchronous	Remission*	31
1	63 F	Renal carcinoma	Sunchronous	Remission*/12 mo alive	30
1	62 M	Prostate carcinoma	Synchronous	NA/NA	4
1	57 M	Lung carcinoma	3 yr before	Remission††/NA	74
1	70 M	Lung carcinoma	3 mo after	No remission*/death at 24 mo	6
1	68 M	Lung carcinoma	Synchronous	Remission**/NA	17
1	79 M	Lung carcinoma	Synchronous	Remission*/NA	3
1	NA	Lung carcinoma	NA	Remission*/NA	78
1	69 M	Lung carcinoma	12 mo before	Remission*/death at 13 mo	5
1	65 M	Lung carcinoma	Synchronous	Remission*/death at 14 mo	32
1	52 M	Pancreatic carcinoma	Synchronous	NA/death at 2 mo	6
1	NA	Pancreatic carcinoma	NA	NA/NA	24
1	62 F	Cholangiocarcinoma	12 mo before	Remission††/NA	73
1	57 F	Breast carcinoma	Synchronous	Remission**/NA	72
1	59 F	Breast carcinoma	7 yr after	NA/NA	3
1	82 F	Breast carcinoma	17 yr after	Remission**/alive at 2 years	3
1	80 F	Breast carcinoma	NA	Remission*/NA	25
1	68 F	Breast carcinoma	NA	NA/NA	27
1	78 F	Uterus carcinoma	NA	NA/NA	27
1	32 F	Uterus carcinoma	2 yr before	Remission*/NA	72
1	53 F	Ovarian cancer	4 mo before	Remssion*/NA	19
1	32 M	Pheochromocytoma	NA	Remission*/NA	21
1	NA	Pheochromocytoma	NA	Remission*/NA	28
1	27 M	Pharingeal carcinoma	NA	Remission*/NA	12
1	73 M	Vocal cord carcinoma	14 yr after	NA/NA	3
1	76 F	Pelvic sarcoma	2 mo after	No treatment/death at 12 mo	6
1	46 M	Hepatocarcinoma	Synchronous	NA/died	20
1	NA	Hepatocarcinoma	NA	Remission*/1R†	76
1	65 F	CUO	NA	Remission*/NA	26

* 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 ± immunosuppressive agents; CUO: cancer of unknown origin; NA: not available.

ment of malignancy, and the frequent resolution of vasculitis concurrently with specific treatment of the cancer. Indeed, in our series vasculitis subsided after effective treatment of the tumor in 80% of patients, and relapsed heralding a tumor recurrence in 46.6% of cases, suggesting that vasculitis was a true paraneoplastic syndrome. Similar findings were reported by Hutson and Hoffman[6], who made a retrospective review of all patients diagnosed with vasculitis and cancer within the same year at their institution during a period of 18.5 years. They identified 12 patients who were diagnosed with vasculitis (7 LCV, 2 GCA, 2 PAN, and 1 WG) and malignancy within 12 months of each other, but only in 4 cases was the associated malignancy a solid tumor. Unfortunately, most patients were lost to followup after a few months, but concordance of disease activity and treatment response for both cancer and vasculitis was reported in 8 out of 10 patients in whom followup was greater than 2 months. Usually, vasculitis failed to respond to treatment with prednisone prior to recognition and treatment of cancer, as in our series. In the same way, Tatsis, *et al*[70] reported 14 of 477 patients with WG who developed a

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Table 4. Reported Shönlein-Henoch purpura associated with solid organ tumors.

Case	Age/Sex	Neoplasia	Occurrence of Vasculitis in Relation to Tumor	Evolution of Vasculitis/Followup	Reference
1	63 M	Lung carcinoma	9 mo before	Partial remission†/death at 21 mo	34
1	73 M	Lung carcinoma	3 mo before	Remission VL*/death at 24 mo	34
1	59 M	Lung carcinoma	3 mo before	Remission VL*/25 mo alive	35
1	NA	Lung carcinoma	Synchronous	NA/NA	69
1	57 M	Lung carcinoma	22 mo after	Remission*/alive 4 yr after	30
1	79 M	Lung carcinoma	6 mo before	Death at 17 mo	38
1	64 M	Lung carcinoma	Synchronous	Remission*/death at 30 mo	41
1	67 M	Lung carcinoma	Synchronous	Remission	37
1	78 M	Lung carcinoma	Synchronous		43
1	55 M	Carcinoid tumor + schwannoma	3 mo before	Death at 6 mo	5
1	55 M	Carcinoid tumor	1.5 mo before	Death at 1.5 mo	10
1	46 F	Renal carcinoma	Synchronous	Remission*/alive 3 yr after	79
1	60 M	Prostate carcinoma	Synchronous	Partial remission**/NA	13
1	77 M	Prostate carcinoma	Synchronous	Remission*/alive 4 yr after	79
1	86 M	Prostate carcinoma	Synchronous	Remission/3 mo	42
1	75 M	Prostate carcinoma	Synchronous	Remission/NA	44
1	58 F	Breast carcinoma	12 mo before	Death at 0.5 mo	39
1	66 F	Breast carcinoma	Synchronous	NA/NA	96
1	67 M	Gastric carcinoma	Synchronous	Death at 1 mo	40
1	NA	Epiglottic carcinoma	Synchronous	NA/NA	69
1	59 M	Esophagus carcinoma	Synchronous	Death at 1.5 mo	41
1	71 M	Prostate carcinoma	Synchronous	Remission/NA	80
1	86 M	Prostate carcinoma	Synchronous		80
1	46 F	Anal carcinoma	Synchronous		80

