Abstract

Background: Giant Cell Arteritis (GCA) is a systemic granulomatous arteritis affecting prevalently elderly patients, also called “temporal arteritis” for its predominant vascular distribution. However other large/medium-size-arteries can be involved. Common manifestations of the disease are headache, fever, visual loss, jaw claudication. Stroke is an infrequent consequence of the arterial damage. Temporal artery biopsy (TAB) has long been considered the golden standard in GCA diagnosis, despite its low sensitivity. According to new European League against Rheumatism (EULAR) recommendations (2017), superficial temporal artery (STA) or axillary artery color Doppler ultrasound (CDUS) is recommended as the first imaging modality in patients with suspected predominantly cranial GCA.

Clinical report: We describe a case of dizziness and gait instability associated with cerebellar stroke and neurosonological evidence of “halo sign” (the most relevant CDUS finding compatible with GCA) in right extracranial vertebral artery (VA) and STAs. A stenotic flow in left VA and a demodulated flow in basilar artery (BA) were also detected. The patient immediately started steroids, before performing computed tomography angiography (CTA) of supra aortic trunks (SAT) and positron emission tomography (PET).

Discussion and Conclusion: in this case of atypical presentation/vascular distribution of GCA, CDUS allowed early diagnosis and therapy. According to 2017 EULAR recommendations TAB was avoided, given the results of CDUS and PET. CDUS is a useful diagnostic tool both in ictal presentation of GCA involving cerebro-afferent arteries, and in classical GCA, as “halo sign” of STAs is highly specific for this condition. To date CDUS have relevance in GCA diagnosis and in perspective it could have a future application also in follow-up. At present, anyway, the role of CDUS in monitoring GCA exacerbation is still a speculative hypothesis.
Keywords: Acute ischemic stroke; Color Doppler ultrasound; Giant Cell Arteritis; Halo sign

Introduction

GCA has a large spectrum of presentation, exhibiting sometimes atypical or overlapping features [1,2]. The diagnosis is based on clinical features, blood tests, instrumental strategies as CDUS, magnetic resonance imaging (MRI), PET, TAB [1,3]. TAB is classically considered the diagnostic gold standard for GCA, but it suffers for low sensitivity because of the segmental nature of vasculitic processes. A negative TAB doesn’t rule out the diagnosis in suspected cases, because in about 10% it’s normal. EULAR recommendations of 2017, consider redundant biopsy role when GCA is confirmed / excluded by clinical features, laboratory and imaging data [4,5]. Schmidt in 1995 [6], proposed CDUS as a quick non-invasive test for GCA identification considering that STAs non compressible “halo sign” (indicative of vasculitic mural inflammation) is the most relevant CDUS finding of this arteritis [4,7]. “Halo sign” has been defined by an Outcome Measures in Rheumatology (OMERACT) working group as a “homogenous, hypoechoic wall thickening that is well delineated towards the luminal side, visible both in longitudinal and transverse planes, most commonly concentric in transverse scans” [8]. “Halo sign”, is not exclusive of STA, having been observed also in other vessels affected by GCA like vertebral, axillary and occipital arteries [7]. Temporal artery (TA) is one of the external carotid artery terminal branches, running behind the temporo-mandibolar joint, emerging from the parotid gland, and then crossing superficially above the posterior root of temporal bone zygomatic process. TA gives rise to middle temporal artery, runs in the pre-auricolar area before dividing, near the zygomatic arch, into its terminal branches: frontal and parietal branch [9]. Up to ten different groups of TA variations had been described in the normal population in consideration on its diameter, branching variability and patterns in the anatomical relation with the zygomatic arch [10]. CDUS allows the assessment of the whole length of STAs because, even if they are small vessels, they are superficially localized (about 4 mm below the skin surface) and easily accessible with ultrasound.

The common STA should be identified at the level of the tragus, then it should be followed with the probe downstream of the bifurcation along the frontal and parietal branches. Both transverse and longitudinal plane should be scanned, roteting the probe 90 degrees [11]. To date the GCA main medical treatment consists in high doses of steroids. Immunosuppressive agents, with a pivotal role for methotrexate, have been used in GCA chronic therapy in order to spare steroid side effects. A new promising therapeutic perspective for the disease is represented by the bDMARDS (biologic disease-modifying anti-rheumatic drugs) [2].

