Concurrent Temporal (Giant Cell) Arteritis and Malignancy: Report of 20 Patients with Review of the Literature

ERIC LIOZON, VÉRONIQUE LOUSTAUD, ANNE-LAURE FAUCHAIS, PASCALE SORIA, KIM LY, BALY OUATTARA, KAÏEF RHAIEM, SYLVIE NADALON, and ELISABETH VIDAL

ABSTRACT. ***Objective***. To determine the frequency of occurrence of malignancy concurrently with temporal arteritis (TA), as well as features and outcome of the vasculitis in such cases.

Methods. In a series of 271 consecutive patients with TA (219 biopsy-proven), we retrospectively analyzed the frequency and type of malignancy concurrent with vasculitis (less than 1 year before or after), as well as the main features and outcome of TA in this setting. We also surveyed all cases published in the French-British literature.

Results. We observed 20 patients with TA and concurrent malignancy and reviewed 27 similar published reports. GCA was documented pathologically in 86% of the cases. The time between diagnosis of TA and that of malignancy averaged 3.5 months (synchronous diagnoses in 27 patients). Various locations of cancers were found, particularly the gastrointestinal tract (9 cases); blood malignancies accounted for 45% of cases (lymphoid disorder in 9, myelodysplastic syndrome in 11, chronic myelogenous leukemia in 1). In our patients, logistic regression analysis failed to demonstrate differences between those with and without malignancy, except for a higher frequency of rheumatic involvement in the former group (60% vs 30%; p = 0.01). The initial response to steroid treatment was good in 92% of 40 assessable patients, and the vasculitis course mirrored that of malignancy in only 2 patients. Regarding the outcome of TA, no differences were observed in our patients with and without malignancy.

Conclusion. Concurrent malignancy in TA is not a rare finding, being observed in up to 7.4% of the cases. Solid malignancies and hematological disorders, especially myelodysplastic syndromes, may represent precipitating factors for development of TA, which infrequently run a paraneoplastic course. Patients with and without malignancy seem almost indistinguishable regarding features and outcome of TA. Physicians who care for patients with TA should be mindful of this potential association, even in typical cases. (First Release July 1 2006; J Rheumatol 2006;33:1606–14)

Key Indexing Terms:
GIANT CELL ARTERITIS TEMPORAL ARTERITIS MALIGNANCY
MYELODYSPLASTIC SYNDROMES CONCURRENT

Temporal (giant cell) arteritis (TA) is a common disorder in the elderly[1]. Its etiology is unknown, although infectious agents, particularly viruses, have been postulated to represent triggering or precipitating factors[2-6]. Vasculitides occasionally associated with malignancy include leukocytoclastic vasculitis, polyarteritis nodosa, digital arteritis, Henoch-Schönlein purpura, erythema nodosum, and giant cell arteritis (GCA). Although past autopsy studies had shown simultaneous presence of malignancy and active GCA in some patients[7,8], TA has seldom been cited in large series of rheumatic and vasculitis disorders associated with cancer[9-14] or blood malignancies[15-21]. In retrospective studies, a high prevalence of malignancy was found in patients with TA[22] and patients with polymyalgia rheumatica (PMR)[22,23]. Conversely, case-control prospective studies have yielded conflicting results regarding an increased risk of malignancy in patients with biopsy-proven TA[24-27]. Further, although it is commonly believed that GCA should not be regarded as a paraneoplastic syndrome, the relationship between this entity and malignancy has not been precisely addressed until now, and there are no established guidelines for investigation of malignancy in patients under treatment for TA.

We recorded and analyzed all reported cases of concurrent malignant disease in a large series of consecutive patients with TA diagnosed and followed at a single institution.

MATERIALS AND METHODS

Patients and data collection. We retrospectively analyzed clinical, laboratory, pathologic features, treatment, and outcome of 271 consecutive patients with

From the Department of Internal Medicine, University Hospital, Limoges, France.

E. Liozon, MD; V. Loustaud, MD; A-L. Fauchais, MD; P. Soria, MD; K. Ly, MD; B. Ouattara, MD; K. Rhaiem, MD, S. Nadalon, MD; E. Vidal, MD.

Address reprint requests to Dr. E. Liozon, Service de Médecine Interne A, CHRU Dupuytren, 2 avenue Martin Luther King, 87042 Limoges, France. E-mail: eric.liozon@unilim.fr

Accepted for publication March 27, 2006.

TA who were referred to the internal medicine department of our hospital from January 1976 through May 2005. Ninety-two percent of the patients were recruited before steroid treatment, the remaining cases being already treated for less than 1 month at the time of admission. Only cases fulfilling at least 3 of the American College of Rheumatology criteria for GCA[28] were included in the study. The diagnosis of GCA was pathologically established according to Huston's criteria[29]. Pretreatment clinical, laboratory, and pathological data were recorded prospectively at the time of diagnosis by a senior internist using in each patient a specifically designed, comprehensive questionnaire that includes a detailed history and 174 items. Special efforts were made in evaluating the delay to diagnosis from the onset of symptoms of vasculitis, the presence of constitutional syndrome (defined by a temperature ≥ 38°C for at least 1 week, severe asthenia, and/or weight loss > 5%), jaw claudication, PMR, abnormal temporal artery on examination (absence of pulses on all or part of its course, nodules, thickening, swelling, or tenderness on palpation), and upper limb artery involvement as defined elsewhere[30]. The occult form of TA has also been defined[31].

All but 6 patients were treated according to the same protocol[30]. One hundred ninety patients received prednisone 0.6–0.8 mg/kg/day until the patient became symptom-free and the C-reactive protein level fell below 5 mg/l. The prednisone dose was then progressively tapered to 0.35 mg/kg within 4 to 6 weeks. Seventy-four patients with ischemic symptoms or threat to their vision (transient ischemic symptoms, abnormal fundus, or abnormal ophthalmic artery flow on Doppler studies) initially received prednisone 0.9 to 1 mg/kg, preceded in 60 by pulse methylprednisolone, then similarly tapered. In addition, dapsone (75–100 mg/day) was given to 30 unselected patients as a glucocorticoid-sparing agent[32], but only 5 patients received an immunosuppressive therapy (azathioprine or methotrexate) during the first year. Recovery from GCA was defined as no clinical or laboratory relapses for at least 6 months after the cessation of treatment.