* Remission of vasculitis after cancer treatment (surgery or chemotherapy); ** remission of vasculitis after cancer treatment and immunosuppressive therapy; † remission of vasculitis with prednisone ± immunosuppressive agents; NA: not available.

concurrent malignancy, which in 13 cases was a solid tumor. Unfortunately, only the treatment and outcome of 5 patients with renal carcinoma was reported, with 4 of the 5 patients receiving standard immunosuppressive treatment in addition to nephrectomy and achieving at least partial remission. In one case WG relapsed after 18 months with no relapse of cancer. No recurrence of cancer was observed in any case after 2 years of followup. Most recently, Pankhurst, *et al*[69] performed a retrospective review of 200 consecutive patients with WG or MPA in order to investigate the association of malignancy and ANCA-associated vasculitis. They found 20 patients (14 with MPA and 6 with WG) who had a malignancy (10 solid tumors), but only in 4 was the diagnosis of both processes concurrent. In the remaining cases malignancy predated vasculitis for a long period of time (median duration 96 mo), and there was no evidence of subsequent relapse of the malignancy following development of vasculitis that supported a paraneoplastic etiology. Finally, Liozon, *et al*[71] investigated the incidence of malignancy concurrently with GCA, as well as the outcome of vasculitis in such cases. The authors reported 20 patients with GCA and concurrent malignancy, 12 of them with solid tumors. However, only in one case GCA ran a paraneoplastic course.

Consistent with prior studies[3-6,9,10], LCV was the most common vasculitis in our series, and carcinomas of the urinary tract, digestive system, and lung were the commonest malignancies. A poor initial response of vasculitis to usually effective therapy with an early relapse of the inflammatory symptoms, as well as a pronounced decline in general health, prompted us to suspect an underlying tumor in the majority of patients, as described[4,6,9,10,71,83]. Additionally, the presence of severe digital ischemia raised our suspicion about a hidden malignancy in 2 patients with LCV, since this finding had been reported as a rare paraneoplastic syndrome in association with different malignancies[53,75,77]. In most of the reported cases the ischemic changes were bilateral and symmetric, involved the upper extremities, and improved following treatment of cancer as in our series[75,77].

Paraneoplastic HSP was observed in 2 elderly male patients, with severe systemic symptoms and no apparent preceding infection or medication that could have been implicated in the cause of vasculitis. Coexistence of HSP and malignancy has been reported by several authors[33-43,79,80], solid tumors being more common than hematological malignancies. To date, 23 patients with HSP and concurrent solid tumors have been described (Table 4). The patients were overwhelmingly male (95%) and elderly (mean age 68 yrs, range 46-86). All of them had palpable purpura, 61% gastrointestinal symptoms, and 87% renal involvement. In most cases (62.5%), HSP and malignancy appeared synchronous. Pertuiset, *et al*[79] reviewed 19 patients with HSP and malignancy and compared them to 158 patients without. They suggested that patients with malignancy were older, more likely to be male and had a lower frequency of prior infection than those without malignancy, and recommended that men older than 40 years of age

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Table 5. Reported PAN and ANCA-vasculitis associated with solid organ tumors.

