Characterization of Extracranial Giant Cell Arteritis with Intracranial Involvement and its Rapidly Progressive Subtype

Carolin Beuker, MD,[1†] Maximilian Christian Wankner,[2†] Christian Thomas, MD,[3] Jan-Kolja Strecker, PhD,[1] Antje Schmidt-Pogoda, MD,[1] Wolfram Schwindt, MD,[4] Andreas Schulte-Mecklenbeck, PhD,[1] Catharina Gross, PhD,[1] Heinz Wiendl, MD,[1] Peter J. Barth, MD,[5] Bernd Eckert, MD,[6] Thomas Raphael Meinel, MD,[7] Marcel Arnold, MD,[7] Jens Schaumberg, MD,[8] Schulamith Krüger, MD,[8] Milani Deb-Chatterji, MD,[9] Tim Magnus, MD,[9] Joachim Röther, MD,[2] and Jens Minnerup, MD[1]

Objective: The objective of this study was to characterize patients with extracranial giant cell arteritis with intracranial involvement.
Methods: In a multicenter retrospective study, we included 31 patients with systemic giant cell arteritis (GCA) with intracranial involvement. Clinical characteristics, pattern of arterial involvement, and cytokine profiles were assessed. Patients with GCA without intracranial involvement (n = 17), and with intracranial atherosclerosis (n = 25) served as controls.
Results: Erythrocyte sedimentation rate (ESR) was elevated in 18 patients (69.2%) with and in 16 patients (100%) without intracranial involvement ($p = 0.02$). Headache was complained by 15 patients (50.0%) with and 13 patients (76.5%) without intracranial involvement ($p = 0.03$). Posterior circulation arteries were affected in 26 patients (83.9%), anterior circulation arteries in 17 patients (54.8%), and both territories in 12 patients (38.7%). Patients with GCA had vertebral artery stenosis proximal and, in contrast, patients with atherosclerosis distal to the origin of posterior inferior cerebellar artery (PICA). Among patients with GCA with intracranial involvement, 11 patients (37.9%) had a rapid progressive disease course characterized by short-term recurrent ischemic events. The median modified Rankin Scale (mRS) at follow-up in these patients was 4 (interquartile range [IQR] = 2.0–6.0) and 4 patients (36.4%) died. Vessel wall expression of IL-6 and IL-17 was significantly increased in patients with rapid progressive course.
Interpretation: Typical characteristics of GCA, headache, and an elevated ESR, are frequently absent in patients with intracranial involvement. However, differentiation of intracranial GCA from atherosclerosis can be facilitated by the typical pattern of vertebral artery stenosis. About one-third of patients with intracranial GCA had a rapid progressive course with poor outcome. IL-17 and IL-6 may represent potential future treatment targets.

ANN NEUROL 2021;00:1–12

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.26101

Received Feb 9, 2021, and in revised form May 10, 2021. Accepted for publication May 10, 2021.

Address correspondence to Dr Jens Minnerup, Department of Neurology with Institute of Translational Neurology, University of Münster, Albert-Schweitzer-Campus 1, D-48149 Muenster, Germany. E-mail: minnerup@uni-muenster.de

[†]These authors contributed equally to this work.

From the [1]Department of Neurology with Institute of Translational Neurology, University of Münster, Münster, Germany; [2]Department of Neurology, Community Hospital Asklepios Klinik Hamburg Altona, Hamburg, Germany; [3]Institute of Neuropathology, University of Münster, Münster, Germany; [4]Department of Clinical Radiology, University Hospital of Münster, Münster, Germany; [5]Institute of Pathology, University of Münster, Münster, Germany; [6]Department of Neuroradiology, Community Hospital Asklepios Klinik Hamburg Altona, Hamburg, Germany; [7]Department of Neurology, Inselspital, Bern University Hospital, and University of Bern, Bern, Switzerland; [8]Department of Neurology, Community Hospital Helios Klinikum Uelzen, Uelzen, Germany; and [9]Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Giant cell arteritis (GCA) is the most common systemic vasculitis.[1] It affects mostly people older than 50 years of age.[2] Inflammation mainly involves the medium- and large-sized arteries, especially the proximal aorta and its branches.[3,4] The clinical findings in GCA commonly include new-onset headache, tenderness of the scalp, fatigue, fever, jaw claudication, and acute vision loss.[3] High-dose systemic glucocorticoids remain the mainstay of treatment and should be instituted promptly once the diagnosis of GCA as the cause of symptoms is strongly suspected.[1] The prevalence of adverse side effects of long term glucocorticoid therapy is high and patients with pre-existing comorbidities and a persisting high burden of inflammatory disease benefit from glucocorticoid-sparing agents, such as methotrexate or tocilizumab.[1,5,6] Data on the involvement of intracranial arteries in GCA are sparse and are reported in approximately 4% of patients with GCA[7–9] with a high potential of cerebrovascular complications.[8,10–12] Intracranial arteritic involvement can occur in the distribution of both the internal carotid and vertebrobasilar arteries, but is conspicuously more common in the posterior circulation.[6–8,13] However, a comprehensive engram of patients with intracranial involvement is lacking so far. Furthermore, pathophysiological differences between patients with and without intracranial involvement are unknown.

The aim of the present study was to characterize clinical, imaging, laboratory, and histological features of patients with GCA with intracranial involvement.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

Written informed consent for usage of biopsy samples and clinical data was obtained in all patients. The study was conducted according to the declaration of Helsinki and approved by the local ethics committee of all participating centers (AZ 2018-623-f-S).

Study Oversight

We conducted a multicenter retrospective study in a cohort of patients with GCA with intracranial involvement from 5 different neurology departments. We included patients with the diagnosis of GCA who met the American College of Rheumatology (ACR) classification criteria for GCA.[14] The GCA diagnosis in patients with intracranial involvement was confirmed by temporal artery biopsy in 18 and by means of imaging in 13 patients. Accordingly, all patients included in our study had an additional extracranial disease manifestation. Therefore, these patients must be distinguished from the previously described disease entity of "Granulomatous Angiitis of the Central Nervous System."[15] This clinicopathologic entity differs from GCA with intracranial involvement analyzed in our cohort, because in the former small intracranial arteries are affected. We included the following control groups and subgroups for the identification and description of typical characteristics in intracranial GCA: to determine specific differences in clinical baseline characteristics we first compared patients with GCA with intracranial involvement (n = 31) to patients with classical GCA without intracranial involvement (n = 17). We next separated patients with GCA with intracranial involvement in patients with (n = 11) and without (n = 20) a rapid progressive disease course to delineate differences in treatment response and outcome among these subtypes. To differentiate patients with GCA with intracranial involvement from patients with atherosclerosis, the relevant differential diagnosis, we compared the pattern of vertebral artery affection in these 2 groups. At least, flow cytometric cerebrospinal fluid (CSF) immune cell characteristics of patients with intracranial GCA were compared to a group of 12 age-matched patients retrospectively diagnosed with somatoform disorders without any signs of inflammatory CSF symptoms.

