Association between Histological Features in Temporal Artery Biopsies and Clinical Features of Patients with Giant Cell Arteritis

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ABSTRACT: **Background:** In most cases of giant cell arteritis (GCA) the diagnosis is confirmed by temporal artery biopsy. Aside from the diagnostic purpose, histological parameters may serve as prognostic markers.

Objectives: To review positive temporal artery biopsies of GCA in an attempt to correlate various histological parameters with clinical features, disease complications and outcome.

Methods: Positive biopsies from 65 GCA patients were randomly selected for review by a single pathologist. In each biopsy the following parameters were scored: intensity and location of the inflammatory infiltrate, presence of giant cells and other cell types, fragmentation and calcification of the internal elastic lamina, intimal thickening, and presence of luminal thrombus. Clinical data were obtained from the patients' charts. Intensity of the initial systemic inflammatory reaction (ISIR) at the time of diagnosis was scored by the presence of five parameters: fever, anemia, thrombocytosis, leukocytosis, and sedimentation rate › 100 mm/hr.

Results: In cases with bilateral positive biopsy (n=27), there was good correlation between the two sides regarding intensity of inflammation ($r = 0.65$, $P < 0.001$), location of the infiltrate ($r = 0.7$, $P < 0.001$), degree of intimal thickening ($r = 0.54$, $P < 0.001$), and presence of giant cells ($r = 0.83$, $P < 0.001$). The rate of corticosteroid discontinuation tended to be quicker in patients with inflammatory infiltrates confined mainly to the adventitia, but other histological parameters did not affect this rate.

Conclusions: Inflammatory infiltrates confined to the adventitia were associated with more neuro-ophthalmic ischemic manifestations, weak/moderate ISIR at the time of diagnosis, and faster rate of corticosteroid discontinuation. No association was found between other temporal artery biopsy histological parameters and clinical features of GCA patients.

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KEY WORDS: giant cell areritis (GCA), temporal artery biopsy, intensity of the systemic inflammatory reaction (ISIR), acute-phase reactants, polymyalgia rheumatica

In most cases of giant cell arteritis the diagnosis is confirmed by a temporal artery biopsy. Aside from the diagnostic purpose, histological parameters may serve as prognostic markers. Kaiser et al. [1] reported that intimal hyperplasia of the temporal artery correlated with ischemic complications of GCA, such as ocular involvement, jaw claudication and aortic arch syndrome. A recent study [2] also suggested that increased thickening of the intima was associated with cerebral or ophthalmic complications. Chatelain and co-researchers [3] found an association between the presence of giant cells and development of permanent visual loss. Symptoms of polymyalgia rheumatica were associated with the presence of giant cells in one report [4] and with small-vessel vasculitis surrounding uninflamed temporal arteries in another [5]. We reviewed temporal artery biopsies of GCA patients in an attempt to correlate various histological parameters with clinical features, disease complications and outcome.

PATIENTS AND METHODS

Temporal artery biopsies (biopsy length of 10 mm or more) of 72 biopsy-proven GCA patients and 7 biopsy-negative GCA patients were reviewed by a single pathologist. Features of some of these patients were described by our group in previous studies [6-8]. Initially, the arteries were processed routinely according to the commonly accepted approach: they were initially fixed in formalin, after which the specimens were cut into serial 2 mm long slices, followed by paraffin embedding. The slices were cut in step sections and stained with hematoxylin and eosin. An experienced pathologist reviewed all slides. Biopsies were considered positive when mononuclear cell infiltrates in the vessel wall, with or without giant cells, were observed. Biopsy-negative GCA was diagnosed when patients fulfilled the American College of Rheumatology 1990 classification criteria, in addition to a favorable rapid response (within 3 days) to corticosteroid therapy, and absence of any medical condition explaining their symptoms during a follow-up of 6 months.

GCA = giant cell arteritis

In each temporal artery biopsy the following histological parameters were scored: intensity of the inflammatory infiltrate (mild, moderate or severe), location and extent of the inflammatory infiltrate (perivascular, adventitia, media, intima, or transmural), presence of giant cells and other cell types (histiocytes, lymphocytes, plasma cells, neutrophils, eosinophils), fragmentation of the internal elastic lamina (mild, moderate or severe), calcification of the internal elastic lamina (present or absent), degree of intimal thickening (mild < 25% reduction in lumen diameter, moderate 25–75% reduction, or severe > 75% reduction), and presence of luminal thrombus (no thrombus, mural thrombus or occluding thrombus).

Clinical data on admission and follow-up were obtained from the patients' charts. Excluded were patients who started corticosteroid therapy prior to the time of biopsy (five with biopsy-proven GCA and two biopsy-negative GCA) and patients with less than a year of follow-up (two with biopsy-proven GCA). Admission data included the patient's age, gender, symptoms at presentation and their duration, significant findings on physical examination, and results of laboratory tests. Follow-up data included the dose of prednisone and development of disease flares.