Malignancies. All pathologically or cytologically-verified malignancies concurrent with TA (less than 1 year before or after) were included in the study. Myelodysplastic syndromes (MDS) were diagnosed on the basis of combined persistent blood abnormalities and bone marrow findings according to the French-American-British classification[33]. The diagnosis of B cell chronic lymphocytic leukemia (CLL) was based on the presence of a clonally expanded mature B cell population in blood and bone marrow. Basal cell carcinoma of the skin (3 patients) and essential thrombocythemia without blastic transformation (2 patients) were not regarded as malignancies. Malignancy and TA were regarded as concurrent illnesses if they were diagnosed within 1 year of each other. However, bulky tumors diagnosed up to 18 months after TA but already symptomatic within the first year were considered concurrent. The status of tumors occurring prior to the vasculitis was reassessed at the time of its onset.

Investigation of malignancy was not standardized. Patients with recent history of cancer were more prone to be meticulously investigated than patients without. The physicians of all patients seen during the last 10 years and lost to followup were contacted by phone or letter to obtain an update on their vasculitis, the appearance of malignancy, or death. Thus, only 15 patients were lost to followup in the early course of TA.

Statistical analyses. We retrospectively analyzed the potential effect of malignancy concurrent with TA on the clinical features, response to glucocorticoid treatment, and outcome of vasculitis. The chi-square test and the Mann-Whitney test were used to compare cases with and without malignancy. To avoid sampling bias and in order to compare only well separated groups, we excluded from the control group 10 patients who had a history of malignancy occurring 1 to 3 years before or after GCA or earlier malignancy that was still active at its onset. Cancer incidence data were obtained from the population-based regional (Limousin) tumor registry available for the period 1989–99.

Review of the literature—data source and extraction. French and English-language articles published since 1960 dealing with GCA and malignancy, cancer, leukemia, MDS, myeloma, or CLL were reviewed using both personal literature data on TA and computer-assisted data extraction. Only reports on patients with certain or probable TA and concurrent proven malignancy (i.e., diagnosed less than 1 year before or after TA onset) were included in the review. Patients with malignancy and non-GCA of the temporal artery (such as polyarteritis nodosa or unclassifiable vasculitis) were considered not eligible for study. Finally, cases where the temporal artery specimen was infiltrated by malignant cells or amyloidosis without vasculitis were also excluded.

RESULTS

Main characteristics of the series. Ninety-one patients (33.6%) were men. Patient age averaged 75.1 years (range 57–94). GCA was biopsy-proven in 219 patients (81%). Permanent ischemic symptoms, which occurred in 45 patients, included visual loss in 34, ocular nerve palsies in one, C5 plexopathy in one, stroke or deafness in 6, and myocardial infarction in 3. Rheumatic symptoms were recorded in 95 patients (35%), including PMR in 70, peripheral synovitis in 15, and both manifestations in 10. Only 2 patients had isolated PMR with a positive result of temporal artery biopsy. Constitutional symptoms were the only features of GCA in 26 biopsy-proven patients. Upper limb artery involvement was diagnosed clinically in 39 patients and confirmed in 15 by selective aortic arch arteriography or noninvasive imaging techniques.

Frequency of concurrent malignancy. The mean followup was 59.2 ± 39 months for 255 patients regularly followed (16 patients lost early to followup), 224 of whom were followed at least 1 year and 136 of whom recovered from TA. Fifty-one malignancies were recorded in 48 patients, 17 being diagnosed before TA, 10 simultaneously with TA, and 24 after TA. Twenty-one malignancies in 20 patients met our criteria for concurrency with TA, representing 7.4% of the series, and 41% of all recorded malignancies. During the first year of followup, the crude yearly incidence of malignancy was thus 8.9%, while it ranged from 1.1% to 2.2% in the general population of this age group in the Limousin region. Five patients with active malignancy (metastatic breast cancer in 2, and B cell lymphoma, chronic lymphatic leukemia, and chronic myelomonocytic leukemia in one patient, respectively) during the course of TA did not meet the mandatory criteria for concurrency.

Malignancy was the most frequent illness diagnosed concurrently with TA, followed by nonmalignant thyroid disorders (10 patients) and Sjögren's syndrome (6 patients)[34]. Recent viral infection or tooth extraction, circumstances that might also trigger GCA, were recorded in 4 patients with malignancy.

Presenting features of malignancy in patients with concurrent TA. The 21 malignancies consisted of 14 cancers, 6 MDS, and one chronic myelogenous leukemia (Table 1). The most frequent tumor site was the gastrointestinal tract (8 patients). The overall time separating the vasculitis and malignancy onset averaged 4.5 months. The malignancy was diagnosed synchronously with the vasculitis in 10 patients and soon after the vasculitis in 10 patients (average delay 8.9 mo). A patient (case 5) with history of smoking had 2 separate cancers closely surrounding the vasculitis onset.

Table 1. Characteristics of patients with temporal arteritis and concurrent malignancy.

Patient	Age/Sex	Presenting Features of Giant Cell Arteritis	TAB Result	ESR (mm/h)/CRP (mg/l)
1	65 F	Cranial arteritis, severe bilateral ULAV	Negative	135/100
2	87 F	Cranial arteritis (acute onset) with PMR and ULAV	Negative	86/97
3	64 M	Masked (or silent) temporal arteritis, then ULAV	GCA	125/292
4	78 F	Cranial arteritis (acute onset) with PVL	GCA	60/NP
5	73 F	Cranial arteritis (acute onset)	Negative*	45/52
6	81 F	Seronegative polysynovitis then cranial arteritis with PVL	GCA	NA
7	80 M	Cranial arteritis with PMR	GCA	114/10
8	86 F	Cranial arteritis with PMR	GCA	130/68
9	79 M	Cranial arteritis (acute onset)	GCA	60/164
10	79 F	Bilateral ULAV	Negative	60/NP
11	80 M	Cranial arteritis	GCA	45/73
12	77 M	Cranial arteritis (acute onset) with peripheral arthritis	GCA	63/NP
13	70 M	Cranial arteritis with PMR	Negative	76/59
14	76 F	Cranial arteritis with PMR	GCA	90/118
15	73 F	Masked (or silent) temporal arteritis	GCA	140/140
16	67 F	Cranial arteritis with PMR	GCA	85/NP
17	68 M	Cranial arteritis with PMR	GCA	92/94
18	70 F	Cranial arteritis with PMR	GCA	82/34
19	87 F	Cranial arteritis with PMR	GCA	90/78
20	74 F	Cranial arteritis with peripheral arthritis	GCA	115/110