Search strategy

We performed a comprehensive search for English language sources through Pubmed, Medscape using the following keywords: Giant Cell Arteritis, halo sign, superficial temporal artery, large vessel vasculitis, ischemic stroke, matched with systematic review, diagnosis/classification, color Doppler ultrasound. The sources preferentially considered were those published within the last 10 years. We focused on literature specialized in rheumatology, neurology, cerebrovascular diseases, and ultrasound. We compared our clinical and neurosonological data with studies and case reports dedicated to the same topic, also collecting the latter in a special table (Table 1).

Case report

A 75 year old male was received in the Emergency Room of S.Benedetto del Tronto Hospital complaining vertigo acutely appeared two days before. Hyperlipemia was the only pathology in his clinical history. A peripheral vestibular disorder was excluded by otorhinolaryngologist, the urgent brain CT scan and the neurological examination were normal, while CDUS performed by an experienced neurosonologist, showed an “halo sign” in right VA and in both STAs, and moreover a flow demodulation in basilar artery (BA) and left VA (see neurosonological data). Arteriosclerotic plaques in carotid and vertebral arteries were excluded. The patient was urgently admitted in the Neurology Unit for the suspicion of arteritis with cerebral involvement. Urgent blood tests detected a slight increase of C-reactive protein (CRP) [2.3 mg/dl, normal value range <0,5] and leucocytes [11.000/ml ^ 3; normal value < 10.000].
Soon after blood tests an immediate therapy with prednisone (1 mg/kg/die), ASA 100 mg/die, and a gastroprotective drug was started. Hepatitis markers, immunological screening and chest X-ray were negative. MRI performed the day after admission showed subacute ischemic lesions in cerebellar site, one on the right and two on the left side, at paramedial level. CTA of SAT and intracranial vessels consolidated the hypothesis of GCA by confirmation of a concentric wall thickening in STAs, as well as in both intracranial and extracranial VAs, here associated to segmental stenosis. PET with 18F-FDG, performed 14 day after admission, revealed a radiotracer uptake increase in subclavian arteries, thoracic-abdominal aorta, and popliteal arteries, confirming the diagnosis of systemic arteritis associated with cerebellar ischemic lesions. Patient’s neurological symptoms progressively improved. Methotrexate was associated to the previous therapy as steroid sparing. After discharge patient’s WBC and CRP were normalized and he was entrusted to a rheumatologist for the management of the immunosuppressive therapy. CDUS follow up demonstrated a progressive reduction of the hypoechoic luminal thickening in STAs and VAs, and normalization of flow velocities parameters in VAs and BA. PET-control performed one year after clinical onset (steroid therapy was stopped one week before PET acquisition).
showed decrease in radiotracer uptake in all the affected vascular districts. The patient is actually symptomless and still taking prednisone 5 mg/die. Regular clinical and CDUS examination are scheduled as follow up.

Ultrasonological data

Examination was performed with Philips IU 22 instruments. The Doppler setting used (PRF, WF, gain) is recorded in each figure. At the SAT CDUS investigation by linear probe 7.5 MHz, normal findings of the endovascular wall and regular flow velocities were recorded in internal and external carotids. In cervical posterior circulation, a significant hypoechoic wall thickening was observed in right V2-VA (Figure 1a) and a stump-like pattern, suggestive of downstream steno-occlusion, was recorded in left distal V2-VA (Figure 1b). No morphological or flow pattern alterations were found in subclavian arteries. The study of STAs showed the presence of thickening in the lumen compatible with bilateral “halo sign” (Figure 1c,d). Willis polygon was insonated, with transcranial approach (sector probe 2.5 MHz), through the transtemporal and suboccipital windows. Through the transtemporal window normal flow values were detected in anterior, siphon, and middle cerebral arteries, whereas demodulated and reduced flow was detected in both posterior cerebral arteries. The venous study showed normodirect flow patterns, with normal velocity parameters in Rosenthal vein and in transverse sinuses. Through the suboccipital window a marked acceleration in left V4-VA was reported, with a peak systolic velocity (PSV)> 4 m/sec (Figure 2a), meanwhile flow parameters in contralateral V4-VA tract were normal. Basilar flow pattern appeared demodulated with a progressive accentuation in caudo-cranial direction. The measurement depths for BA were 6.2 and 8.3 cm (Figure 2b,c).