Disease flares were defined as signs or symptoms related to GCA, occurring during therapy or following cessation of therapy, and resulting in a dose increment of prednisone or resumption of corticosteroid therapy. Increasing erythrocyte sedimentation rate or C-reactive protein when not associated with GCA-related signs or symptoms were not considered GCA exacerbation.

Intensity of the systemic inflammatory reaction at the time of diagnosis was determined by the presence of five parameters: ESR > 100 mm/hr, thrombocytosis (platelet count > 400,000/μl), anemia (hemoglobin < 11 g/dl), leukocytosis (leukocytes > 11,000/μl), and fever (> 37.5°C). Patients were divided into three groups according to the ISIR before analysis of the data, as reported previously [8]. Patients with four to five parameters were considered to have strong ISIR, patients with two to three had moderate ISIR, and patients with zero to one had weak ISIR.

Linear regression was used for correlation between variables. Categorical variables were compared using the Fisher exact test, and survival curves were used to compare rates of corticosteroid discontinuation. Ethical approval was obtained, and the study was performed in accordance with our medical center's Helsinki Committee regulations.

RESULTS

All five patients with biopsy-negative GCA had bilateral biopsies. Of the 65 patients with biopsy-proven GCA 40 had bilateral biopsies, and 13 of them had inflammation on one side only. Twenty-seven patients had bilateral inflammation, with good correlation of histological inflammatory parameters between the two sides. The coefficients of correlation (r) between right and left sides for the degree of intimal thickening, intensity of the inflammatory infiltrate, location of the inflammatory infiltrate, and presence of giant cells were 0.54, 0.65, 0.70 and 0.83, respectively, with $P < 0.001$ for all correlations. When histological findings were not similar between sides, the more severe or advanced findings were considered for each patient.

Table 1. Correlation between intensity of the ISIR and several histopathological parameters in temporal artery biopsy of patients with biopsy-proven GCA

Correlation between ISIR and	*r*	*P*
Extent of tissue inflammation	0.30	0.02
Intensity of tissue inflammation	0.05	0.66
Presence of giant cells	0.02	0.8
Severity of internal elastic lamina fragmentation	0.1	0.4
Degree of intimal thickening	0.1	0.4

ASSOCIATION BETWEEN ISIR LEVEL AND HISTOLOGICAL FINDINGS

Among patients with biopsy-proven GCA, ISIR level correlated positively with extent of the inflammatory infiltrate in the vessel wall ($r = 0.3$, $P = 0.02$) [Table 1]. Strong ISIR was associated with transmural inflammation: 13 patients had strong ISIR and all of them (100%) had transmural inflammatory infiltrate, compared to only 32 cases (61%) with transmural inflammatory infiltrates among 52 patients with moderate or weak ISIR ($P = 0.006$). There was no correlation between ISIR level and intensity of arterial inflammation, degree of intimal thickening, fragmentation of the internal elastic lamina, or presence of giant cells.

ASSOCIATION BETWEEN CEREBRAL-OPHTHALMIC MANIFESTATIONS AND HISTOLOGY

Cerebral-ophthalmic ischemic manifestations were present in 19 patients at the time of diagnosis [Table 2]. All had biopsy-proven GCA; 11 had vision loss, 5 had transient vision loss and 3 had strokes. Transmural inflammatory infiltrates were present in 47% of the 19 patients with ischemic manifestations, compared to 78% of the 46 patients without cerebral-ophthalmic ischemic manifestations ($P = 0.02$) There was no association of ischemic manifestations with any of the other histological features [Table 2].

ASSOCIATION BETWEEN THE DISEASE COURSE AND HISTOLOGICAL FINDINGS

Disease flares were observed in 19 patients (17 with biopsy-proven GCA and 2 with biopsy-negative GCA) during the first year of therapy, but there was no association with any histologi-

ESR = erythrocyte sedimentation rate
ISIR = intensity of the systemic inflammatory reaction

Table 2. Association between neuro-ophthalmic ischemic manifestations and histological findings in temporal artery biopsy of patients with biopsy-proven GCA

Histological parameter	Ischemic manifestations (n=19)	No ischemic manifestations (n=46)	*P*
Transmural inflammation	9 (47%)	36 (78%)	0.02
Intense inflammation	7 (37%)	15 (33%)	0.78
Giant cells	8 (42%)	18 (39%)	1.0
Neutrophils	4 (21%)	5 (11%)	0.43
Eosinophils	4 (21%)	8 (17%)	0.73
Histiocytes	10 (53%)	32 (70%)	0.26
Plasma cells	3 (16%)	12 (26%)	0.52
Severe intimal thickening	10 (53)	27 (59%)	0.78
Luminal thrombus	2 (10%)	7 (15%)	1.0
Vessel-wall calcifications	10 (53%)	17 (37%)	0.28
Severe fragmentation of internal elastic lamina	7 (37%)	17 (37%)	1.0

Values are no. (%)

cal parameter. There was a trend towards faster discontinuation rate of cocticosteroid therapy in patients with inflammatory infiltrates confined to the adventitia, but this did not reach statistical significance. There was no statistically significant association between duration of corticosteroid therapy and any histological feature.