* Bilateral TAB (organized thrombus in a collateral artery). ULAV: upper limb artery vasculitis. PVL: permanent visual loss. TAB: temporal artery biopsy. GCA: giant cell arteritis. NA: not assessable (patient receiving prednisone 8 mg/day for polysynovitis at onset of temporal arteritis). NP: not performed.

Gross blood cell count abnormalities that persisted upon controlling the inflammatory response readily pointed to an underlying blood dyscrasia in most patients with MDS or leukemia. Conversely, symptoms and/or routine laboratory tests pointing to cancer were lacking in 5 patients with a carcinoma (cases 4, 6, 8, 10, 11), which was often discovered at a complicated stage. Three solid tumors (cases 7, 10, 12) were found between the 12th and 18th month followup. In retrospect, all were locally advanced tumors that were symptomatic for months and could have been diagnosed earlier. Recurrent inflammatory response during treatment raised the suspicion of cancer in 2 patients. One patient (case 5) developed TA 3 months after surgery for cancer of the colon. She experienced an early TA relapse with headache and jaw claudication, while taking prednisone 25 mg/day. Because she complained of intermittent chest pain and dyspnea, a computed tomography scan was performed. A bulky mediastinal tumor was found, and was confirmed malignant on mediastinoscopy. This is the only patient in whom malignancy masqueraded as a typical TA relapse.

Presenting features of TA in patients with concurrent malignancy. GCA was pathologically-documented in 15 patients with malignancy (Table 2). The patient described above underwent a second biopsy, which revealed only an organized thrombus in a small collateral temporal artery, indicating a possible cancer-induced prothrombotic state. The temporal artery biopsy yielded unequivocal negative results in the remaining 4 patients. Significant clinical findings included cranial arteritis in 17 patients, upper limb artery involvement in 4, and rheumatic involvement in 12. Five out of 8 patients who denied fever, weight loss, or severe asthenia had a blood malignancy.

Comparative study of presenting features of TA in patients with malignancy and without. We found no statistical differences (Table 3) between patients with and without a history of malignancy for age, gender, cephalic features, large artery involvement, constitutional symptoms, temporal artery biopsy findings, mean erythrocyte sedimentation rate, acute serologic phase response, hemoglobin levels, blood cell counts, or liver enzyme abnormalities. However, rheumatic manifestations, including PMR, were more prevalent in the malignancy group (60% vs 30%; $p = 0.012$).

Outcome of patients with TA and malignancy — comparison with the rest of the series. Eight patients received curative treatment for malignancy, whereas 12, including 6 with MDS, received only supportive care or no treatment (Table 4). With a followup of 51 ± 43 months, 8 patients experienced at least one vasculitis relapse, 12 recovered from TA in a mean delay of 25.1 months, and 3 are still receiving corticosteroid treatment (duration of therapy 29 to 48 mo). One patient (case 16) suffered multiple relapses and was still receiving 11 mg/day prednisone 3 years after diagnosis. In no other longterm survivors did the vasculitis appear significantly steroid-resistant. Eight patients died of progression or complication of their

Table 2. Characteristics of malignancies in patients with concurrent temporal arteritis.

Patient	Malignancy	Delay (mo)*	Symptoms and/or Signs Related to the Malignancy	Stage or Extension
1	Thyroid	Synchronous	Nodular goiter	Local
2	Rectum	Synchronous	Hematochezia	Local
3	Prostate	Synchronous	Routine rectal examination	Local
4	Sigmoid colon	After (11)**	Diastatic perforation of the cecum	Local (bulky)
5	Mediastinum	After (2)†	CS, chest pain, relapsing TA	Regional (bulky)
6	Bladder	Synchronous	CS, pulmonary embolism	Local (bulky)
7	Gastric	After (17)**	CS, dermatologic paraneoplastic syndrome	Regional (huge)
8	Neuroendocrine	After (8)	CS, relapsing inflammatory response	Hepatic metastases
9	Rectum	After (9)	Hematochezia	Local
10	Uterus	After (14)**	Digital necrosis, metrorrhagia	Regional
11	Gastric	Synchronous	Epigastric pain upon starting steroid treatment	Local
12	Brain (astrocytoma)	After (16)**	Absentia epileptica, abnormal behavior, hemiparesia	Local (bulky)
13	B cell CLL	Synchronous	Blood lymphocytosis	Early stage
14	RA	After (6)	Macrocytic anemia + thrombocytopenia	NA
15	RA	Synchronous	Blood count abnormalities	NA
16	CMML	Synchronous	Isolated blood monocytosis	NA
17	ASIA	Synchronous	Isolated macrocytic anemia	Early transformation into AML
18	CMML	After (3)	Isolated blood monocytosis	NA
19	RAEB	Synchronous	Isolated macrocytic anemia	NA
20	CML	After (3)	Blood leukocytosis with myelemia	Chronic phase

* Delay between temporal arteritis onset and diagnosis of malignancy. ** Malignancies were, in retrospect, symptomatic for months but were not promptly investigated (Patients 4 and 10) or were initially misdiagnosed (Patients 7 and 12). † Patient also had a history of cancer of the rectum 3 months before GCA. CLL: chronic lymphocytic leukemia. RA: refractory anemia. CMML: chronic myelomonocytic leukemia. CML: chronic myelogenous leukemia. ASIA: acquired sideroblastic idiopathic anemia. AML: acute myeloblastic leukemia. GCA: giant cell arteritis. TA: temporal arteritis. CS: constitutional symptoms. NA: not assessable.

