Silent, or Masked, Giant Cell Arteritis Is Associated with a Strong Inflammatory Response and a Benign Short Term Course

ERIC LIOZON, FERNAND BOUTROS-TONI, KIM LY, VÉRONIQUE LOUSTAUD-RATTI, PASCALE SORIA, and ELISABETH VIDAL

ABSTRACT. ***Objective***. To determine the frequency, characteristics, and short term outcome of patients who have biopsy-proven giant cell arteritis (GCA) but no local symptoms that can be attributed to vasculitis inflammation [silent temporal arteritis (TA)] throughout the pretreatment course of the disease or an observational period lasting at least 2 months.

Methods. Of 175 consecutive patients with biopsy-proven GCA, 130 had typical cranial arteritis, 21 had silent vasculitis, and the remaining 24 had either discrete cranial symptoms (19 cases) or isolated extracranial vasculitis (5 cases). We sought to determine which of 15 pretreatment characteristics were associated with silent TA, as compared with typical cranial arteritis, and assessed the short term outcome in these patients.

Results. Of 21 patients with silent GCA, 14 met criteria for fever of unknown origin. Aside from their different clinical presentation, this population was characterized by a longer delay in diagnosis ($p = 0.003$), a higher mean erythrocyte sedimentation rate ($p = 0.002$), higher C-reactive protein ($p = 0.002$), and lower levels of albumin ($p = 0.01$) and hemoglobin ($p < 0.0001$). Permanent visual loss, which occurred in 24 patients (13.7%), exclusively involved those presenting with symptoms and/or signs suggesting cranial arteritis, especially those with frank cranial arteritis. This complication was associated negatively with the delay in diagnosis ($p = 0.01$), and marginally with the number of symptoms and/or signs suggesting cranial arteritis recorded in each patient ($p = 0.07$). Oral prednisone at a mean daily dose of 0.7 mg/kg resulted in satisfactory control of silent TA within 4 weeks in all patients but one, and could subsequently be safely tapered by half in a mean delay of 38 ± 23 days. No differences were observed between patients with silent TA and other forms of the disease regarding the mean prednisone dose at 3 month followup (18.2 ± 4.5 vs 20.9 ± 5.9 mg/day) and 6 month followup (14 ± 4.4 vs 15.6 ± 6 mg/day).

Conclusion. Silent TA may represent a distinct subset of giant cell arteritis, marked by a protracted inflammatory response and a relatively benign short term outcome, excellent response to corticosteroids, and no visual ischemic events, despite the long period of exposure to this complication before appropriate treatment. (J Rheumatol 2003;30:1272–6)

Key Indexing Terms:
TEMPORAL ARTERITIS CONSTITUTIONAL SYMPTOMS
INFLAMMATORY RESPONSE FEVER OF UNKNOWN ORIGIN VISUAL RISK

Giant cell arteritis (GCA), or temporal arteritis (TA), is a clinically protean vasculitis of the aged, which is easily recognized when it presents in its typical form[1]. However, instead of the classic finding of headaches, tender temporal arteries, blindness, and polymyalgia rheumatica, patients may present with prominent constitutional symptoms such as fever, malaise, and weight loss, which may point to infection or underlying malignancy rather than vasculitis[2,3]. Patients with such atypical, or "silent," form of the disease often meet the criteria for the diagnosis of fever of unknown origin (FUO)[4-7] and are therefore exposed to unnecessary investigations and antibiotic treatment tests, with their respective risks and additional costs. Whether the further delay in diagnosis that usually occurs with systemic presentation of temporal arteritis[8] is harmful to the patient is largely unknown.

During the last 2 decades, several studies have attempted to determine the frequency of silent TA and its relationship to FUO[2,4-7], but investigators have not directly compared the characteristics of such patients to those of patients presenting with the classical picture[4,6,7] or, if so, have included in the former group many patients with early discrete or late typical manifestations of cranial arteritis[5].

From the Departments of Internal Medicine and Biostatistics, Dupuytren's University Hospital, Limoges, France.

E. Liozon, MD, Department of Internal Medicine; F. Boutros-Toni, PhD, Department of Biostatistics; K. Ly, MD; V. Loustaud-Ratti, MD; P. Soria, MD; E. Vidal, MD, Department of Internal Medicine.