The first control (performed one week after admission) was substantially similar to the previous examination, except for a decrease of stenosis in left V4-VA, with a slight reduction of local velocimetric values. In the second control at SAT examination (performed a month after hospitalization), attenuation of the hypoechoic “halo sign” on the right V2-VA tract (Figure 3a) and the disappearance of the stump-flow on the left V2-VA with the presence of the diastolic component, were recorded. The “hypoechoic halo” in STAs was not detectable anymore in axial and longitudinal scanning plane (Figure 3b,c,d). With transcranial approach, a clear improvement of the flow pattern was recorded in the left V4-VA (PSV 2 m/sec, Figure 4a) and in BA, which did not show up the demodulated pattern of the previous examination in the distal tract (Figure 4b,c). It must be emphasized that the depths of sample volumes in left V4-VA, BA and STAs evaluation were exactly the same in both first examination and control.

Figure 1: a Echo-color-doppler of supra-aortic trunks (linear probe 7.5 MHz): hypoechoic wall thickening (“halo sign”) at the level of the V2 segment of the right VA. b Echo-color-doppler of supra-aortic trunks. Left VA presented a stump-like flow (steno-occlusion in distal segment). c, d Echo-color-doppler of supra-aortic trunks (linear probe): both superficial TAs showed a wall thickening compatible with bilateral “hypoechoic halo”. The location for STAs assessment was the same in first examination and control.

Figure 2: a Transcranial echo-color-doppler, suboccipital window (Phased array probe 2.5 MHz): marked acceleration in V4 segment of left VA (PSV > 4 m/sec), suggesting an important local hemodynamic stenosis. Depth of sample volume: 4.7 cm. b, c Transacranial echo-color-doppler, suboccipital window: BA flow appeared demodulated with progressive proximal-distal worsening. Depths of flow measurement: 6.2 and 8.3 cm, respectively.
Figure 3: a Control, echo-color-doppler of the over aortic trunks (linear probe 7.5 MHz): disappearance of the “hypoechoic halo” in V2 segment of right VA. b, c, d Control, echo-color-doppler of the over aortic trunks (linear probe): disappearance of “hypoechoic halo” in superficial TAs, both in longitudinal and transverse scanning.

Figure 4: a Control, transcranial echo-color-doppler, suboccipital window (Phased array probe 2.5 MHz): the marked acceleration in V4 segment of left VA was decreased at control examination (PSV = 2 m/sec). Depth of sample volume is the same, 4.7 cm, in initial examination and control (Fig. 2 a, and 4 a). b, c Control, transcranial echo-color-doppler: disappearance of the demodulated pattern previously found in BA, especially in its distal tract. Depths of flow measurement: 6.2 and 8.3 cm, respectively. Depths were the same in first examination and control (Fig. 2 b, c and 4 b, c).

Discussion

The relevance of the reported case is due to the atypical presentation of GCA (which implied the fast evaluation of VAs, infrequently examined and symptomatic in this vasculitis); the diffuse extension of vascular damage; the unconventional diagnostic path performed. Patient’s symptom at onset was vertigo and he did not complain for systemic feature. So, despite an ischaemic event in vertebro-basilar territory was supposed (later confirmed by mean of MRI), GCA was not suspected being the underlying cause at first. GCA is a very infrequent cause of stroke, due to involvement of extradural vertebral and carotid arteries rather than to intracranial vasculitis, as suggested by clinical / pathological findings [7]. In GCA VAs involvement is rare with reported rates of 3%-4% for ischemic events, secondary to VA stenosis / occlusion [3,23-25]. The turning point of investigation was CDUS examination of SAT and intracranial arteries performed by an experienced neurosonologist. The hypothesis of vasculitis emerged when a significant hypoechoic wall thickening, the “halo sign” was observed in V2 level of right VA. The examination was then extended to STAs, also demonstrating the typical “halo sign” in both vessels. The stenotic pattern flow in left V2 and V4, the BA flow demodulation (venous like flow) justified the symptomatology of vertebrobasilar circulation involvement. A differential CDUS diagnosis between mural edema and other intimal arteries abnormalities was due. The hypoechoic mural thickening may be misdiagnosed as a wall hematoma caused by vessel dissection, but in our case the hypoechoic area was concentric around the lumen, while the hypoechoic area resulting from a wall hematoma is usually eccentric and crescent toward cranial direction. In CDUS differential diagnosis, also arterial hypoechoic atherosclerotic plaques must be taken into consideration: these are usually short and irregular, not homogeneously spread along the entire wall vessel as observed in cases of arteritis with mural edema and inflammation [7,26]. Moreover other vasculitis had to be taken into consideration, because “halo sign” in large sovra-aortic arteries is not an exclusive hallmark of GCA, being evident also in other arteritis such as Takayasu’s arteritis (Milchert et al, 2016) [27]. On the other hand “halo sign” is highly suspect for GCA if found in STAs, site usually spared in Takayasu’s arteritis. Bilateral STAs “halo sign” is highly indicative of GCA with a sensibility of 77-79% and a specificity of 100% in patients with clinical suspicion [2,4,28].