Table 3. Treatment and outcome of patients with temporal arteritis and concurrent malignancy.

Patient	Treatment of Malignancy	Prednisone Dose*	Use of Dapsone	TA Relapses	Final Outcome
1	Total thyroidectomy§	0.7/14/30	No	Yes (× 3)	Recovered from TA, died of cancer (105 mo)
2	None	0.7/6/16	No	No	Died of stroke (6 mo)
3	Prostatectomy, radiotherapy	0.7/21/49	No	Yes (× 2)	Recovered from TA, died (153 mo)
4	Emergency surgery	0.95/11/10	Yes	No	Died post-surgery (11 mo)
5	Palliative radiotherapy	0.7/22/6	No	Yes, early (× 1)	Died of cancer (6 mo)
6	Tumorectomy	1/13/22	No	No	Recovered from TA, alive and well (29 mo)
7	Total gastrectomy	0.7/12/12	Yes	No	Recovered from TA, died of cancer (19 mo)
8	None	0.8/9/11	No	No	Died of cancer (11 mo)
9	Surgery	0.7/17/27	No	No	Recovered from TA, alive and well (76 mo)
10	Total hysterectomy	0.7/1/6	Yes	No	Recovered from TA, followup After hysterectomy, unknown (17 mo)
11	Total gastrectomy	0.75/15/16	No	No	Recovered from TA, died of cancer relapse (29 mo)
12	None	0.7/17/20	No	Yes (× 2)	Died of cancer progression (20 mo)
13	None	0.7/17/25	No	No	Recovered from TA, alive, without progression of CLL (48 mo)
14	None	0.7/12/28+	No	Yes (× 1)	Ongoing treatment for TA (28 mo)
15	None	0.7/15/21	No	No	Recovered from TA (30 mo)
16	None	0.8/15/37	No	Yes (× 3)	Recovered from TA, alive (49 mo)
17	Various antileukemic chemotherapeutic regimens	0.6/NA/18	No	No	Recovered from both TA and leukemia, died of Hodgkin's disease (134 mo)
18	None	0.6/16/48+	No	Yes (× 3)	Ongoing treatment for TA relapse, without progression of MDS (48 mo)
19	None	0.7/NA/38+	No	Yes (× 1)	Lost to followup (38 mo)
20	Chemotherapy	0.7/10/11	Yes	No	Recovered from TA, died of CML (72 mo)

* Initially (mg/kg)/at 6 mo (mg/day)/treatment duration (mo). § Papillar cancer of the thyroid was overlooked and was disclosed several years later, when metastases developed. CLL: chronic lymphocytic leukemia. ASIA: acquired sideroblastic idiopathic anemia. AML: acute myeloblastic leukemia. CMML: chronic myelomonocytic leukemia. CML: chronic myelogenous leukemia. GCA: giant cell arteritis. TA: temporal arteritis. CS: constitutional symptoms.

Table 4. Comparison of various clinical and laboratory variables in patients with temporal arteritis with a concurrent malignancy and without. Values are number of assessed, mean ± SD (%).

Variable	Malignancy (n = 20) N Assessed, mean ± SD/%		No Malignancy* (n = 241) N Assessed, mean ± SD/%	
Age, yrs	20	75.7 ± 7	241	75 ± 7.7
Male	20	35	241	34.9
Positive TAB	20	75	241	88.3
Delay in diagnosis, days	19	60.4 ± 41.5	238	81.4 ± 88.8
Acute onset of GCA	20	21.4	237	38.7
Constitutional symptoms	19	68.4	240	73.8
Fever > 38°C	19	36.8	237	56.1
Systemic symptoms alone	20	10	241	10.4
Headaches	20	90	241	83.4
Occipitalgia	20	60	237	47.7
Scalp tenderness	17	41.2	229	52.4
Facial swelling	20	15	241	5.8
Jaw claudication	20	40	240	33.8
Mean number of ENT symptoms per patient	20	1.35 ± 2	240	1.21 ± 1.4
Physical changes on temporal arteries	20	40	238	55.5
Upper limb artery involvement	20	25	241	14.1
Ischemic symptoms	20	25	241	33.8
Permanent visual loss	20	10	241	12.4
Rheumatic symptoms	20	60	241	29.9**
Polymyalgia rheumatica	20	50	241	26.1†
Peripheral synovitis	20	15	241	7.5
ESR, mm/h	18	90.7 ± 33	233	90.5 ± 26.6
C-reactive protein, mg/l	16	107.8 ± 74.5	207	100 ± 62.6
Fibrinogen, g/l	14	6.49 ± 2.18	160	6.35 ± 1.65
Hemoglobin, g/dl	19	11.5 ± 2.1	232	11.3 ± 1.6
Leukocyte counts, g/l	18	8841 ± 3126	229	9118 ± 2862
Platelet count, g/l	17	444 ± 167	220	435 ± 149
Liver enzyme abnormalities	14	57.1	202	44.1

p values were calculated using chi-square test or Mann-Whitney U test, as needed. ** p = 0.01; † p = 0.04 (chi-square test); *10 patients who had a history of malignancy 1 to 3 years before or after GCA or earlier malignancy that was still active at its onset were excluded from this group. ENT: ear/nose/throat.

concurrent malignancy, representing 12% of all fatalities observed in the series. We found no statistical differences between patients with and without history of malignancy in terms of the initial dose of prednisone, frequency of concurrent use of dapsone, short-term response to corticosteroid therapy, rate of subsequent flare or relapse during and after treatment, mean prednisone dose at 3, 6 and 12 months, or mean duration of treatment in patients who recovered from TA (Table 5).