Patients

We included patients admitted to the Departments of Neurology at the University Hospital Münster, the Asklepios Klinik Hamburg Altona, the HELIOS Hospital Uelzen, the University Hospital Hamburg-Eppendorf, and the University Hospital Bern. Data collection included (1) demographics; (2) laboratory investigations (CSF and blood); (3) imaging results (computed tomography [CT] imaging, magnetic resonance [MR] imaging, and conventional angiogram findings); (4) disease characteristics (presenting symptoms and disease course); (5) histopathology of biopsy specimen; (6) treatment course; and (7) outcome.

Using Adobe Illustrator (Adobe Ilustrator CS5), HeatMaps of involved artery segments were drawn from imaging findings (CT or MR angiography or cerebral angiography) of 21 patients with GCA with intracranial involvement and were compared to 25 patients with atherosclerotic disease (7 women and 18 men; mean = 76 years, range = 53–95 years). Disability at follow-up was assessed by the modified Rankin scale (mRS).[16]

Immunohistochemical Analysis of GCA Biopsy Samples

Immunohistochemistry was performed on tissue samples from arteries of patients with GCA and intracranial involvement (n = 6) and compared to patients with GCA

without involvement of intracranial arteries (n = 6). Temporal artery samples from 3 healthy patients without GCA served as reference. Paraffin-embedded sections from the tonsils and appendix were used as positive controls for cytokine staining. Human artery and control sections were rehydrated and antigens unmasked (EnVisionTM FLEX Target Retrieval Solution, pH 9.0) under heat. After washing (phosphate-buffered saline [PBS], 0.02% Tween 20), sections were incubated in PBS (10% fetal bovine serum [FBS], 20 minutes) and stained using the following primary antibodies (4°C overnight): CD3 (1:20, mouse anti-human; Biolegend), CD68 (1:10, mouse anti-human; Biolegend), IL-1 (1:250, rabbit anti-human; Abcam), IL-6 (1:250, rabbit anti-human; Abcam), IL-12 (1:250, goat anti-human; Abcam), IL-17 (1:250, rabbit anti-human; Abcam), IL-23 (1:250, rabbit anti-human; Abcam), and TNFα (1:150, mouse anti-human; Abcam). After washing in PBS (3 times for 10 minutes), we used a biotinylated goat anti-mouse (1:100; Jackson), donkey anti-goat (1:100; Abcam), or a donkey anti-rabbit (1:100; Abcam) antibody for detection of primary antibodies. Subsequently, slides were washed again (PBS, 3 times 10 minutes) and sections were stained with Streptavidin AF488 (1:100; Life Technologies Ltd.). In case of double stainings, epitopes were detected with primary antibodies accordingly. Cell-specific markers (CD3 and CD68) were labeled directly using secondary goat anti-mouse594 antibody (1:100; Life Technologies Ltd.). All stainings were mounted with Vectashield Mounting Medium with DAPI (Vector). Images were taken with a Nikon Eclipse 80i fluorescence microscope (Nikon) and a Zeiss AxioVision Apotome (Carl Zeiss). High-definition photographs of fluorescence-stained vessels for densitometric analyses were taken with a Keyence BZ-9000 (Biorevo). ImageJ software version 1.48 was used for densitometric quantification. Cytokine signal intensities were measured using a modified densitometric analysis technique described elsewhere.[17] Briefly, whole vessel images (8 bit) underwent 2 processing steps using ImageJ: background noise was reduced with a 20 pixels wide rolling-ball subtraction followed by median filter (2 pixels wide). Remaining pixels between gray values 11 to 100 were considered cytokine-positive and summed for each vessel. Signal intensity of control vessel tissue was set as reference (100%). Cytokine expression was analyzed separately within intima, media, and adventitia. Final values were expressed as relative expression between patients and controls.

Specimen Handling and Routine CSF Evaluation

Patients with rapid progressive GCA were compared to a group of 12 age-matched patients retrospectively diagnosed with somatoform disorders without any signs of inflammatory CSF conditions (ie, <5 cells/µl CSF, <2 mmol/l lactate, no blood/CSF-barrier disruption, no intrathecal immunoglobulin synthesis [Reiber/OCB]). CSF samples were analyzed within 1 hour after lumbar puncture by centrifugation at 290 g for 15 minutes at 4°C in parallel with 100 µl peripheral blood. Blood-tinged CSF samples were excluded from the study. After treatment with VersaLyse buffer (Beckman Coulter) for 10 minutes, the samples were washed twice by addition of 3 ml FC-buffer (PBS [Sigma] supplemented with 2% heat-inactivated FCS Gold [BioSell] and 2 mM EDTA [Sigma]) and subsequent centrifugation at 290 g for 4 minutes. Following staining with CD14-FITC, CD3-PC5.5, CD56-PC7, CD4-APC, CD19-APC-AF700, CD8-PacificBlue, and CD45-KromeOrange (all Beckman Coulter), samples were washed once with FC buffer. After aspirating the supernatant, samples were resuspended and 20 µl flow count fluorospheres (Beckman Coulter) were added prior to acquisition using a Navios flow cytometer (Beckman Coulter). Resulting files were analyzed by Kaluza 2.1 (Beckman Coulter).

Statistical Analysis

Categorical variables are expressed as numbers (%), and quantitative variables are expressed as medians (interquartile range [IQR]). Statistical analysis was performed using GraphPad Prism version 8 (GraphPad Software, La Jolla, CA). Data were checked for normal distribution applying the Shapiro–Wilk normality test followed by group comparison using the Student's t test or Mann–Whitney U test. Patient groups were compared by use of Pearson chi-square test for categorical variables and Student's t test or Mann–Whitney U test for continuous variables. A p value of <0.05 was considered significant.

Results

Patient Characteristics

The baseline characteristics of the study population are shown in Table 1. We included 31 patients with GCA with and 17 patients with GCA without intracranial involvement. The median time from symptom onset until diagnosis of GCA was 2 weeks (IQR = 1–4 weeks) and did not differ between patients with and without involvement of intracranial arteries (3 weeks [IQR = 1–5] vs 1 week [1–4], respectively; $p = 0.57$). Demographic characteristics did not differ between these 2 groups. Patients with intracranial involvement less frequently presented with headache (50.0% vs 76.5%, $p = 0.03$) and elevated erythrocyte sedimentation rate (ESR; 69.2% vs 100%, $p = 0.02$).

