Journal of Autoimmunity 69 (2016) 94–101

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Correlations between histopathological findings and clinical manifestations in biopsy-proven giant cell arteritis

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ARTICLE INFO

Article history:
Received 16 January 2016
Received in revised form
9 March 2016
Accepted 9 March 2016
Available online 20 March 2016

Keywords:
Temporal artery biopsy
Giant cell arteritis
Temporal arteritis
Visual loss
Ischemic complications
Histopathology
Colour duplex ultrasonography

ABSTRACT

Objective: To correlate histopathological features of positive temporal artery biopsy (TAB) and clinical manifestations of the disease in a large single-center population-based cohort of patients with biopsy-proven giant cell arteritis (GCA).

Methods: A pathologist with expertise in vasculitis and blinded to clinical data and final diagnosis reviewed all TABs performed for suspected GCA at our hospital between January 1986 and December 2013. Histopathologic features evaluated were: the severity of inflammation and intimal hyperplasia, both graded on a semiquantitative scale (mild = 1, moderate = 2, severe = 3), the presence of intraluminal acute thrombosis, calcifications, giant cells, fibrinoid necrosis and laminar necrosis.

Results: 274 patients had a final diagnosis of biopsy-proven GCA and were included in the study. Cranial ischemic events (CIEs) were observed in 161 (58.8%), visual manifestations in 79 (28.8%) and permanent (partial or complete) visual loss in 51 (18.6%) patients. Predictors for the development of CIEs were older age (OR = 1.057, 95% CI 1.019–1.097, p = 0.003), lower ESR values (OR = 0.990, 95% CI 0.981–0.999, p = 0.026) as well as the presence of giant cells (OR = 1.848, 95% CI 1.045–3.269, p = 0.035) and laminar necrosis at TAB (OR = 2.334, 95% CI 1.187–4.587, p = 0.014). Predictors for the development of permanent visual loss were lower CRP values (OR = 0.906, 95% CI 0.827–0.992, p = 0.033) and the presence of calcifications at TAB (OR = 3.672, 95% CI 1.479–9.121, p = 0.005). Fibrinoid necrosis was not observed in any of the TABs evaluated.

Conclusion: Pathological features of TAB may predict some manifestations of GCA. These findings may have implications for patients' management.

1. Introduction

Giant cell arteritis (GCA) is the most common vasculitis in Western countries in individuals older than 50 years. It mainly involves the large and medium-sized arteries, especially the branches of the proximal aorta, and may produce a wide spectrum of clinical symptoms. Inflammatory involvement of the extracranial branches of the external carotid artery gives rise to the classic cranial symptoms of the disease. GCA-related cranial ischemic events (CIEs) include visual loss, jaw claudication and the less common cerebrovascular accidents (CVAs). Permanent (partial or complete) visual loss in one or both eyes occurs in up to 20% of patients with GCA and is often an early manifestation of the disease. Systemic symptoms and polymylgia rheumatica (PMR) occur in about 40–50% of patients, and differently from CIEs, are not related to reduction in cranial blood flow. Finally, inflammatory involvement of the aorta and its major branches may lead to aortic aneurysm formation, with the risk of dissection and rupture, and large artery stenoses with vascular insufficiency [1].

Temporal artery biopsy (TAB) is considered the gold standard for the diagnosis of GCA [2]. The classic histological picture of this

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http://dx.doi.org/10.1016/j.jaut.2016.03.005
0896-8411/

vasculitis is a transmural inflammatory infiltrate associated with marked disruption of the internal elastic membrane and various degree of intimal hyperplasia. A granulomatous inflammation with giant cells at the intima-media junction is observed in about 50% of cases, while the remaining 50% have a panarteritis with a mixed-cell inflammatory infiltrate that is predominantly composed of lymphomononuclear cells [1,3]. More limited inflammation restricted to the adventitial or periadventitial tissue without medial involvement may also be associated with GCA [3,4]. A positive TAB may additionally demonstrates intraluminal thrombosis, calcifications and laminar necrosis, and rarely fibrinoid necrosis [3]. In addition to the diagnostic role, histological parameters of positive TABs may have clinical and prognostic significance and thus implications for patients' management.

Previous studies have tried to correlate histological features of positive TABs with clinical manifestations and ischemic complications of GCA, but the results were controversial. The degree of intimal hyperplasia and the presence of giant cells were correlated respectively with the ischemic complications of the disease [5,6] and with permanent visual loss [7], but these data have not been confirmed by other studies [8–13].

The aim of our study was to investigate the correlations between histopathological features of positive TABs and clinical manifestations of the disease in a large single-center population-based incident cohort of consecutive patients with biopsy-proven GCA.