Results of pooled data (including the present series and the literature survey). We found 27 other reports of patients with concurrent TA and malignancy (Table 6)[7,8,13,17,35-51]. Forty-seven patients, including our patients, were thus analyzed. The mean age was 73 years; 39% were men. GCA was biopsy-proven in 85% of the cases. The delay between the documentation of TA and that of malignancy averaged 4.3 months, with synchronous diagnoses in 26 patients. The most frequent types of malignancies were the MDS (11 cases), lymphoid malignancies (9 cases), and cancers of the gastrointestinal tract (9 cases). Overall, 15 distinct types or sites of malignancy were represented. Among 27 cancers, 10 were bulky, regional, or metastatic tumors. Rheumatic symptoms (PMR and/or peripheral arthritis) were observed in 18 patients (40%), and aortitis in 4 patients. The initial response of vasculitis to corticosteroid treatment was stated as good in 92% of the cases, and GCA never ran a paraneoplastic course, except in 2 patients, one in our series and one in the literature survey[46]. In the latter report, GCA subsided after removal of a cancer of the kidney. The authors stated, however, that the patient also had received an azathioprine-prednisone regimen.

DISCUSSION

In our large, unselected, series of patients with TA, homogeneously treated and followed, we found an incidence of temporally associated malignancy of 7.4%. This is a minimal estimate, since the initial investigations in patients with TA did not include cancer screening, and the followup was less than 1 year in 20% of the cases. In retrospective studies, the incidence of malignancy found in the followup of patients with GCA varied from 0% to 15%[22,52-59], probably due to non-uniform criteria used to define their association, differences in methodology in searching for cancer and length of followup, and the proportion of patients with pure PMR included in studies. In prospective studies, the incidence of malignancy in

Table 5. Comparison of therapeutic and outcome variables in patients with temporal arteritis with a concurrent malignancy and without.

	Malignancy (n = 20) N Assessed, mean ± SD/%		No Malignancy* (n = 241) N Assessed, mean ± SD/%	
Mean initial prednisone dose, mg/kg	20	0.74 ± 0.12	240	0.76 ± 0.17
Mean prednisone dose at 3 mo, mg/day	18	20.3 ± 7.6	196	19.8 ± 5.8
Mean prednisone dose at 6 mo, mg/day	17	13.8 ± 4.9	173	14.7 ± 5.5
Mean prednisone dose at 12 mo, mg/day	16	7.1 ± 4.6	139	8.8 ± 4.9
Additional treatment with dapsone	20	15	241	14.9
No. of GCA flares per patient	20	0.95 ± 1.32	222	0.82 ± 0.9
Mean duration of treatment, mo	20	22.3 ± 12.9	241	22.9 ± 17.8
Rates of recovery from GCA	20	55	241	45.8
Death rates	20	50	241	19.6**

* p values calculated using chi-square test or Mann-Whitney U test, as needed. ** p = 0.01 (chi-square test).

Table 6. Published cases of concurrent temporal (giant cell) arteritis and malignancy.

Study	Age/Sex	TAB Result	Type of Malignancy (location)	Stage	Delay (mo)†
Hamrin[7]	74 M	GCA (healed)	K (prostate)	Local	After (12)
Östberg[8]	77 M	GCA	K (cecum)	Local (bulky)	After (12)
	73 M	GCA	K (bladder)	Regional	After (6)
	72 F	GCA	K (sigmoid colon)	NR	Synchronous
	82 F	GCA	K (kidney)	Local	Synchronous
von Knorring[35]	62 M	GCA	K (brain)**	Local	After (9)
Larregain-Fournier[36]	73 M	GCA	B cell CLL	Early	Synchronous
Dupuy-Braud[37]	81 F	GCA	Myeloma	Early	Synchronous
Hoag[38]	77 F	GCA	K (kidney)	Local	Synchronous
No author[39]	84 M	GCA	WMG	NA	Synchronous
Bensaïd[40]	76 M	GCA	B cell CLL	Early	After (6)
Lie[41]	45 F	GCA	K (lung)	Local	Synchronous
Billström[17]	67 F	Fibrosis	RAEB-t	NA	Before (4)
Speed[42]	60 M	GCA	K (lung)	Regional	After (18)
	60 M	NA	K (lung)	Local, advanced	Synchronous
Gonzalez-Gay[43]	73 M	GCA	B cell CLL	Early	Synchronous
Estrada[44]	68 F	GCA + amyloidosis	Myeloma	NR	Synchronous
Keung[45]	68 F	GCA*	Myeloma	NA	Synchronous
Solans[46]	61 M	NA	K (kidney)	Local	After (4)
Hutson[13]	72 F	NA	K (breast)	Local	Synchronous
	79 F	NA	Lymphoma	NA	Before (2)
Orbo[47]	68 F	GCA	Uterus	Local	Synchronous
Kohli[48]	68 F	GCA	RA	NA	Synchronous††
Espinosa[49]	75 F	GCA	RAEB	NA	Synchronous
	79 F	Not Done	CMML	NA	Synchronous
Mouadeb[50]	74 F	GCA	K (esophageal)	Local	Synchronous
Steurer[51]	67 M	Large-vessel arteritis	RAEB	NA	Synchronous

* With concurrent amyloidosis. ** No histological examination. † Between the documentation of temporal arteritis (TA) and that of malignancy. †† Synchronous with PMR onset (TA 2 yrs after). GCA: giant cell arteritis. NR: not reported. NA: not assessable. K: cancer. CLL: chronic lymphocytic leukemia. WMG: Waldenström's macroglobulinemia. RAEB: refractory anemia with excess blasts (RAEB-t: RAEB in transformation). CMML: chronic myelomonocytic leukemia.

GCA has ranged from 9.3% to 19.8%[24-27], but the incidence of concurrent malignancy has not been stated.

Whether subjects with recently diagnosed TA are at increased risk of developing malignancy has been disputed[22,24-27]. Several investigators found that patients with GCA had a higher cancer risk than controls[22,24,25], but recent large-scale, prospective case-control studies do not support an increased incidence of malignancy in patients with TA[26,27]. In this respect, no conclusion can be drawn from our study, due to the retrospective design and lack of a control population. However, during the first year of followup, the crude yearly incidence of malignancy was more than 4-fold the value

obtained for the general population (age 65–85 yrs) in the Limousin region, pointing to a possible excess cancer risk in the early course of TA in our patients. Moreover, the time interval from TA diagnosis to registered malignancy did not exceed 2 years in 56% of the cases in our patients, vasculitis and malignancy being synchronously diagnosed in 10 patients, i.e., 4% of the series. These figures are probably higher than those expected by chance occurrence, although our study may involve biases such as closer patient followup under treatment and a greater awareness of senior internists of the risk of cancer, leading to more careful investigation of any abnormal finding. Our findings suggest, therefore, that malignancy may represent in some patients a trigger for the development of TA.