GCA remains a clinical diagnosis even today. In 1990 the American College of Rheumatology listed five classification criteria for GCA: patient’s age> 50 years; new onset of headache; STA abnormality on physical examination; elevated erythrocyte sedimentation rate (ESR) ≥ 50 mm/hour; abnormal TAB showing features of vasculitis. Presence of three criteria has 93.55% sensibility and 91.25 % specificity for GCA diagnosis [29]. Extended criteria have recently been proposed with the addition of: tenderness at palpation or low pulse at the TA and/or extracranial arteries; ESR ≥ 50 mm/h and/or CRP ≥ 10 mg/L; positive TAB and/or imaging diagnostics (MRI and/or FDG-PET [4]. In our patient
the clinical features were not typical for GCA: he had a posterior circle stroke and showed only one clinical criteria of GCA (age > 50 years). Garcia-Garcia et al. described vertebrobasilar stroke cases in which vertebral “halo sign” was determinant for early diagnosis of GCA [7]. As in those subjects, our patient had stroke as the main clinical manifestation, and the classical symptoms of the disease were poor. However, cervical CDUS examination and recognition of the VA “halo sign” led to STAs “halo sign” identification and GCA suspicious in both works. The following CTA of SAT and FDG-PET agreed with our diagnostic hypothesis, also unmasking the real extent of the disease, which led to the addition of methotrexate. Despite classic GCA manifestations result from involvement of external carotid artery and ophthalmic artery branches, recent studies disclosed that the aorta and its major branches are affected in up to two thirds of all cases, and extracranial GCA may occur without apparent involvement of cranial arteries. Segments most frequently involved in extracranial GCA are axillary arteries (from 29 to 50% of cases) with bilateral involvement in almost all cases. Common carotid arteries are affected in 6%–25% of GCA cases [30]. Some Authors report that wall thickening, suggestive of vasculitis in VAs, is present in only 5% of all patients with GCA [20]. Confined involvement of proximal limb arteries without aortic and TAs extension is rare, usually interesting superior limbs (86%). Very rare is the solitary involvement of inferior limbs (5%) [31].

EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice consider CDUS fast track strategies fundamental in early diagnosis of GCA and Takayasu’s vasculitis in order to immediately start corticosteroid therapy and avoid permanent disabilities [4,5,32]. According to EULAR recommendations, in our patient steroid therapy was agreed soon after CDUS examination, for the high suspicion of GCA and the high impairment of vertebrobasilar hemodynamic documented. Methotrexate was started after the subsequent diagnostic tools. Addition of methotrexate as steroid-sparing in treating GCA is raccomended [33], although some Authors [3,34], recently tend to suggest bDMARDs (tollicizumab, ustekinumab, abatacept, adalimumab). EULAR recommendations establish that the diagnosis may be confirmed without additional test as TAB in case of high clinical suspicion of GCA and a positive imaging test [4,5]. TAB has important limits: it is an invasive exam; STA specimen should be at least 2 cm; its sensitivity is low; false-negative rate is high (15%–40%); the running time between the clinical suspicion of GCA and biopic results is usually not immediate, while this condition has to be considered a medical emergency [2]. Some Authors indicate better sensitivity but poorer specificity of CDUS compared with biopsy [35,36]. A negative TAB is reported in 50% of patients diagnosed with GCA and involvement of thoracic aorta and its branches, which is present in more than 45% of cases [37]. TAB was avoided in our subject, according to EULAR recommendations, considering the positive results of previous examinations. Our diagnostic hypothesis was further supported by the excellent response to anti-inflammatory/ immunosuppressive therapy during follow up. Remote normalization of the patient’s clinical, bioimual/instrumental framework reinforces the correctness of our diagnostic and therapeutic procedure. In our case CDUS investigation has played a fundamental role both in the early non-invasive diagnosis and in follow up, demonstrating the hemodynamic variations of the vasculitic process in each phase of the disease.