TABLE 1. Baseline Characteristics of GCA Study Population

	Patients with GCA with intracranial involvement (n = 31)	Patients with GCA without intracranial involvement (n = 17)	*p* value[a]
Demographics			
Age, mean (SD), years	73.6 (7.0)	70.9 (8.2)	0.33
Women, n (%)	21 (67.7)	13 (76.5)	0.74
Comorbidities, n (%)			
Hypertension	21/29 (72.4)	10/17 (58.8)	0.52
Diabetes mellitus	9/29 (31.0)	2/17 (11.8)	0.17
Nicotine abuse	6/29 (20.7)	0/17 (0)	0.07
Hyperlipidemia	8/29 (27.6)	6/17 (35.3)	0.74
Atrial fibrillation	2/29 (6.9)	1/17 (5.9)	1.0
GCA symptoms, n (%)			
Visual disturbances	19/30 (63.3)	8/17 (47.1)	0.36
Headache	15/30 (50.0)	13/17 (76.5)	0.03
Weight loss	3/30 (10.0)	3/17 (17.6)	1.0
Jaw claudication	8/30 (26.7)	2/17 (11.8)	0.29
STA abnormalities	19/30 (63.3)	7/17 (41.2)	0.22
Laboratory findings, n (%)			
Elevated CRP	25/30 (83.3)	13/16 (81.2)	1.0
Elevated ESR	18/26 (69.2)	16/16 (100)	0.02
Elevated CRP and ESR	16/25 (64.0)	13/16 (81.2)	0.31

Clinical (average age, sex, and GCA symptoms) and laboratory characteristics of all patients with GCA with (n = 31) and without (n = 17) intracranial involvement included in the study after screening are depicted. Values are the number (%) or mean (SD).

[a]The *p* value for comparisons of patients in all 2 groups.

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; GCA = giant cell arteritis; STA = superficial temporal artery.

Characteristics of Central Nervous System Involvement

In patients with GCA with intracranial involvement, focal neurological deficits due to intracranial vasculitis at disease onset mainly consisted of motor (33.3%), speech (33.3%), and cerebellar (30.0%) deficits. Table 2 summarizes the central nervous system (CNS) affection in patients with intracranial involvement.

Of 31 patients with GCA with intracranial involvement, neuroimaging showed ischemic strokes in 25 patients (80.6%), 10 patients (32.3%) had supratentorial, 21 patients (67.7%) had infratentorial, and 7 patients (22.6%) had both supra- and infratentorial strokes (see Table 2). Fourteen patients (45.2%) had bilateral ischemic strokes. Twenty-six patients (83.9%) had vertebral artery stenosis. Within this group, 15 patients (57.7%) had bilateral involvement of the vertebral artery, occlusion occurred in 8 patients (31.0%). Heatmaps illustrating the pattern of intracranial vertebral artery stenosis are shown in Figure 1. The V3 and V4 segment of the vertebral artery were most commonly affected (Fig 1A, B). As vertebral artery changes due to GCA are difficult to distinguish from atherosclerosis, we systematically compared stenosis pattern in patients with GCA to those with atherosclerosis (control group). Patients in the control group were found to have involvement of the V4 segment of the vertebral artery after the posterior inferior cerebellar artery (PICA) origin, whereas in patients with GCA, the V3 segment as well as the V4 segment before the PICA origin were affected (Fig 1A–D). This difference was statistically significant ($p = 0.03$). In addition, in GCA, stenoses were rather spreading over a long arterial segment in line with the "slope sign" known from axillary artery affection in GCA.[18] This pattern stands in marked contrast to the short-segment stenoses observable in patients with atherosclerosis. Heatmaps of carotid artery involvement

TABLE 2. CNS Affection in Patients with Intracranial Involvement

	Patients with intracranial involvement (n = 31)
Focal neurological deficit,[a] n[b] (%)	
Cerebellar	9 (30.0)
Motor	10 (33.3)
Speech	10 (33.3)
Sensory	1 (3.3)
Vigilance disturbance	4 (13.3)
NIHSS score, median (IQR)	
At onset	2 (0–4)
At disease course	2 (0.5–11.5)
Affected arteries, n (%)	
Internal carotid artery	15 (48.4)
Middle cerebral artery	6 (19.4)
Posterior cerebral artery	6 (19.4)
Vertebral artery	26 (83.9)
Basilar artery	5 (16.1)
Carotid and vertebrobasilar	12 (38.7)
Cerebral infarction, n (%)	
Carotid territory	10 (32.3)
Cerebellar	18 (58.1)
Brain stem	9 (29.0)
Bilateral infarction	14 (45.2)
Abnormal CSF, n (%)	5/7 (71.4)
Pleocytosis,[c] n (%)	1/7 (14.3)
Leucocyte count, median (IQR), cells/mm^3	0 (0–2)
Increased protein level,[d] n (%)	4/7 (57.1)
Protein level, median (IQR), mg/dl	49.9 (39.2–83.8)
Flow cytometry (CSF), n (%)	
Lymphocytic profile	3/5
Lympho-monocytic profile	1/5
Mixed cellular profile	1/5

Values are the number (%) or median (IQR). CSF parameters of patients with GCA with intracranial involvement (n = 31) included in the study are depicted. CSF samples analyzed by flow cytometry of controls (IIH, n = 15) compared to patients with intracranial involvement (n = 5).
[a]At disease manifestation.
[b]Of 28 patients.
[c]Greater than or equal to 5cells/µl.
[d]Greater than 45 mg/dl.
CSF = cerebrospinal fluid; CNS = central nervous system; IIH = idiopathic intracranial hypertension; IQR = interquartile range; NIHSS = National Institutes of Health Stroke Scale.

showed predominantly bilateral stenosis located within the carotid siphon (Fig 1E, F).

Cerebrospinal fluid (CSF) examinations were performed in 7 patients (24.1%) with GCA with intracranial involvement (see Table 2). Abnormal CSF was found in 5 patients (71.4%), including lymphocytic pleocytosis in 1 patient (14.3%) and an increased total protein in 4 patients (57.1%). Flow cytometry based analysis of CSF and peripheral blood immune cell subsets of 4 patients with intracranial involvement GCA were compared to a group of 12 age-matched patients retrospectively diagnosed with somatoform disorders without any signs of inflammatory CSF symptoms (Fig 2A–H).[19] Comparison of major CSF leukocyte subsets revealed a reduction of total lymphocyte cell count in the CSF of patients with GCA (see Fig 2C–E). The number of granulocytes in the peripheral blood was increased in patients with GCA compared to the control group (see Fig 2A). Overall, proportions of leukocyte subsets, including monocytes, $CD4^+$ and $CD8^+$T cells, $CD19^+$B cells, NK cells, and NKT cells, did not differ between controls and patients with GCA, neither in the peripheral blood nor in the CSF.

Clinical Course and Treatment

In our study, 11 patients (37.9%) had a rapid progressive disease course characterized by recurrent ischemic events and thus representing a distinct subgroup of patients with GCA with intracranial involvement. Figure 3 illustrates the clinical disease course and treatment strategies in these patients. The median time from symptom onset until first ischemic stroke was 2 months (range = 1–52 months). Three patients developed stroke at the same time they presented with GCA symptoms.

All patients with intracranial involvement received treatment with oral or intravenous glucocorticoids (Table 3), 19 patients in combination with an immunosuppressant agent (azathioprine, cyclophosphamide, methotrexate, or tocilizumab). Tocilizumab was added to the regimen for 6 patients with either severe disease course or insufficient response to initial therapy.