Type of Vasculitis	n	Age/Sex	Neoplasia	Occurrence of Vasculitis in Relation to Tumor	Evolution of Vasculitis/Followup	Reference
PAN	1	63 M	Urinary bladder	Synchronous	Remission**/NA	10
	1	56 M	Urinary bladder	Synchronous	Remission*/alive at 7 yr	5
	1	83 M	Duodenum carcinoma	6 mo before	Remission*/death at 1.5 mo	10
	1	NA	Liver carcinoma	Synchronous	Remission*/NA	49
	1	62 M	Cholangiocarcinoma	6 mo before	Partial remission†/death 4 mo	53
	1	62 M	Gastric carcinoma	Synchronous	Resolution*/alive at 24 mo	52
	1	50 M	Gastric carcinoma	Synchronous	Death	50
	1	58 M	Colon carcinoma	3 mo before	Resolution**/NA	46
	1	75 F	Colon carcinoma	Synchronous	Resolution**/death at 11 mo	54
	1	62 F	Colon carcinoma	Synchronous	Remission†/NA	56
	1	65 M	Colon carcinoma	Synchronous	NA	57
	1	56 F	Colon carcinoma	Synchronous	Resolution**/alive at 4 mo	58
	1	NA M	Lung carcinoma*	25 mo before	Remission**/death	47
	1	37 M	Lung carcinoma*	17 mo before	Remission**/death at 22 mo	45
	1	49 M	Lung carcinoma*	Synchronous	No treatment/death	5
	1	65 M	Lung carcinoma*	9 mo before	Remission†/death at 11 mo	54
	1	58 M	Lung carcinoma*	7 mo before	Partial remission†/death 10 mo	5
	1	83 M	Lung carcinoma*	Before	Remission**/NA	59
	1	63 M	Prostate carcinoma + mesothelioma	9 mo after	Remission†/death at 13 mo	48
	1	66 M	Pharyngeal carcinoma	Synchronous	Resolution**/NA	49
	1	NA	CUO	NA	Resolution*/NA	55
	1	NA	CUO	NA	Death	55
MPA	1	NA	Lung carcinoma*	NA	Remission**/death	60
	1	62 F	Lung carcinoma*	Synchronous	Death	63
	1	68 M	Mediastinal carcinoma	4 mo before	Death at 2 mo	61
	1	NA	Prostate carcinoma	NA	Remission**/NA	60
	1	NA	Urinary bladder	NA	Remission**/NA	60
	1	69 F	Liver carcinoma	Synchronous	No treatment/death	62
	1	NA	Breast carcinoma	Synchronous	Remission**/NA	69
	1	NA	Colon carcinoma	Synchronous	Remission**/NA	69
	1	NA	Renal carcinoma	Synchronous	Remission**/NA	69
CSS	1	31 F	Melanoma	Synchronous R*	Death	67
WG	1	45 M	Renal carcinoma	7 mo before	Remission**/NA	6
	1	41 F	Renal carcinoma	Synchronous	Resolution**/alive at 2 yr	70
	1	45 M	Renal carcinoma	Synchronous	Partial resolution**/alive at 2 yr	70
	1	49 F	Renal carcinoma	Synchronous	Resolution**/VL relapse††	70
	1	54 M	Renal carcinoma	Synchronous	Partial remission**/death 12 mo	70
	1	62 F	Renal carcinoma	Synchronous	Partial remission**/alive at 2 yr	70
	1	58 M	Bladder carcinoma	Synchronous	NA/NA	70
	1	59 F	Thyroid carcinoma	Synchronous	Partial improvement**/death	64
	1	63 F	Thyroid carcinoma	Synchronous	NA/NA	70
	1	67 F	Gastric carcinoma	Synchronous	NA/NA	70
	1	64 M	Gastric carcinoma	Synchronous	Death	65
	1	62 M	Colon carcinoma	Synchronous	NA/NA	70
	1	46 F	Uterus carcinoma	Synchronous	NA/NA	70
	1	72 F	Breast carcinoma	Synchronous	NA/NA	70
	1	68 F	Breast carcinoma	Synchronous	Remission*/NA	69
	1	63 M	Lung carcinoma*	Synchronous	NA/NA	70
	1	55 F	Vocal cord carcinoma	Synchronous	NA/NA	70
	1	58 M	Urinary bladder	Synchronous	NA/NA	70
	1	81 M	Pancreatic carcinoma	Synchronous	Improvement/death 5 days	66

CUO: cancer of unknown origin; PAN: polyarteritis nodosa; ANCA: antineutrophil cytoplasmic antibodies; MPA: microscopic polyangiitis; CSS: Churg-Strauss syndrome; WG: Wegener's granulomatosis. * Remission after cancer treatment (surgery or chemotherapy); ** remission after cancer treatment and immunosuppressive therapy; † remission with prednisone ± immunosuppressive agents; †† relapse of WG after 18 months with no relapse of tumor; NA: not available. Note: from references 57 and 58, only patients who developed concurrently vasculitis and solid tumors were considered.

who develop HSP in the absence of infection or medication use should be investigated for neoplasia.