The clinical and laboratory findings of GCA with or without a history of malignancy did not differ statistically in our patients, except for a higher frequency of rheumatic features in the former group. This is not an unexpected finding considering cancer and MDS may be more prevalent in patients with PMR symptoms than in the general population[23,49]. However, whether patients with the TA/PMR overlap have an increased cancer risk needs to be clarified, since our results differed from those of previous studies[24,25]. In disagreement with Haga, *et al*[25], we did not find that a positive temporal artery biopsy represented a risk factor for malignancy, but the retrospective design of our study may account for the observed discrepancy. Nevertheless, GCA may be overdiagnosed clinically in patients with malignancy[60,61].

A pooling of our 20 personal cases with 27 other published reports of TA and concurrent malignancy allowed us to draw several interesting observations. The association involved many types of malignancy, notably cancers of the gastrointestinal tract, whose incidence is known to increase with age. However, blood malignancies emerged as a major group of malignancy (45%). In a report to the US government on the status of cancer, 1973–99, the incidence of new cases of non-Hodgkin's lymphoma and leukemia in men and women aged 75 years and over was 13-fold lower than that of other cancers (besides leukemia and NHL)[62]. Thus, blood malignant diseases could be overrepresented in patients with TA, as compared with the general elderly population. In our series, no patient developed lymphoma or Hodgkin's disease concurrently with TA. In the survey, of 5 patients with lymphoma, 4 had myeloma and one had Waldenström's macroglobulinemia. In light of these data, plasma cell dyscrasia appears to be the only type of lymphoma potentially associated temporally with GCA. B cell CLL was reported in 4 patients, including one in our series. This number seems rather low, regarding the high frequency of CLL in an elderly population. Taboada-Martinez, *et al*, conducting a Mayo Clinic database search to identify patients that developed GCA after the onset of CLL, found only 3 such patients, including one with nearly concurrent disease[63]. From these data, the association between CLL and TA appears merely casual. Interestingly, in the survey, MDS was the most frequent type of malignancy associated with TA. There was no predominant subtype, with respect to the French-American-British classification[33].

Whether true excess MDS exists in active TA is not known, since publication biases may partially account for this finding, and no study has confirmed such an association statistically. In studies on MDS, the frequency of autoimmune or systemic disorders has varied from 7% to 60%[15-21,64], cutaneous vasculitis being the most frequent manifestation[15-17,19,64], followed by seronegative inflammatory arthritis[16,65], systemic medium-size vasculitis[16,66,67], relapsing polychondritis[68,69], and lupus-like syndrome[15,16]. PMR has also been ascribed as a consequence of MDS[48,49], but TA seemed very infrequent in these patients[17,69], although aortitis has occasionally been described[51,70]. Further, the association of TA with MDS could be coincidental, in view of the age-related increasing incidence of both diseases in the general population. In our patients, however, a strong temporal association between MDS and TA was found, with only one of 7 occurrences of MDS being diagnosed more than 6 months before or after TA. In the series of Mycklebust, *et al*, a previous or incident hematological malignancy was registered in only 0.5% of the patients[26], in contrast with 3.6% found in our patients. This discrepancy may in part reflect partial inability to detect early stages of MDS using nationwide public registries as the sole source of identification of malignancy. In light of these data, a relationship between TA and MDS seems plausible but warrants further study.

Finally, the course of GCA almost never mirrored that of the malignancy in patients included in this survey, in agreement with most studies. Similarly, the overall prognosis of TA did not appear worse in our patients, even though many received only supportive care or no treatment for malignancy. Thus, TA as a paraneoplastic phenomenon appears to be an exceedingly rare occurrence.

To summarize, concurrent malignancy in TA is not a rare finding. Solid malignancies and hematological disorders, especially MDS, may represent precipitating factors for the development of TA. Patients with and without malignancy seem indistinguishable regarding features and outcome of TA, even though we found a higher frequency of rheumatic symptoms in the former group. All patients with TA that experience unusual symptoms or a recurring inflammatory response without clinical signs of active vasculitis should be carefully screened for malignancy.

REFERENCES

1. Salvarani C, Cantini F, Boiardi L, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. N Engl J Med 2002;347:261-71.
2. Russo MG, Waxman J, Abdoh AA, Serebro LH. Correlation between infection and the onset of the giant cell (temporal) arteritis syndrome. A trigger mechanism? Arthritis Rheum 1995;38:374-80.
3. Salvarani C, Gabriel SE, O'Fallon WM, Hunder GG. The incidence of giant cell arteritis in Olmsted County, Minnesota: apparent fluctuations in a cyclic pattern. Ann Intern Med 1995;123:192-4.
4. Elling P, Olsson AT, Elling H. Synchronous variations of the