Follow-up was available in 24 patients with a median of 6 months (IQR = 3.5–49.0) after hospital discharge (see Table 3). In 2 patients, outcome data were only available at hospital discharge. Patients with rapid progressive disease course had a higher level of disability (median mRS 4.0 vs 1.5, $p = 0.035$) at the last follow-up. Mortality rate was numerically higher in cases of rapid progressive disease course (4/11 [36.4%] vs 2/20 [10.0%], $p = 0.15$). In 1 patient with rapid progressive disease, percutaneous transluminal angioplasty (PTA)/stenting was performed as last resort treatment. No complications were reported and the patient was discharged with partial

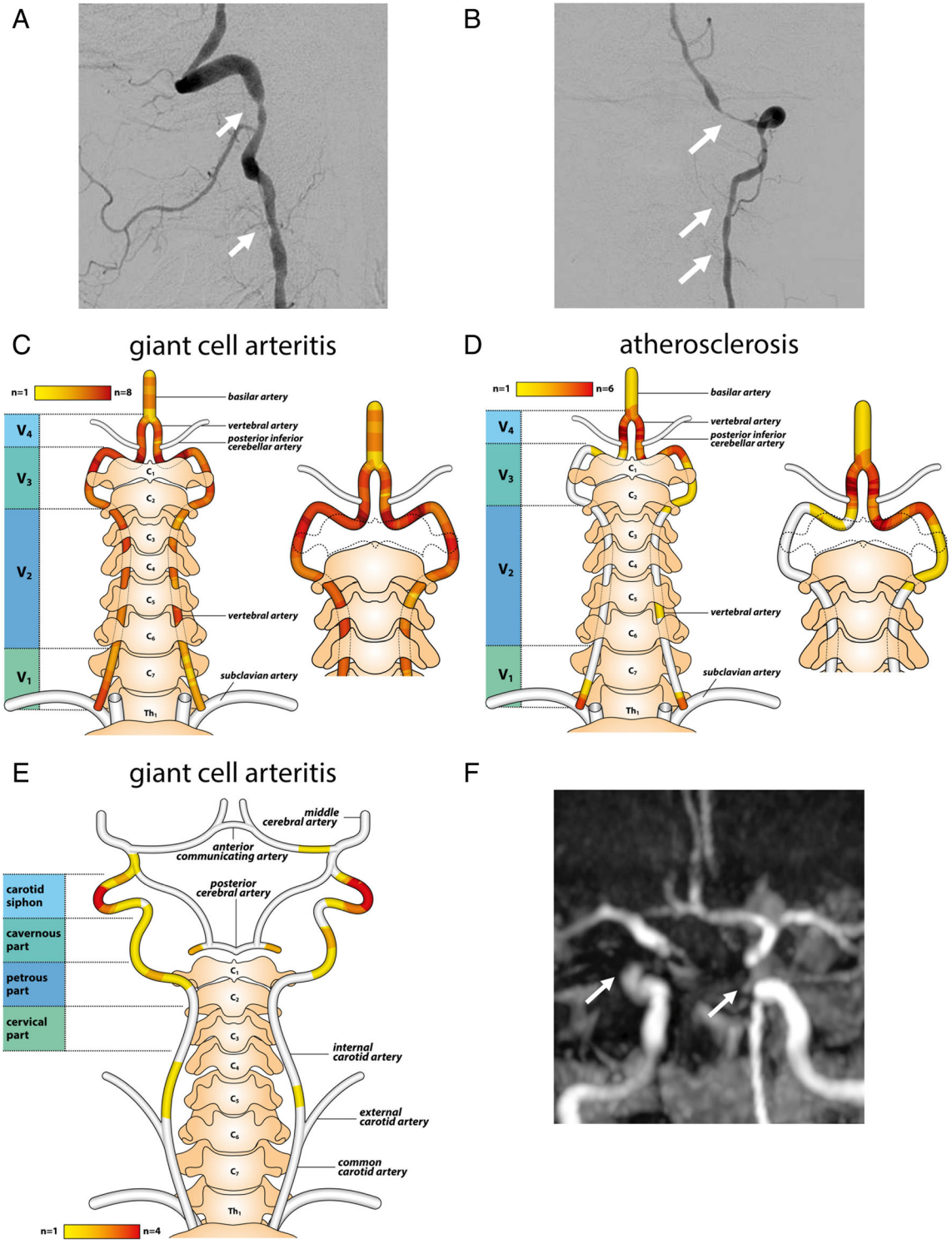

FIGURE 1: Imaging findings and HeatMaps of involved arteries. (A) Cerebral angiogram demonstrating short-segment stenosis (white arrows) of the vertebral artery distal to the PICA origin in a patient with atherosclerosis. (B) Cerebral angiogram demonstrating multiple distal artery stenoses (white arrows) in a patient with intracranial involvement in GCA. (C) HeatMap with color legend indicating the location of vertebral artery stenosis was constructed by combining pattern of patients with GCA with intracranial involvement (n = 21). (D) HeatMap with color legend indicating the location of vertebral artery stenosis in control patients with atherosclerosis (n = 25). (E) HeatMap with color legend indicating the location of internal carotid artery and medial cerebral artery stenosis was constructed by combining pattern of patients with intracranial involvement (n = 10). (F) Patient with bilateral carotid siphon stenosis on MRI-TOF-angiography.