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

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We sought to determine the frequency, main characteristics, and short term outcome of patients with silent TA as compared to patients with typical cranial arteritis.

MATERIALS AND METHODS

Patients and data collection. Between January 1977 and April 2002, 215 consecutive patients in the Department of Internal Medicine of the University Hospital were diagnosed as having TA[9]. Temporal artery biopsy was performed in all patients and showed pathologic evidence of GCA in 175[10]. None of them had isolated visual ischemic symptoms, as defined by Simmons and Cogan[11]. Patients who had a negative result of temporal artery biopsy were excluded from the study.

Pretreatment clinical, laboratory, and pathological data were recorded prospectively at the time of diagnosis using a specifically designed, comprehensive questionnaire. Special efforts were made in evaluating the delay to diagnosis from the onset of symptoms of GCA, the presence of constitutional symptoms (defined by a temperature ± 38°C for at least one week, severe asthenia, and/or weight loss > 5%), a recent history of headaches, scalp burning pain, jaw claudication[12], polymyalgia rheumatica[13], 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 (presence of intermittent arm claudication, absent or decreased radial pulse, Raynaud phenomenon of recent onset, suggestive findings on selective aortic arch arteriography[14], or at least a murmur heard over subclavian-axillary arteries at admission or within a month). FUO was defined according to recently revised Petersdorf's criteria[15,16]. Permanent visual loss included amaurosis due to either anterior ischemic optic neuropathy or central retinal artery occlusion and permanently impaired visual acuity with normal funduscopy.

According to the main symptoms and signs at the time of diagnosis, 3 different clinical pictures were recognized: (1) overt (or typical) cranial arteritis, i.e., presence of 2 or more among the major cephalic symptoms/signs (i.e., recent headache, scalp tenderness, jaw claudication, and abnormal temporal artery on examination); (2) silent TA, characterized by constitutional symptoms and raised erythrocyte sedimentation rate (ESR) but no evidence of cranial arteritis, polymyalgia rheumatica, or large artery involvement during the pretreatment course of disease or at least for an observational period of 2 months or more; and (3) patients with other clinical pictures, i.e., those with less than 2 cephalic symptoms/signs and those with isolated polymyalgia rheumatica or upper limb artery involvement.

All patients were treated according to a preestablished protocol. Prednisone was given to 141 patients at the daily dose of 0.75 ± 15 mg/kg, progressively tapered to 0.35 mg/kg within 4 to 6 weeks, then more slowly, for a planned total duration of 24 months. Thirty-four patients with ischemic symptoms or whose vision was threatened initially received prednisone 1 mg/kg, preceded in 27 cases by pulse methylprednisolone, which was tapered thereafter as above. Complete response to treatment was defined by absence of clinical symptoms and C-reactive protein (CRP) level less than 5 mg/l.

Laboratory measurements. Laboratory variables included ESR, CRP, fibrinogen, haptoglobin, hemoglobin, platelet counts, albumin, and liver function tests. Pretreatment measurement of at least 3 of the 4 aforementioned inflammatory variables was available in 74% of the cases, hemoglobin in 97%, platelet count in 91%, albumin in 78%, and liver function tests in 83% of the cases.

Statistical analyses. We determined which of 15 pretreatment characteristics were associated with silent TA. To exclude sampling biases, only patients with biopsy-proven silent TA and patients with overt cranial arteritis were evaluated. Comparisons of continuous variables were performed using Mann-Whitney rank-sum test. Proportions were analyzed using chi-square or Fisher's exact tests. The relation between 2 quantitative variables (time to diagnosis from the onset of symptoms, ESR, CRP, albumin, hemoglobin, and platelet counts) was assessed using the coefficient correlation test. Analyses were performed using Statview (release 5.0, SAS Institute Inc., 1998).