incidence of temporal arteritis and polymyalgia rheumatica in different regions of Denmark: association with epidemics of mycoplasma pneumoniae infection. J Rheumatol 1996;23:112-9.
5. Duhaut P, Bosshard S, Calvet A, et al. Giant cell arteritis, polymyalgia rheumatica, and viral hypotheses: a multicenter, prospective case-control study. Groupe de Recherche sur l'Artérite à Cellules Géantes. J Rheumatol 1999;26:361-9.
6. Nordborg E, Nordborg C. Giant cell arteritis: epidemiological clues to its pathogenesis and update on its treatment. Rheumatology Oxford 2003;42:413-21.
7. Hamrin B, Jonsson N, Hellsten S. "Polymyalgia arteritica". Further clinical and histopathological studies with a report of six autopsy cases. Ann Rheum Dis 1968;27:397-405.
8. Ostberg G. Temporal arteritis in a large necropsy series. Ann Rheum Dis 1971;30:224-35.
9. Greer JM, Longley S, Edwards NL, Elfenbeim GJ, Panush RS. Vasculitis associated with malignancy. Experience with 13 patients and literature review. Medicine 1988;67:220-30.
10. Fain O, Guillevin L, Kaplan G, et al. Vasculitis and neoplasms. 14 cases [French]. Ann Med Interne 1991;142:486-504.
11. Kurzroch R, Cohen PR, Markowitz A. Clinical manifestations of vasculitis in patients with solid tumors. A case report and review of the literature. Arch Intern Med 1994;154:334-40.
12. Naschitz JE, Yeshurun D, Rosmer I. Rheumatic manifestations of occult cancer. Cancer 1995;75:2954-8.
13. Hutson TE, Hoffman GS. Temporal concurrence of vasculitis and cancer: a report of 12 cases. Arthritis Care Res 2000;13:417-23.
14. Fain O. Vasculitis and cancers [French]. Rev Med Interne 2002;23 Suppl 5:559s.
15. Castro M, Conn DL, Su WPD, Garton JP. Rheumatic manifestations in myelodysplastic syndromes. J Rheumatol 1991;18:721-7.
16. Enright H, Jacob HS, Vercellotti G, Howe R, Belzer M, Miller W. Paraneoplastic autoimmune phenomena in patients with myelodysplastic syndromes: response to immunosuppressive therapy. Br J Haematol 1995;91:403-8.
17. Billstrom R, Johansson H, Johansson B, Mitelman F. Immune-mediated complications in patients with myelodysplastic syndromes. Eur J Haematol 1995;55:42-8.
18. Hamidou MA, Derenne S, Audrain MA, Berthelot JM, Boumalassa A, Grolleau JY. Prevalence of rheumatic manifestations and antineutrophil cytoplasmic antibodies in haematological malignancies. A prospective study. Rheumatology Oxford 2000;39:417-20.
19. Saif MW, Hopkins JL, Gore SD. Autoimmune phenomena in patients with myelodysplastic syndromes and chronic myelomonocytic leukemia. Leuk Lymphoma 2002;43:2083-92.
20. Roy-Peaud F, Paccalin M, Le Moal G, et al. Association of systemic diseases and myelodysplastic syndromes. A retrospective study of 14 cases [French]. Presse Med 2003;32:538-43.
21. Giannouli S, Voulgarelis M, Zintzaras E, Tzioufas AG, Moutsopoulos HM. Autoimmune phenomena in myelodysplastic syndromes: a 4-year prospective study. Rheumatology Oxford 2004;43:626-32.
22. Schmidt J, Merlet V, Aublet-Cuvelier B, André M, Aumaître O. Prévalence du cancer chez 75 patients porteurs d'une maladie de Horton et/ou d'une pseudo-polyarthrite rhizomélique. Rev Méd Interne 1999;20 Suppl 1:85s.
23. Haugeberg G, Dovland H, Johnsen V. Increased frequency of malignancy found in patients with new-onset polymyalgic symptoms suggested to have polymyalgia rheumatica. Arthritis Care Res 2002;47:346-8.
24. Plouvier B, De Coninck P, Bushges-Seraphin B, Bouton Y, Thouvenin T, Auxenfants E. Relations of Horton's disease, polymyalgia rheumatica and cancer [French]. Presse Med 1989;18:1977.
25. Haga HJ, Eide GE, Brun J, Johansen A, Langmark F. Cancer in association with polymyalgia rheumatica and temporal arteritis. J Rheumatol 1993;20:1335-9.
26. Mycklebust G, Wilsgaard T, Jacobsen BK, Gran JT. No increased frequency of malignant neoplasms in polymyalgia rheumatica and temporal arteritis. A prospective longitudinal study of 398 cases and matched population controls. J Rheumatol 2002;29:2143-7.
27. Duhaut P, Le Page L, Bosshard S, et al. Incidence des cancers et des maladies auto-immunes dans les maladies de Horton à biopsie positive et négative au cours du suivi: étude prospective multicentrique en double cohorte GRACG. Rev Méd Interne 2004;25 Suppl 1:S81.
28. Hunder GG, Bloch DA, Michel DA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33:1122-8.
29. Huston KA, Hunder GG, Lie JT, Kennedy RH, Elvebach LR. Temporal arteritis. A 25-year epidemiologic, clinical and pathologic study. Ann Intern Med 1978;88:162-7.
30. Liozon E, Herrmann F, Ly K, et al. Risk factors for visual loss in giant cell (temporal) arteritis: a prospective study of 174 patients. Am J Med 2001;111:211-7.
31. Liozon E, Boutros-Toni F, Loustaud-Ratti, Ly K, Soria P, Vidal E. Silent, or occult, giant cell (temporal) arteritis is associated with a strong inflammatory response and a benign short term course. J Rheumatol 2003;30:1272-6.
32. Liozon F, Vidal E, Barrier JH. Dapsone in giant cell arteritis treatment. Eur J Intern Med 1993;4:207-14.
33. Bennet JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol 1982;51:189-99.
34. Liozon E, Loustaud-Ratti V, Soria P, et al. Maladie de Horton: associations morbides chez 250 malades. Presse Med 2004;6:1304-12.
35. Von Knorring J, Sommer T. Malignancy in association with polymyalgia rheumatica and temporal arteritis. Scand J Rheumatol 1974;3:129-35.
36. Larregain-Fournier D, Adoue P, Arlet P, Le Tallec Y. Maladie de Horton et pseudo-polyarthrite rhizomélique associée à une leucémie lymphoïde chronique. Presse Med 1984;13:2210.
37. Dupuy-Braud E, Galley P, Manciet G, Decamps A, Emeriau JP. Maladie de Horton et myélome. Semin Hop Paris 1986;62:2221-4.
38. Hoag GN. Renal carcinoma and vasculitis: report of two cases. J Surg Oncol 1987;35:35-8.
39. Case records of the Massachusetts General Hospital. Case 23-1990. New Engl J Med 1990;322:1656-65.
40. Bensaid P, Vaillant L, Machet L, De Muret A, Roquejoffre P, Lorette G. Horton's disease and myelodysplastic syndrome associated with unusual cutaneous manifestations [French]. Ann Dermatol Venereol 1992;119:217-20.
41. Lie JT. Simultaneous clinical manifestations of malignancy and giant cell temporal arteritis in a young woman. J Rheumatol 1995;22:367-9.
42. Speed CA, Haslock I. Polymyalgia rheumatica, temporal arteritis and malignancy. Postgrad Med J 1995;71:500-2.
43. Gonzalez-Gay MA, Blanco R, Gonzalez-Lopez MA. Simultaneous presentation of giant cell arteritis and chronic lymphocytic leukemia. J Rheumatol 1997;24:407-8.
44. Estrada A, Stenzel TT, Burchette JL, Allen NB. Multiple myeloma-associated amyloïdosis and giant cell arteritis. Arthritis Rheum 1998;41:1312-7.
45. Keung YK, Yung C, Wong JW, Shah F, Cobos E. Association of temporal arteritis, retinal vasculitis, and xanthomatosis with multiple myeloma: case report and literature review. Mayo Clin Proc 1998;73:657-60.