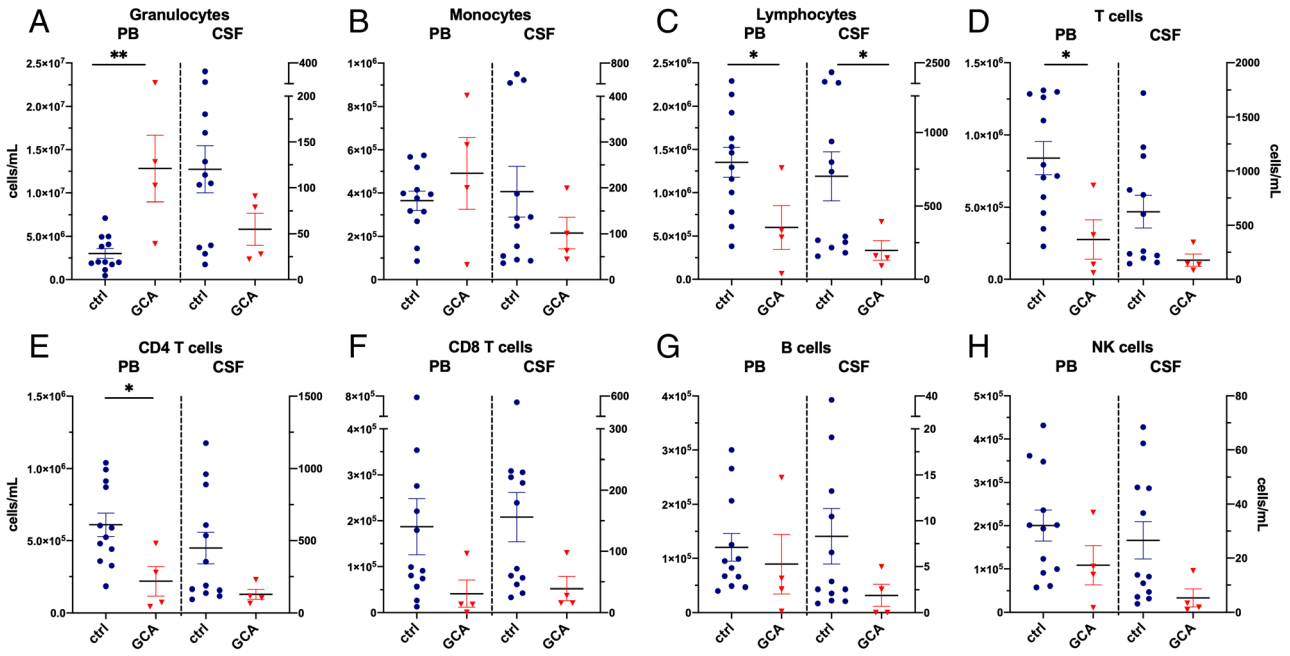

FIGURE 2: Leukocyte subsets in GCA. Leukocytes from the peripheral blood (PB) and cerebrospinal fluid (CSF) from four patients with GCA with intracranial involvement compared to 12 age-matched patients retrospectively diagnosed with somatoform disorders were stained with fluorochrome-conjugated antibodies and analyzed by flow cytometry. Leukocytes were selected based on forward scatter channel (FSC) characteristics as CD45 expressing cells and further divided into (A) granulocytes, (B) monocytes, and (C) lymphocytes by side scatter channel (SSC) versus CD14 characteristics. (D) T cells and (E) CD4 as well as (F) CD8 T-cell subsets were identified by flow cytometry as $CD3^+$ $CD56^-$ lymphocytes expressing CD4 or CD8. (G) B cells were characterized as $CD19^+$ $CD138^-$ lymphocytes. (H) NK cells were identified as $CD56^+$ $CD3^-$ lymphocytes. Cell numbers from controls (blue circle) and patients with GCA (red triangle down) are displayed. Error bars indicate the SEM. Results from different groups were compared using Mann–Whitney *U* test; *$p < 0.05$, **$p > 0.01$. GCA = giant cell arteritis.

remission. In patients without rapid progressive disease, PTA/stenting was performed in only 2 patients leading to death due to procedural complications in both patients. However, interpretation and comparison of response to treatment (immunosuppressive regimen, interventional treatment, and outcome) is limited by the retrospective design of the study and the comparably small simple size.

Cytokine Expression Pattern in Patients with Rapid Progressive Intracranial GCA

Histological samples from temporal artery biopsy from 6 patients with GCA with intracranial involvement and rapid progressive disease course were compared to 6 patients with GCA without involvement of intracranial arteries as controls. Tissue was obtained from biopsy samples, whereas in 2 patients, autopsy tissue was analyzed. In these cases, postmortem examination of the vertebral arteries was performed in addition to the histological assessment of temporal artery biopsy. Hematoxylin–eosin and Elastica van Gieson staining of superficial temporal artery (STA) showed characteristic histopathologic findings including a panarteritis composed of CD4+ lymphocytes and macrophages with fragmentation of internal elastic lamina and a few giant cells in all biopsy specimen (Fig 4A). In GCA, inflammation typically starts in the adventitia and spreads to the inner layers of the vessel wall (media and intima).[1] Distinct patterns of arterial wall involvement were observed when comparing the expression profiles of cytokines known to be involved in the pathophysiology of GCA (IL-1, IL-6, IL-12, IL-17, IL-23, and TNFα)[1] among tissue samples (see Fig 4B–G). The expression profile of IL-1, IL-12, and TNFα was comparable between patients with and without rapid progressive disease course (see Fig 4B, F, G). These cytokines were predominantly detectable in the adventitia and to a lesser extent in the media in both disease subtypes. In contrast, IL-17 and IL-23 were mainly expressed in the media layer in both disease subtypes (see Fig 4C, E). Notably, we observed an increase of IL-6 in the intimal and of IL-17 in the medial wall segment in the rapid progressive subtype in comparison to patients without rapid progressive disease course indicating an increased inflammation in these patients (see Fig 4C, D). We labeled these markers together with CD68 (macrophages) and CD3 (T cells). In line with pathogenetic pathways in GCA,[20] IL-6 was frequently expressed by $CD68^+$ cells that were morphologically classified as macrophages (see Fig 4D). The marker IL-17 was expressed by $CD3^+$ cells (see