RESULTS

Clinical findings. The demographics and main characteristics of the patients are given in Tables 1 and 2. One hundred thirty patients had overt cranial arteritis, 21 patients had silent TA (12% of all biopsy-proven cases), and 24 patients had other clinical pictures (19 had discrete cranial arteritis with only one major cephalic symptom/sign and 5 had extracranial GCA). All patients with silent GCA complained of fatigue, and 14 (66.7%) met the current criteria for FUO. In this group, the delay to diagnosis from onset of fever, malaise, or laboratory disturbances ranged from 30 days to 1 year (mean 4.3 ± 1 mo) and the average delay to diagnosis from the first hospital admission was 41 days. The presentation of GCA remained silent throughout its pretreatment course in 18 cases, whereas symptoms or signs suggesting vasculitis appeared tardily in the remaining patients: isolated upper limb artery involvement in 2, angina pectoris and bilateral upper limb ischemia in one, and typical cranial arteritis in one. The latter patient was a 77-year-old woman with a 7 year history of episodic fever, which resolved upon satisfactory control of the vasculitis, with a 4 year followup. One patient was found to have concurrent prostatic cancer and one concurrent Sjögren's syndrome, with severe lower limb neuropathy. Upon starting glucocorticoid treatment,

Table 1. Main clinical data of the study population.

Data	Number (%)
Number of patients	175
Proportion of women	64.6
Age, years, mean (± SD)	75.2 (7.1)
Delay in diagnosis, days, mean (± SD)	79 (83.5)
Cranial symptoms	149 (85.1)
Temporal headaches	135 (77.1)
Occipitalgia	77 (44.5)
Scalp tenderness	88 (51.8)
Abnormal temporal arteries	105 (60.3)
Jaw claudication	69 (39.4)
Other ear-mouth-throat symptoms	79 (45.9)
Transient visual ischemic symptoms*	34 (19.4)
Permanent visual loss†	22 (12.6)
Cerebrovascular accidents	9 (5.1)
Upper limb artery involvement§	27 (15.5)
Angina and/or myocardial infarction	5 (2.8)
Systemic manifestations	124 (71.2)
Polymyalgia rheumatica	47 (26.9)
Peripheral arthritis	17 (9.7)
Fever > 38°C	95 (54.9)
Weight loss > 5%	88 (51.2)
Severe asthenia	69 (45.4)

* Including amaurosis fugax, episodes of blurred vision, diplopia and visual hallucinations. † Including accidents occurring within the first week of treatment from onset of symptoms. § Including bruits heard over axillary-humeral arteries within the first 2 weeks of treatment.

Table 2. Main laboratory data of the study population.

Data	Number (%)
ESR > 50 mm/h	157 (93.5)
CRP > 15 mg/dl	136 (95.1)
Fibrinogen > 4.5 g/l	95 (84.1)
Haptoglobin > 2 g/l	106 (95.5)
Albumin < 35 g/l	71 (51.4)
Anemia, Hb < 12 g/dl	109 (64.1)
Severe, Hb < 10 g/dl	34 (20)
Thrombocytosis, platelet count > 400 g/l	84 (53.2)
Severe, platelet count > 500 g/l	45 (28.5)
Liver enzyme abnormalities*	67 (46.5)
Elevated ANA	21 (22.8)
Positive RF	3 (3.8)
Elevated IgG aCL	39 (49.4)

* At least one test above normal among the following: alkaline phosphatase, gammaglutamyl-transpeptidase, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase.
Hb: hemoglobin; ANA: antinuclar antibodies; aCL: anticardiolipin antibodies; RF: rheumatoid factor.

bruits over large arteries were regularly investigated and were found to appear over axillary arteries in another 2 patients. Thus, large artery involvement was unmasked late in 5 of 21 patients (24%).

Comparison of pretreatment characteristics. As can be seen in Table 3, patients with silent vasculitis differed significantly from patients with overt cranial arteritis by a longer delay between the first symptoms and diagnosis, a higher mean ESR, a more protracted acute phase reactant response, and more severe repercussions on albumin and hemoglobin levels, but not platelet levels or liver function tests. An inverse correlation was observed between the mean CRP level and the mean hemoglobin level ($p = 0.01$), the mean albumin level ($p < 0.001$), and mean platelet count ($p = 0.006$), but no correlation between delay in diagnosis and ESR or CRP level. Permanent visual loss, which was an exclusion criterion for defining silent vasculitis, occurred in 24 other patients, most often before treatment; all these patients complained for days or weeks of frank headache and/or jaw claudication. There was a trend toward association between the number of symptoms/signs suggesting cranial arteritis and permanent visual loss ($p = 0.07$). In addition, 6 patients with overt cranial arteritis and one patient with silent vasculitis developed other permanent ischemic complications (stroke, hearing loss, or myocardial infarction) before or within the first few days of treatment.