46. Solans R, Selva A, Matas L, Simeon CP, Bosch JA, Vilardell M. Paraneoplastic vasculitis in patients with solid tumors. Eur J Intern Med 1999;10 Suppl 1:S60.
47. Orbo A, Steffensen A. Endometrial cancer, vasculitis of the genital tract and occult temporal arteritis. Histopathology 2001;38:177-9.
48. Kohli M, Bennet RM. An association of polymyalgia rheumatica with myelodysplastic syndromes. J Rheumatol 1994;2:1357-9.
49. Espinosa G, Font J, Munoz-Rodriguez FJ, Cervera R, Ingelmo M. Myelodysplastic and myeloproliferative syndromes associated with giant cell arteritis and polymyalgia rheumatica: a coincidental coexistence or a causal relationship? Clin Rheumatol 2002;21:309-13.
50. Mouadeb D, Campisi P, Rochon L, Hier MP, Black MJ. Tongue necrosis, temporal arteritis, and esophageal carcinoma: is there a connection? J Otolaryngol 2004;33:50-2.
51. Steurer M, Fritsche G, Tzankov A, et al. Large-vessel arteritis and myelodysplastic syndrome: report of two cases. Eur J Haematol 2004;73:128-33.
52. Von Knorring J. Treatments and prognosis in polymyalgia rheumatica and giant cell arteritis. Acta Med Scand 1979;205:429-35.
53. Bengtsson BA, Malmvall BE. Prognosis of giant cell arteritis including temporal arteritis and polymyalgia rheumatica. A follow-up study on ninety patients treated with corticosteroids. Acta Med Scand 1981;209:337-45.
54. Barrier JH, Tournemaire N, Maulaz D, et al. Evolution, traitement et pronostic de la maladie de Horton. Ann Med Interne 1983;134:428-35.
55. Andersson R, Malmvall BE, Bengtsson BA. Long term corticosteroid treatment in giant cell arteritis. Acta Med Scand 1986;220:465-9.
56. Mertens JCC, Willemsen G, van Saase JLCM, Bolk JH, Dijkmans BAC. Polymyalgia rheumatica and temporal arteritis: a retrospective study of 111 patients. Clin Rheumatol 1995;14:650-5.
57. Gonzalez EB, Varner WT, Lisse JR, Daniels JC, Hokanson JA. Giant cell arteritis in the Southern United States. An 11-year retrospective study from the Texas Gulf Coast. Arch Intern Med 1989;149:1561-5.
58. Myklebust G, Gran JT. A prospective study of 287 patients with polymyalgia rheumatica and giant cell arteritis: clinical and laboratory manifestations at onset of disease and at the time of diagnosis. Br J Rheumatol 1996;35:1161-8.
59. Bahlas S, Ramos-Remus C, Davis P. Clinical outcome of 149 patients with polymyalgia rheumatica and giant cell arteritis. J Rheumatol 1998;25:99-104.
60. Hedges TR III, Gieger DL, Albert DM. The clinical value of negative temporal artery biopsy. Arch Ophthalmol 1983;101:1251-4.
61. Roth AM, Milsow L, Keltner JL. The ultimate diagnosis of patients undergoing temporal artery biopsy. Arch Ophthalmol 1984;102:901-3.
62. Edwards BK, Howe HL, Ries LAG, et al. Annual report to the Nation on the status of cancer, 1973-1999, featuring implications of age and aging on U.S. cancer burden. Cancer 2002;94:2766-92.
63. Taboada-Martinez V, Brack A, Hunder GG, Goronzy JJ, Weyand CM. The inflammatory infiltrate in giant cell arteritis selects against B lymphocytes. J Rheumatol 1996;23:1011-4.
64. Chandran G, Ahern MJ, Seshadri P, Coglhan D. Rheumatic manifestations of the myelodysplastic syndromes: a comparative study. Aust NZ J Med 1996;26:683-8.
65. George SW, Newman ED. Seronegative inflammatory arthritis in the myelodysplastic syndromes. Semin Arthritis Rheum 1992;21:345-54.
66. Hamidou MA, Derenne S, Audrain MA, Berthelot JM, Boumalassa A, Grolleau JY. Prevalence of rheumatic manifestations and antineutrophil cytoplasmic antibodies in haematological malignancies. A prospective study. Rheumatology Oxford 2000;39:417-20.
67. Hamidou MA, Boumalassa A, Larroche C, Houri DE, Bletry O, Grolleau JY. Systemic medium-sized vasculitis associated with chronic myelomonocytic leukemia. Semin Arthritis Rheum 2001;31:119-26.
68. Hebbar M, Brouillard M, Wattel E, et al. Association of myelodysplastic syndrome and polychondritis: further evidence. Leukemia 1995;9:731-3.
69. Diebold J, Rauh G, Jäger K, Löhrs U. Bone marrow pathology in relapsing polychondritis: high frequency of myelodysplastic syndromes. Br J Haematol 1995;89:820-30.
70. Lopez FF, Vaidyan PB, Mega AE, Schiffman FJ. Aortitis as a manifestation of myelodysplastic syndrome. Postgrad Med J 2001;77:116-8.