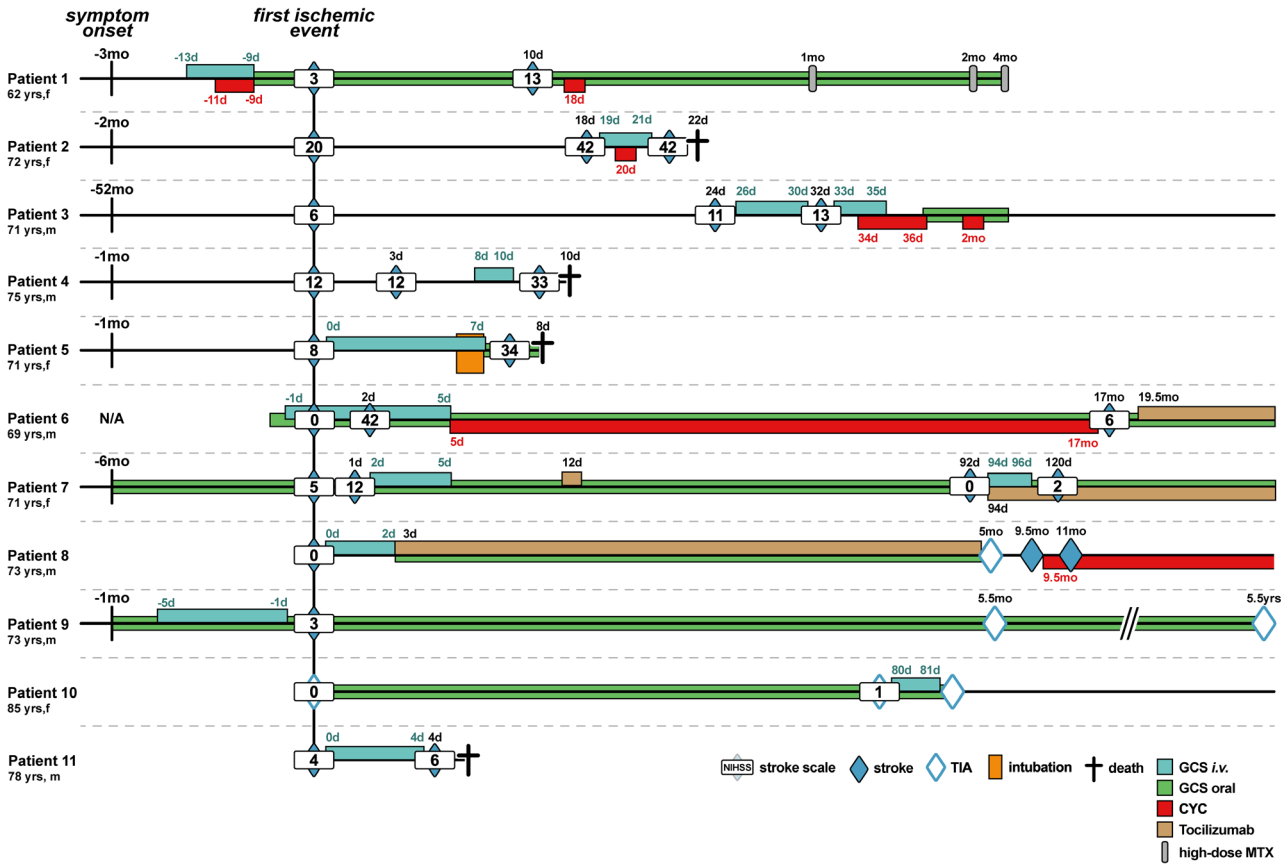

FIGURE 3: Disease course and immune therapies of patients with rapid progressive GCA. Shown are timeline data of 11 patients with GCA with intracranial involvement and rapid progressive disease course. Included are clinical episodes, NIHSS, treatments, time of intubation, and death. Black cross indicates death; blue diamond indicates ischemic stroke; brown line indicates tocilizumab; D = days; empty blue diamond indicates transient ischemic attack (TIA); GCS indicates glucocorticoids; green line indicates oral glucocorticoids; grey block indicates high-dose MTX; orange block indicates intubation; red line indicates iv cyclophosphamide; and turquoise line indicates iv pulses of glucocorticoids. GCA = giant cell arteritis; GCS = glucosylceramide synthase; Mo = months; MTX = methotrexate; N/A = not applicable; NIHSS = National Institutes of Health Stroke Scale.

Fig 4C) indicating T_H17 cells that are known to attract new macrophages via the production of IL-17 as a pathogenetic mechanism in GCA.[21]

Discussion

In this multicenter retrospective study, we provide a comprehensive characterization of patients with GCA with intracranial involvement. Our findings extend current knowledge on this distinct disease subtype. Typical clinical findings, such as headache and elevated ESR, are frequently absent in these patients. Notably, we identified a specific vessel pattern in patients with intracranial involvement (ie, stenosis of the V3 and V4 segment of the vertebral artery) that might help in distinguishing from atherosclerotic stenoses by affection prior to the PICA origin. About one third of patients had a rapid progressive disease course characterized by short-term recurrent ischemic events, poor neurological outcome, high mortality, and a specific vessel wall cytokine expression profile.

So far, there are only a few case reports and case series on patients with intracranial involvement in GCA.[7–9] In 1968, Kolodny et al were one of the first to describe granulomatous angiitis of the CNS.[15] However, in contrast to our cohort, the patients in their study did not have extracranial involvement. GCA with involvement of intracranial arteries is difficult to diagnose for several reasons. First, typical clinical GCA findings, such as headache and elevated ESR, may be absent in these patients. In previous studies, elevated ESR rates were reported in virtually all patients with GCA,[2,22,23] whereas our results indicate a relevant number of normal ESR rates among patients with intracranial involvement. Second, onset of GCA symptoms and stroke frequently occur simultaneously. A third reason is that the distinction from atherosclerosis is difficult, because cerebrovascular risk factors that might in turn cause atherosclerotic disease, are often found in patients with intracranial GCA.

TABLE 3. Treatment and Outcome of Patients with Intracranial Involvement

	All patients with GCA with intracranial involvement (n = 31)	Patients with GCA with intracranial involvement with rapid progressive course (n = 11)	Patients with GCA with intracranial involvement without rapid progressive course (n = 20)
Treatment, n (%)			
GC alone	11 (35.5)	5 (45.4)	6 (30.0)
GC and CYC	6 (19.4)	2 (18.2)	4 (20.0)
GC and AZA	1 (3.2)	0 (0)	1 (5.0)
GC and MTX	2 (6.5)	0 (0)	2 (10.0)
GC and tocilizumab	4 (12.9)	1 (9.1)	3 (15.0)
GC, CYC, and tocilizumab	3 (9.7)	2 (18.2)	1 (5.0)
GC, CYC, and MTX	4 (12.9)	1 (9.1)	3 (15.0)
Follow-up			
Time of follow-up, median (IQR), months	8.5 (3.5–49.0)	5.5 (3.5–9.8)	19.5 (4.8–62.3)
Death, n (%)	6 (19.4)	4 (36.4)	2[a] (11.8)
mRS			
At last follow-up, median (IQR)	2.1 (1.0–4.5)	4 (2.0–6.0)	1.5 (1.0–2.8)
0–2, n (%)	17 (54.8)	4 (36.4)	14 (70.0)
3–4, n (%)	5 (16.1)	2 (18.2)	3 (15.0)
5–6, n (%)	8 (25.8)	5 (45.4)	3 (15.0)

Treatment and outcome information of patients with GCA with intracranial involvement (n = 31) included in the study after screening are depicted. These patients were divided into 2 subgroup cohorts, cohort 1 = patients with rapid progressive disease course (n = 11) and cohort 2 = patients without rapid progressive disease course (n = 20). Values are the number (%) or median (IQR).

[a]Due to complication from intervention.

AZA = azathioprine; CYC = cyclophosphamide; GC = glucocorticoids; GCA = giant cell arteritis; IQR = interquartile range; mRS = modified Rankin Scale; MTX = methotrexate.

Moreover, our results show that, in comparison to other vasculitides of the CNS,[24] intracranial arteritis in GCA was not reflected by changes in CSF immune cell composition. However, immunosuppressive therapy in these patients (glucocorticoids and/or cyclophosphamide) was initiated before CSF analysis and might have contributed to this observation. Consequently, the pattern of vertebral artery involvement affecting the V3 and V4 segment before the origin of the PICA may be helpful in establishing the diagnosis correctly.