Conclusion

CDUS is the ideal fast track imaging technique in this scenario for the prompt access, absence of radiation or procedural risks, low costs if compared with other modalities. CDUS is a useful diagnostic tool both in ictal presentation of GCA involving cerebro-afferent arteries and GCA classical presentation. At present CDUS role in monitoring GCA exacerbation is debated but maybe they could have relevance also in follow-up, in light of further necessary investigations. High ultrasound expertise and suitable technical equipment must be assumed for a reliable diagnosis because CDUS remains an operator dependent approach [3,11]. Other diagnostic tools such as PET and CTA are necessary in a second step for unmask the true vascular extension of the disease. According to EULAR raccomendations TAB should be carried out only in ambivalent cases. Instead of TAB a more widespread fast track diagnosis with CDUS could be proposed for GCA diagnosis in the future.

Compliance with Ethical Standards

Funding and Conflict of Interest: All authors disclose any sponsorship or funding arrangements relating to this work, and any possible conflicts of interest.

Ethical approval: All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from the patient, subject of the case report.

References

1. Ninan I, Lester S, Hill C. (2016) Giant cell arteritis. Best Practice & Research Clinical Rheumatology, 30: 169-188.
2. Laria A, Lurati A, Scarpettini M. (2017). Color duplex ultrasonography findings of temporal arteries in a case of giant cell arteritis: role in diagnosis and follow-up. Open Access Rheumatology: Research and Reviews, 9.
3. Bajko Z, Balasa R, Maier S, Motataianu A, Bocutean L, et al. (2021). Stroke secondary to giant-cell arteritis: a literature review. Exp Ther Med, 22: 876.
4. Dejaco C, Ramiro S, Dufnner C, Besson F.L, Bley T.A, et al. (2018). EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. Ann Rheum Dis, 22.
6. Reinhard M, Schmidt D, Schumacher M, Hetzel A. (2003). Involvement of peripheral arteries in giant cell arteritis: a color Doppler sonography study. Clin Exp Rheumatol, 21: 148-153.
7. Pfadenhauer K, et Behr C. (2007). The contribution of ultrasound of the craniovascular arteries to the diagnosis of giant cell arteritis. Clinical Ophthalmology, 1: 461-470.
8. Pfadenhauer K, Weinert J, Hrdina C. (2011). Vertebral arteries: a target for FDG-PET imaging in giant cell arteritis? Clinical, ultrasonographic and PET study in 46 patients. Nuklearmedizin, 50: 28-32.
9. Gehlen M, Schaefer N, Schwarz-Eywill M, Maier A. (2018). Ultrasound to detect involvement of vertebral artery in giant cell arteritis. Clin Exp Rheumatol, 36 Suppl 111: 169-170.
10. Chomlak R.D, Ghazanfari F, Datta M. (2016). Case Study: Giant Cell Arteritis with Vertebral Artery Stenosis. Clin Med Insights Arthritis Musculoskeletal Disord, 9: 103.
11. Haisa T, Tsuda T, Hagiwara K, Kikuchi T, Seki K. (2015). Verteobasilar Infarction Related to Giant Cell (Temporal) Arteritis: Case Report. Neurol Med Chir (Tokyo) 55: 95-100.
12. Milchert M, Fischer K, Fliciński J, Przepiiera-Będzak H, Brzosko M. (2012). Arteriosclerosis or vasculitis? Color duplex sonography in giant cell arteritis. J Rheumatol, 39: 1898-1899.
13. Czihal M, Lottspeich C, and Hoffmann U. (2017). Ultrasound imaging in the diagnosis of large vessel vasculitis. Vasa, 46: 241-253.
14. Berti A, Campochiaro C, Cavalli G, Pepe G, Praderio L, Sabbadini M.G, Dagna L. (2015). Giant cell arteritis restricted to the limb arteries: An overlooked clinical entity. Autoimmun Rev, 14: 352-357.
15. Luqmani R, Lee E, Singh S, Gillet M, Schmidt W.A, et al. (2016). The Role of Ultrasound Compared to Biopsy of Temporal Arteries in the Diagnosis and Treatment of Giant Cell Arteritis (TABUL): a diagnostic accuracy and cost-effectiveness study. Health Technology Assessment, No. 20.90. Southampton (UK): NIHR Journals Library, Nov.
16. Dufner C, Dejaco C, Sepiano A, Falzon L, Schmidt W.A, Ramiro S. (2018). Imaging in diagnosis, monitoring and outcome prediction of large vessel vasculitis: a systematic literature review and meta-analysis informing the EULAR recommendations. RMD Open, 4: e000612.
17. Puppo C, Massolino M, Paparo F, Camellino D, Piccardo A, et al. (2014). Giant cell arteritis: systemic review of the qualitative and semi-quantitative methods to assess vasculitis with 18F-fluorodeoxyglucose positron emission tomography. Biomed Res Int, 574248.