2. Patients and methods

We reviewed the computerized register of the Pathology laboratory of Santa Maria Nuova Hospital, which includes records of all TABs performed in Reggio Emilia, Italy, between January 1, 1986 and December 31, 2013. Santa Maria Nuova Hospital is the only referral center for a population of 519,480 people living in the Reggio Emilia area. All patients referred by medical practitioners and community-based specialists for suspected GCA are usually assessed by a Rheumatologist in the Rheumatology Department at Reggio Emilia Hospital within 24 h, and TAB routinely performed within 5 days from the first referral in all patients in which the clinical suspicion of GCA is confirmed. TAB procedures in Reggio Emilia are detailed elsewhere [14,15]. The same protocol for histological evaluation of TABs was followed throughout the entire study period. The biopsies (all with a length $\geq$0.5 cm after fixation) were transversally sectioned into pieces of 3–4 mm in length, fixed in formalin and embedded in paraffin. Four-micrometer-thick sections were cut from paraffin blocks and stained with hematoxylin and eosin.

888 TABs performed in 871 patients were retrieved. All the biopsies were reviewed by a single pathologist (AC), who had no access to the clinical data. Forty-four biopsies (4.9%) did not sample the muscular artery and were considered inadequate. 490 adequate biopsies (55.2%) were devoid of inflammation and were considered negative. The remaining 354 biopsies (39.9%) showed inflammation and were classified as positive. The blocks of all the inadequate and negative biopsies were retrieved from the pathological archive and additional multiple sections were cut and stained with hematoxylin and eosin in order to avoid missing arterial tissue or skip lesions, respectively. No new cases of transmural inflammation were observed after the additional sections were cut. According to a recent article by our group [3], positive TABs were further classified into 4 categories based on the localization of the inflammation: 32 cases (9% of the positive biopsies) were classified as small vessel vasculitis, 23 cases (6.5%) as vasa vasorum vasculitis, 25 cases (7%) as inflammation limited to adventitia, and 274 cases (77.5%) as transmural inflammation. For the purpose of our study, positive TABs showing only small vessel vasculitis and vasa vasorum vasculitis were excluded. Of the remaining 299 patients, comprehensive informations about clinical and laboratory manifestations were available for 274, who were included in the cohort of the present study. The characteristics of the inflammatory process of these 274 TABs was further analyzed. The following histopathologic features were evaluated: the severity of inflammation graded on a semiquantitative scale (mild, moderate and severe) (Fig. 1A–C), the severity of intimal hyperplasia graded on a semiquantitative scale (mild <25% reduction in lumen diameter, moderate from 25% to 75% and severe >75%) (Fig. 1A–C), giant cells (present or absent), calcifications (present or absent), intraluminal acute thrombosis (present or absent), fibrinoid necrosis (present or absent) and laminar necrosis (present or absent). Laminar necrosis is characterized by a band of acellular eosinophilic material sometimes bordered by palisading histiocytes along the internal elastic lamina (Fig. 1D). The localization along the internal elastic lamina and the negativity of the histochemical stains with phosphotungstic acid hematoxylin (PTAH) were used to differentiate laminar necrosis from fibrinoid necrosis [3].

All inpatient and outpatient medical records were carefully reviewed. Besides demographic features, the following clinical data at the time of diagnosis were evaluated: cranial symptoms and signs: headache, scalp tenderness and abnormal temporal arteries on physical examination; cranial ischemic events (CIEs): jaw claudication, visual manifestations (amaurosis fugax, permanent visual loss and diplopia) and CVAs (stroke and transient ischemic attacks); systemic symptoms and signs (at least one of the following: fatigue, anorexia, weight loss of at least 4 Kg, or fever); and PMR defined as marked bilateral aching and stiffness in at least two of the three regions, namely shoulder girdle, hip girdle or neck.

CVAs were attributed to GCA only if they occurred within the time from the onset of GCA symptoms/signs until one months after the onset of glucocorticoid therapy.

Fever >38 °C was considered a marker of severe systemic response.

In our center, routine colour duplex sonography (CDS) of the temporal arteries for patients with suspected GCA is been performed as part of a standard screening since 1998, and standardized reports for all ultrasonographic examinations are stored in a computerized database. A dark, hypoechoic circumferential wall thickening ("halo sign") was considered consistent with vasculitis.

The ESR was determined using the Westergren method (because most of our patients were females >50 years of age, the upper limit of the normal reference range was considered 30 mm/first hour). CRP was measured by nephelometry (NA latex CRP kit, Behringwerke, Marburg, Germany; upper limit of the normal reference range was 0.5 mg/dl).

The study was approved by the Ethics Committee of Reggio Emilia Hospital and informed consent was obtained from all patients.

2.1. Statistical analysis

Continuous data were described as mean and standard deviation (mean ± SD) or median and interquartile range (Q1,Q3), and categorical variables as absolute frequencies and percentages. Continuous variables were compared by using *t*-test or Mann-Whitney test when the distributions were skewed. Comparison of categorical variables was performed by using chi-square or Fischer's exact test, as appropriate. A logistic regression model with the backward stepwise approach ($p = 0.10$ for removal, $p = 0.05$ for addition to the model) was performed including significant variables at the univariate analysis. Odds ratios (ORs) with 95% confidence intervals (CIs) were computed. All test were two-sided; significance was defined at $p < 0.05$. Statistical analysis was