Glucocorticoids and immunosuppressive agents, such as methotrexate and tocilizumab, are currently the standard for treating GCA. However, we observed a poor response rate in patients with rapid progressive disease course to these established therapy regimens. Several case reports suggest that cyclophosphamide has been successfully used in GCA with intracranial involvement.[9,10,25] Remarkably, in our series, early initiation and combination with cyclophosphamide (in 3 cases) did not prevent the patients from recurrent stroke and poor outcome. Thus, very early implementation of sufficient immunosuppressant therapy (other than cyclophosphamide) might increase possible beneficial outcomes. We therefore analyzed biopsy samples from patients with intracranial involvement in order to determine new treatment targets. Histologically, we found IL-6 and IL-17, both known to be involved in the pathogenesis of GCA,[20] highly

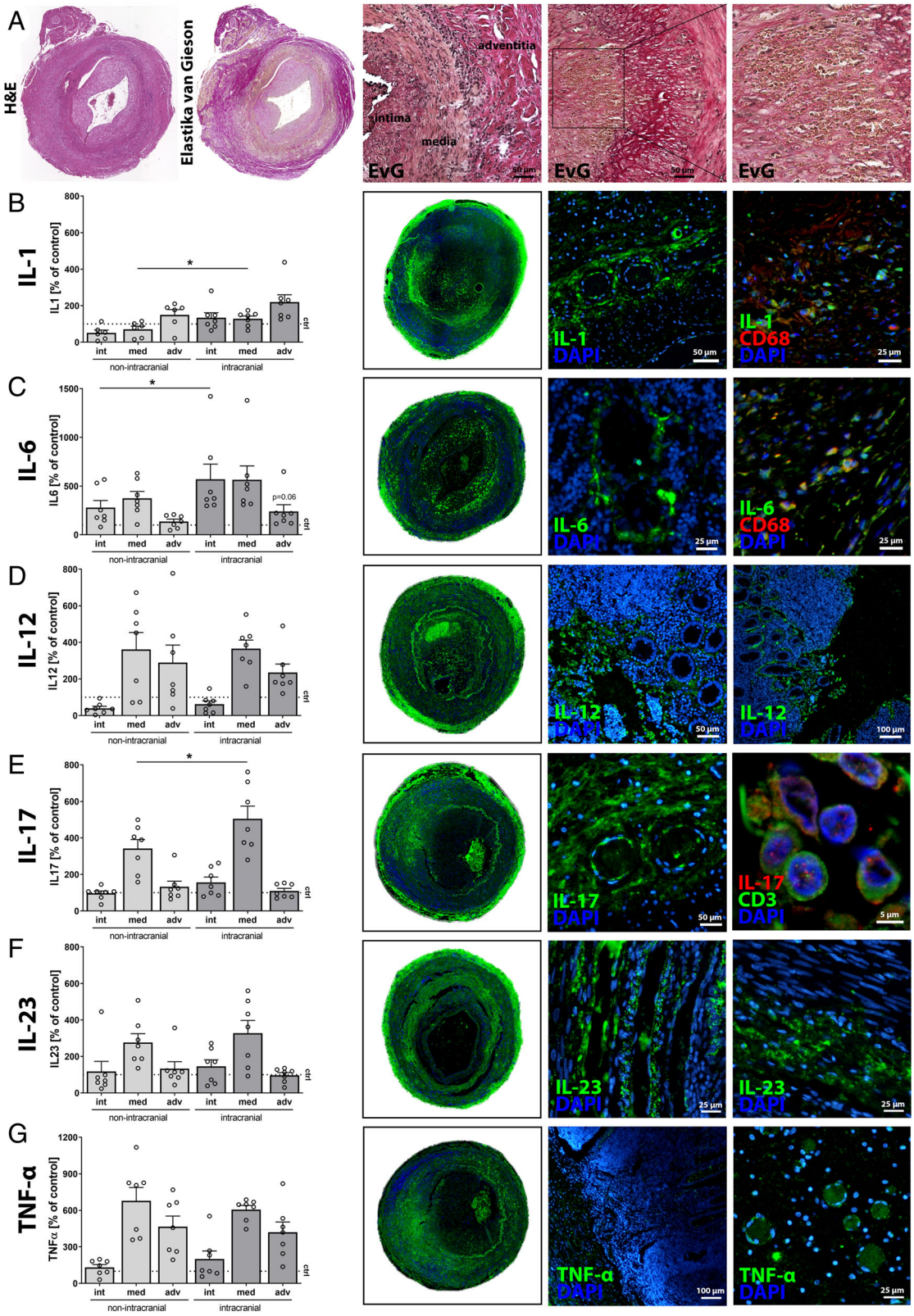

FIGURE 4: Cytokine expression pattern in patients with GCA. (A) Representative H&E and EvG-staining of TBA sample with transmural inflammation, intimal thickening, luminal stenosis, giant cells, and fragmentation of internal elastic lamina. (B–G) Cytokine expression was quantified within the intimal, medial, and adventitial layer of the vessel wall. Patients were divided in 2 groups, group 1 = patients with GCA without intracranial involvement (n = 6) and group 2 = patients with GCA with intracranial involvement and rapid progressive disease course (n = 6). Data of control patients (n = 3) are shown with dotted lines. Data are presented as mean ± SEM (*t* test, $*p < 0.05$). TBA samples were stained with IL-1, IL-17, IL-6, IL-23, IL-12, or TNFα. Scale bars represent 25, 50, or 100 μm (as indicated). (B–D) Samples were co-stained for IL-1 or IL-6 together with CD68, and IL-17 together with CD3 indicating the cellular source of cytokine production. GCA = giant cell arteritis; H&E = hematoxylin and eosin stain; TBA = total bile acid.

expressed in the vessel wall of biopsy samples from patients with intracranial involvement. Strong evidence suggests that IL-6 inhibition with tocilizumab plays a major role in suppressing disease activity in GCA and, recently, tocilizumab in combination with prednisone was superior to prednisone alone.[5,26,27] In our cohort, 2 patients experienced relapsing disease with recurrent ischemic events despite treatment with tocilizumab (initiation: iv n = 1, sc n = 1), whereas in 2 other patients stable, remission had been achieved. The efficacy and safety of IL-17A inhibitors (eg, secukinumab) is currently being tested in clinical trials. In conclusion, early administration of IL-6 or IL-17A receptor blocker in patients with intracranial GCA should be the subject of future research.

In our cohort, 2 patients with multiple intracranial stenosis within the vertebrobasilar and the carotid vascular territory died from complications of endovascular treatment. In contrast, previous studies report successful endovascular treatment in patients with progressive intracranial stenosis in GCA.[28–32] However, reports of endovascular intervention with favorable results are more likely to be published than failed attempts. On the other side, these data must be judged considering the retrospective study design. Thus, it is possible, that balloon dilatation and/or stenting of edematous and inflamed vessels harbors a high risk of rupture and re-occlusion and should be considered a rescue therapy in patients with progressive strokes.

Our study has limitations due to its retrospective design; given that comparisons of differences in evaluation and treatment are difficult and control data are limited. Therefore, conclusions about superiority of different treatments cannot be drawn from our study. Furthermore, the interpretation is limited by the comparably small size. The latter, though, is a result of the rareness of this specific disease subtype. Additionally, the high number of strokes in our cohort may be confounded by the fact that only patients with GCA from neurology departments were included. A strength of our study is the comprehensive and multimodal characterization, which includes comparison with patients with atherosclerotic disease, GCA without intracranial involvement, and healthy controls. Moreover, our study has high clinical implication as it identifies a distinct disease subtype and provides evidence for different pathophysiological mechanisms among the latter.