Finally, concurrent GCA and malignancy was recorded in 3 patients in our series, but only in 2 cases ran a clear paraneoplastic course. To date, 30 patients with GCA and concurrent solid tumors have been reported (Table 6). In 19 of them,

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Table 6. Reported giant cell arteritis (GCA) associated with solid organ tumors.

n	Age/Sex	Neoplasia	Occurrence of GCA Related to Tumor Diagnosis	Followup Vasculitis/Malignancy	Reference
1	NA	Lung carcinoma	3 yr before	NA/died of cancer	85
1	45 F	Lung carcinoma	Synchronous	Remission*/alive and well (36 mo)	68
1	60 M	Lung carcinoma	1.5 yr before	Remission*/alive and well	88
1	60 M	Lung carcinoma	Synchronous	NA/died of cancer	88
1	77 M	Colon carcinoma	3 yr before	Remission*/died of cancer (36 mo)	86
1	72 M	Colon carcinoma	Synchronous	Died	86
1	87 F	Colon carcinoma	Synchronous	NA/died of stroke (6 mo)	71
1	78 F	Colon carcinoma	Synchronous	NA/died post-surgery (11 mo)	71
1	79 M	Colon carcinoma	Synchronous	Remission*/alive and well (76 mo)	71
1	82 F	Renal carcinoma	Synchronous	Remission*/NA	86
1	77 F	Renal cell carcinoma	Synchronous	Died	23
1	72 M	Bladder carcinoma	6 mo before	NA/NA	86
1	81 F	Bladder carcinoma	Synchronous	Remission*/alive and well (29 mo)	71
1	74 M	Prostate carcinoma	19 mo before	NA/died of cancer at 2 yr	87
1	64 M	Prostate carcinoma	Synchronous	Remssion*/died (153 mo)	71
1	72 F	Breast carcinoma	Synchronous	VL remission†	82
1	NA	Uterus carcinoma	4 yr before	Died	81
1	68 F	Uterus carcinoma	Synchronous	Remission*/NA	89
1	79 F	Uterus carcinoma	Synchronous	Remission*/lost followup (17 mo)	71
1	65 F	Thyroid carcinoma	Synchronous	Remission*/died of cancer (105 mo)	71
1	80 M	Gastric carcinoma	Synchronous	Remission*/died of cancer (19 mo)	71
1	80 M	Gastric carcinoma	Synchronous	Remission*/died of cancer (29 mo)	71
1	77 M	Brain tumor	Synchronous	NA/died of cancer (20 mo)	71
1	62 M	Brain tumor	11 mo before	Remission*/died of cancer (6 mo)	83
1	73 F	Mediastinum	Synchronous	NA/died of cancer (6 mo)	71
1	86 F	Neuroendocrine	Synchronous	NA/died of cancer (11 mo)	71
1	NA	Maxillar carcinoma	2 yr before	Remission*/died of cancer (24 mo)	86
1	70 F	CUO	2 yr before	Remission*/died of cancer (24 mo)	83
1	NA	CUO	4 yr before	No treatment/died of cancer	81
1	NA	CUO	4 yr before	No treatment/died of cancer	81

CUO: cancer of unknown origin. * Remission of vasculitis with prednisone; † remission of vasculitis after cancer treatment and immunosuppressive therapy; NA: not available.

diagnosis of GCA and cancer were synchronous, but only in 1 case[71] GCA ran a paraneoplastic course. Although some studies suggested that patients with newly diagnosed GCA had a higher cancer risk than controls[83,84], recent large-scale, prospective case-control studies[90] have shown that the overall risk of cancer following GCA is not increased. In this respect, no conclusion can be drawn from our study. However, despite the low occurrence of paraneoplastic GCA, our findings suggest that patients with unusual symptoms and/or atypical GCA course should be evaluated for an underlying malignancy, as recommended[71,83,84,90].

In our series, all patients were followed until death or this report, allowing us to investigate concordance of disease activity and treatment response for both cancer and vasculitis. Resolution of vasculitis following effective treatment of the putatively linked malignancy and recurrence of vasculitis concurrently with progression of cancer provided strong additional support for vasculitis being a true paraneoplastic syndrome. Since 86.7% of our patients were older than 65 years, we recommend that chronic or recurrent vasculitis with poor response to usually effective therapy, especially in elderly patients, should arouse suspicion and merit evaluation for an occult malignancy.

Taking into account our findings and those published in the literature we can draw some conclusions: (1) malignancy may present initially with an acute vasculitis; (2) 2.5 to 5% of patients with vasculitis have a related malignancy that may not be obvious at presentation; (3) chronic or persistent vasculitis with poor response to usually effective therapy, especially in elderly patients, should be evaluated bearing in mind the possibility of them being paraneoplastic; (4) recurrence of a tumor might be suspected when vasculitis appears or relapses in patients diagnosed as having malignancy.

Large prospective studies are needed, not only for better understanding the mechanisms underlying the association of cancer and vasculitis, but also to help select subpopulations of patients more prone to undergo a malignancy screening in the setting of vasculitis, and guide the malignancy search strategy, according to the most frequently encountered tumors and current standards of test and examinations.

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