Treatment and outcome. All patients with silent vasculitis responded favorably to prednisone dose of 0.6 to 0.9 mg/kg/day (average 0.7 mg/kg/day). Fever, constitutional symptoms, elevated platelet count, and raised CRP level were no longer present in most patients within the first 4 weeks after start of therapy, which allowed physicians to begin tapering of prednisone with a mean delay of 16 days (range 4–30). The further mean delay was 35 days to reach a prednisone dose of 0.35 mg/kg/day (range 24–45) without significant relapse in 16 assessable patients. One patient died of myocardial infarction after 40 days of treatment. This 70-year-old woman had been admitted to our department for unexplained constitutional symptoms and strong inflammatory response that had lasted one year. In retrospect, she complained for several weeks of de novo angina pectoris and progressive bilateral upper limb ischemia. Bruits were heard over the 4 limb arteries and a rereading of the initial temporal artery biopsy yielded a positive result. Permission for an autopsy was not granted.

Table 3. Comparative study between patients with masked temporal arteritis and those with overt temporal arteritis.

Variable	Patients with Silent Temporal Arteritis (n = 21) No. (%)	Patients with Overt Cranial Arteritis (n = 130) No. (%)	p Value
Age, yrs, mean ± SD	74.3 ± 7.9	75.6 ± 6.9	0.89
Proportion of women	14 (66.7)	83 (63.8)	0.99
Delay in diagnosis, days, mean (range)	123 (30–360)	70 (4–350)	0.003
Permanent visual loss*	0	20 (15.4)	0.11
Other permanent ischemic accidents	1 (5.6)	6 (4.6)	0.58
Upper limb artery involvement *	5 (23.8)	13 (10)	0.15
ESR, mm/h	108.7 ± 23.8	89.3 ± 28.4	0.002
CRP, mg/l, (mean ± SD)	136.5 ± 54.8	93.1 ± 59.2	0.002
Haptoglobin, mg/l, (mean ± SD)	5267 ± 1556	4822 ± 1648	0.30
Fibrinogen, mg/l, (mean ± SD)	6939 ± 1982	6093 ± 1676	0.17
Hemoglobin, g/dl, (mean ± SD)	9.92 ± 1.25	11.46 ± 1.8	< 0.0001
Platelet count, mm^3, (mean ± SD)	440 ± 166	428 ± 135	0.90
Albumin, mean ± SD	30.7 ± 5.1	34.8 ± 5.8	0.008
Liver enzyme abnormalities§	10 (47.6)	47 (45.2)	0.99
Anticardiolipin antibodies	4 (36.4)	32 (47.8)	0.17

* As defined in Table 1. § As defined in Table 2.

No differences were observed between patients with silent TA and those sharing other forms of the disease regarding the mean prednisone dose at 3 months' followup (18.2 ± 4.5 vs 20.9 ± 5.9 mg/day) and 6 months (14 ± 4.4 vs 15.6 ± 6 mg/day).

DISCUSSION

We present our overall experience with "silent temporal arteritis" in a large sample of patients recruited in a single department of internal medicine through a 25 year period. Of 175 biopsy-proven patients, 72% presented with constitutional symptoms, 55% with fever, and 51% with weight loss. Similar or even higher figures have been described in other series[5,7,17-20].

The reported frequency of silent TA has ranged from 6.7% to 38%[2,5,7,8] and was 12% in our series. The figure is obviously highly dependent on awareness of this condition and also on the criteria used in defining clinically silent vasculitis. It is also possible that the clinical spectrum of TA has imperceptibly evolved since its early descriptions toward a more systemic disease that is less well defined and has fewer characteristic manifestations[21,22]. Since 1977, we have collected data prospectively using a comprehensive 174 item questionnaire that allowed us to identify several clearly defined clinical subsets of patients: those with totally silent TA, as defined above, those with overt cranial arteritis, and those with less clearly defined cephalic symptoms or extracranial vasculitis.