In summary, we describe patients with GCA with intracranial involvement and its subtype with progressive disease course. Above that, our study identifies a specific pattern of vertebral artery affection, which helps distinguishing GCA from stenosis due to atherosclerosis (ie, vertebral artery stenosis proximal versus distal to the origin of the PICA). Enhanced knowledge of the pathophysiology of distinct disease subtypes in GCA will help to identify therapeutic targets to halt or even reverse disease progression in severe cases.

Acknowledgments

The authors thank Birgit Schmeddes and Maike Hoppen for technical support. This study was supported by the Deutsche Forschungsgemeinschaft (DFG; MI 1547/3-1, MI 1547/4-1, and FOR 2879/1). Open Access funding enabled and organized byProjekt DEAL.

Author Contributions

C.B., M.C.W., J.R., and J.M. contributed to the conception and design of the study. C.B., M.C.W., C.T., A.S.P., W.S., A.S.M., P.F.B., B.E., T.R.M., J.S., S.K., M.D.C., and T.M. contributed to the acquisition and analysis of data. C.B., M.C.W., J.K.S., H.W., J.R., and J.M. contributed to drafting the text or preparing the figures. All authors read and critically revised the manuscript.

Potential Conflicts of Interest

J.M. receives speaking fees from Chugai Pharma. The other authors declared no conflict of interest.

References

1. Buttgereit F, Dejaco C, Matteson EL, Dasgupta B. Polymyalgia rheumatica and giant cell arteritis: a systematic review. JAMA 2016; 315:2442–2458.
2. Kermani TA, Schäfer VS, Crowson CS, et al. Increase in age at onset of giant cell arteritis: a population-based study. Ann Rheum Dis 2010;69:780–781.
3. Salvarani C, Cantini F, Boiardi L, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. N Engl J Med 2002;347:261–271.
4. Wilkinson IMS, Russell RWR. Arteries of the head and neck in Giant cell arteritis: a pathological study to show the pattern of arterial involvement. Arch Neurol 1972;27:378–391.
5. Stone JH, Tuckwell K, Dimonaco S, et al. Trial of tocilizumab in giant-cell arteritis. N Engl J Med 2017;377:317–328.
6. Ad M, Ja J, Rf S, et al. Adjunctive methotrexate for treatment of giant cell arteritis: an individual patient data meta-analysis. Arthritis Rheum 2007;56:2789–2797.
7. Larivière D, Sacre K, Klein I, et al. Extra- and intracranial cerebral vasculitis in giant cell arteritis. Medicine (Baltimore) 2014;93:e265.
8. Salvarani C, Giannini C, Miller DV, Hunder G. Giant cell arteritis: involvement of intracranial arteries. Arthritis Care Res 2006;55: 985–989.
9. Alsolaimani RS, Bhavsar SV, Khalidi NA, et al. Severe intracranial involvement in giant cell arteritis: 5 cases and literature review. J Rheumatol 2016;43:648–656.
10. Rüegg S, Engelter S, Jeanneret C, et al. Bilateral vertebral artery occlusion resulting from giant cell arteritis: report of 3 cases and review of the literature. Medicine (Baltimore) 2003;82:1–12.

11. Gonzalez-Gay MA, Vazquez-Rodriguez TR, Gomez-Acebo I, et al. Strokes at time of disease diagnosis in a series of 287 patients with biopsy-proven giant cell arteritis. Medicine (Baltimore) 2009;88:227.
12. Caselli RJ, Hunder GG, Whisnant JP. Neurologic disease in biopsy-proven giant cell (temporal) arteritis. Neurology 1988;38:352–352.
13. de Boysson H, Liozon E, Larivière D, et al. Giant cell arteritis–related stroke: a retrospective multicenter case-control study. J Rheumatol 2017;44:297–303.
14. Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33:1122–1128.
15. Kolodny EH, Rebeiz JJ, Caviness VS, Richardson EP. Granulomatous angiitis of the central nervous system. Arch Neurol 1968;19:510–524.
16. van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988; 19:604–607.
17. Lee S-R. Involvement of matrix metalloproteinase in neuroblast cell migration from the subventricular zone after stroke. J Neurosci 2006; 26:3491–3495.
18. Dasgupta B, Smith K, Khan AAS, et al. 'Slope sign': a feature of large vessel vasculitis? Ann Rheum Dis 2019;78:1738–1738.
19. Lueg G, Gross CC, Lohmann H, et al. Clinical relevance of specific T-cell activation in the blood and cerebrospinal fluid of patients with mild Alzheimer's disease. Neurobiol Aging 2015;36:81–89.
20. Dejaco C, Brouwer E, Mason JC, et al. Giant cell arteritis and polymyalgia rheumatica: current challenges and opportunities. Nat Rev Rheumatol 2017;13:578–592.
21. Deng J, Younge BR, Olshen RA, et al. Th17 and Th1 T-cell responses in giant cell arteritis. Circulation 2010;121:906–915.
22. Salvarani C, Hunder GG. Giant cell arteritis with low erythrocyte sedimentation rate: frequency of occurrence in a population-based study. Arthritis Care Res 2001;45:140–145.
23. Liozon E, Jauberteau-Marchan M-O, Ly K, et al. Giant cell arteritis with a low erythrocyte sedimentation rate: comments on the article by Salvarani and Hunder. Arthritis Rheum 2002;47:692–693; author reply 693–694.
24. Strunk D, Schulte-Mecklenbeck A, Golombeck KS, et al. Immune cell profiling in the cerebrospinal fluid of patients with primary angiitis of the central nervous system reflects the heterogeneity of the disease. J Neuroimmunol 2018;321:109–116.
25. Büttner T, Heye N, Przuntek H. Temporal arteritis with cerebral complications: report of four cases. Eur Neurol 1994;34:162–167.
26. Weyand CM, Fulbright JW, Hunder GG, et al. Treatment of giant cell arteritis: interleukin-6 as a biologic marker of disease activity. Arthritis Rheum 2000;43:1041–1048.
27. Villiger PM, Adler S, Kuchen S, et al. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. Lancet 2016; 387:1921–1927.
28. Simonsen CZ, Speiser L, Hansen IT, et al. Endovascular treatment of intracerebral giant cell arteritis. Front Neurol 2020;11:287.
29. Togo M, Kono T, Hoshi T, et al. Successful endovascular therapy for multiple intracranial arterial stenosis associated with medically intractable giant cell arteritis. J Neurol Sci 2018;384:104–106.
30. Dementovych N, Mishra R, Shah QA. Angioplasty and stent placement for complete occlusion of the vertebral artery secondary to giant cell arteritis. J Neurointerv Surg 2012;4:110–113.
31. Guerrero AM, Sierra-Hidalgo F, Calleja P, et al. Intracranial internal carotid artery angioplasthy and stenting in giant cell arteritis. J Neuroimaging 2015;25:307–309.
32. Neutel D, Biscoito L, Campos J, et al. Giant cell arteritis with symptomatic intracranial stenosis and endovascular treatment. Neurol Sci 2014;35:609–610.