DISCUSSION

Transmural inflammatory infiltrates were associated with strong ISIR and with lower rate of cerebral-ophthalmic ischemic manifestations. Several studies described an association between strong inflammatory response and low risk of developing visual loss and other cranial ischemic complications [9-13]. Data in this study are in agreement with those reports, adding a histological aspect to the association between strong ISIR and lower risk of developing cerebral-ophthalmic ischemic manifestations.

No association was found between other temporal artery histological features and clinical features or outcome of GCA patients. In contrast with other reports [1-3], we did not find an association between the presence of giant cells, or the degree of intimal hyperplasia, and occurrence of cerebral-ophthalmic ischemic complications. Makkuni and colleagues [2] studied 30 cases of biopsy-proven GCA and categorized the degree of luminal narrowing due to intimal hyperplasia. They reported higher intimal hyperplasia scores among 12 patients with cerebral-ophthalmic complications compared to patients without ischemic events. Chatelain et al. [3] reported that permanent visual loss in 29 patients with GCA was associated with presence of thickened intima and arterial occlusion in temporal artery biopsies, in addition to other histological features, such as presence of giant cells, plasma cells, and neoangiogenesis [3]. However, following multivariate analysis, intimal hyperplasia and occlusion of the lumen did not remain significantly associated with visual loss.

Weak ISIR was reported to be associated with a milder course of GCA and lower corticosteroid requirements [8,14], possibly related to altered tissue production of cytokines [15]. Similar findings were reported by ter Borg et al. [16]: a subgroup of patients with mild histological inflammatory reaction in their temporal artery biopsies had significantly lower levels of ESR and higher hemoglobin levels, suggestive of weak ISIR. Fifty percent of patients in this subgroup were off steroids after 2 years, compared to only 9% and 18% of patients in subgroups with moderate or severe histological inflammatory changes. In our study patients with inflammatory infiltrates confined to the adventitia tended to have shorter duration of corticosteroid therapy, but this did not reach statistical significance.

In general, histological studies attempting to correlate histological parameters with clinical features in GCA are potentially subject to sampling errors. Although in the 27 patients with positive bilateral biopsies the histological parameters were concordant for the most part, it is well known that temporal artery histology may transmute throughout the involved segment. Therefore, histological findings in one or even several samples may not reflect the full intensity and extent of the inflammatory reaction and intimal thickening, and may not reflect histological changes in other head and neck arteries. This may explain in part the variability in the reported associations between histological and clinical features in GCA, making it difficult to draw definite conclusions. In addition, variation in the methods of temporal artery biopsy processing, and the probable effects of corticosteroid therapy before the time of biopsy [17] may further contribute to the variability in the reported associations between histological and clinical features. Notwithstanding, the clinically applicable finding of this study is the apparent association between transmural inflammation, strong ISIR, and lower rate of cerebral-ophthalmic ischemic manifestations in GCA.

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Capsule

The microbiota may be able to regulate sex hormones

Both genetic and environmental factors contribute to an individual's susceptibility to autoimmune disease, but the specific environmental influences are not well characterized. Markle et al. explored how microbial factors, in particular the gut microbiota, influence susceptibility to type 1 diabetes in mice. In the non-obese diabetic (NOD) mouse model of type 1 diabetes, female mice are significantly more susceptible to disease than males; however, this difference was not apparent under germ-free conditions. Transfer of cecal contents from male NOD mice to female NOD mice prior to disease onset protected against pancreatic islet inflammation, autoantibody production, and the development of diabetes and was associated with increased testosterone in female mice. Blocking androgen receptor activity abrogated protection. Thus, the microbiota may be able to regulate sex hormones and influence an individual's susceptibility to autoimmunity.

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Eitan Israeli

Capsule

Ovarian surface epithelium at the junction area contains a cancer-prone stem cell niche

Epithelial ovarian cancer (EOC) is the fifth leading cause of cancer deaths among women in the United States, but its pathogenesis is poorly understood. Some epithelial cancers are known to occur in transitional zones between two types of epithelium, whereas others have been shown to originate in epithelial tissue stem cells. The stem cell niche of the ovarian surface epithelium (OSE), which is ruptured and regenerates during ovulation, has not yet been defined unequivocally. Flesken-Nikitin et al. identified the hilum region of the mouse ovary, the transitional (or junction) area between the OSE, mesothelium and tubal (oviductal) epithelium, as a previously unrecognized stem cell niche of the OSE. They found that cells of the hilum OSE cycle slowly and express stem and/or progenitor cell markers ALDH1, LGR5, LEF1, CD133 and CK6B. These cells display long-term stem cell properties ex vivo and in vivo, as shown by serial sphere generation and long-term lineage-tracing assays. Importantly, the hilum cells show increased transformation potential after inactivation of tumor suppressor genes *Trp53* and *Rb1*, whose pathways are altered frequently in the most aggressive and common type of human EOC, high grade serous adenocarcinoma. This study supports experimentally the idea that susceptibility of transitional zones to malignant transformation may be explained by the presence of stem cell niches in those areas. Identification of a stem cell niche for the OSE may have important implications for understanding EOC pathogenesis.

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