In our experience, biopsy-proven TA masqueraded as FUO in 7.5% of the cases. This number is a minimal estimate, since we may have omitted performing temporal artery biopsy in some elderly patients with unexplained abnormal inflammatory response. Although we could not precisely calculate the proportion of GCA among older patients with FUO, other large studies of FUO have reported an incidence of biopsy-proven cases ranging from 2% to 21%[7,16,23-25], and up to 17% in patients older than 65 years[26,27]. Thus, our study reemphasizes the value of early random temporal artery biopsy in the investigations of such patients, despite unremarkable diagnostic evaluations and no symptoms or findings suggestive of arteritis[5,27].

Undiagnosed for months, silent TA may run a more protracted course[26]. Typical cranial arteritis developed in a patient with long-standing episodic fever that had been thoroughly investigated by us at different times — although blind temporal artery biopsy had never been considered. To our knowledge, this is the first description of episodic FUO terminating in TA[28]. It is also noteworthy that large artery involvement was only apparent after 2 to 10 months (average 4.5) in 5 of our 21 patients. Similarly, a review of 72 patients with well documented aortic and extracranial large vessel GCA revealed that 25% of such patients in fact had occult TA[29]. These findings not only point to the possible overlap existing between 2 apparently different pictures of the disease but also stress the value of regular examination for bruits over limb arteries in elderly patients with unexplained raised inflammatory response or FUO. Moreover, noninvasive arterial diagnostic procedures should be considered in such patients where temporal artery biopsy has yielded negative results[30-33].

Whether silent TA carries a low risk of visual loss is difficult to ascertain from our study, due to our study design and the fact that most visual complications occurred before treatment. Strikingly, however, most patients with constitutional symptoms ran a long pretreatment course without developing any visual problems — even transient — whereas all patients but one who developed permanent blindness had other symptoms for days or weeks that strongly suggested cranial arteritis, a finding that has been reported[34-36]. Interestingly, other investigators found a negative association between constitutional symptoms and irreversible cranial ischemic events or visual loss[2,18,20,37,38]. Liu, *et al* reported fever in only 5 of 41 patients with biopsy-verified GCA and visual loss[39]. Finally, visual disturbances were reported in only one of 31 patients with TA masquerading as FUO[5,26]. Thus, patients with clinically silent TA might be truly protected from visual sequelae, although our results do not support this statement with certainty.

Aside from criteria used in separating subsets of patients, silent TA differed clinically from overt cranial arteritis by a longer delay to diagnosis from onset of disease. This was either because random temporal artery biopsy was not always an early consideration, or because the initial biopsy fragment was too short and re-biopsy would have been required[27]. For Strachan, *et al* the delay in reaching diagnosis of masked GCA is a major factor in the emergence of serious sequelae[40]. Fortunately, this lateness apparently did no harm to our patients, except a 70-year-old woman who died of disseminated large vessel GCA and myocardial infarction, due to an unacceptably long delay before referral.

Our patients with silent TA also had a more protracted inflammatory response and more severe repercussions for albumin and hemoglobin values. Calamia and Hunder found similar differences in a series of 100 biopsy-proven cases of GCA including 15 FUO[5]. Of importance, in our patients, neither ESR, CRP, hemoglobin, nor albumin levels were correlated with delay in diagnosis. Thus, the observed stronger inflammatory response was not a time-dependent effect but was probably related to a distinct cytokine profile in inflamed arteries of such patients[41-44]. Based on the clinical and laboratory findings, silent TA may actually represent a subset of GCA, next to cranial arteritis, polymyalgia rheumatica, and arteritis of large trunks[45]. Further, 7 patients with silent TA in our series (33%) presented without fever. The suspicion of GCA should, therefore, remain a high diagnostic possibility in patients over age 55 with an unexplained strong inflammatory response, regardless of their body temperature.

Finally, our observations, including a good short term response to prednisone, suggest that silent temporal arteritis may be a relatively benign disease.

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