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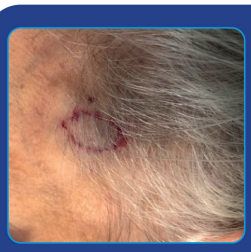
Hacettepe Giant Cell Arteritis & Polimyalgia Rheumatica Workshop

Hacettepe Üniversitesi Vaskülit Tanı ve Tedavi Uygulama ve Araştırma Merkezi
&
Hacettepe Romatoloji Derneği Ortak Programı

Dev hücreli arterit ve Polimiyaljia Romatika Çalıştayı
Klinik, Görüntüleme ve Histopatolojik Perspektif

24 Aralık 2021, Cuma
13:00 - 17:30 Sheraton Ankara Hotel



	Oturum Başkanları: Servet Akar, M.Akif Topçuoğlu	
13:00-13:10	Kursun amaçları	Ömer Karadağ
13:10-13:20	Dev hücreli arterit& Polimiyaljiya Romatika Epidemiyoloji: Türkiye'de gerçekten az mı?	Emre Bilgin
13:20-13:40	Dev hücreli arterit semptom ve bulgular • Romatoloji perspektifi • Nöroloji perspektifi • Oftalmoloji perspektifi	Fatma Alibaz İlksen Işıkay Sibel Kadayıfçılar
13:40-13:55	Polimiyaljiya Romatika: Ne zaman DHA ile birlikte, ne zaman değil?	Ediz Dalkılıç
13:55-14:10	DHA oftalmolojik değerlendirme	Sibel Kadayıfçılar
14:10-14:25	Nörolojik ve nöroftalmolojik açıdan DHA	İlksen Işıkay
14:25-14:40	Kahve arası	
	Oturum Başkanları: Tuncay Hazırolan, Kenan Aksu	
14:40-15:00	Normal arterlerin histolojisi Temporal arter biyopsilerindeki patolojik bulgular	Özay Gököz
15:00-15:20	DHA'de Doppler Ultrasonografi: • Temporal arterler • Karotis arterler, Subklaviyan ve aksiller arterler	M.Ruhi Onur İlkay İdilman
15:20-15:40	DHA'de Aorta ve Dalları BT/MR Anjiografi: Normal Görünüm, ateroskleroz ve vaskülit bulguları	Selin Ardalı
15:40-16:00	DHA'de PET-BT	Murat Tuncel
16:00-16:15	Kahve arası	
	Oturum Başkanları: Haner Direskeneli, Cemal Bes	
16:15-16:30	Dev hücreli arterit tanısı ve sınıflandırma kriterleri	Burak İnce
16:30-16:40	İndeks DHA hastasının TRVaS ve Trials Network web tabanlı sitemlere girilmesi	Gül Sandal Uzun
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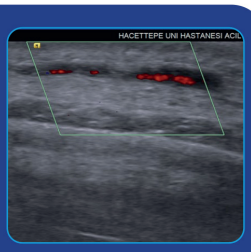
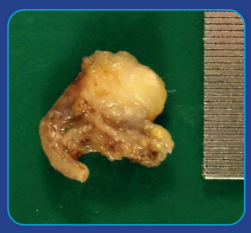
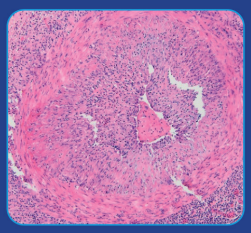
17:00-17:30	Precision Medicine in GCA: A Look Towards the Future	Peter Grayson







- **Toplantı, Vaskülitler konusunda ilgi duyan tüm meslektaşlarımıza açıktır.** Toplantıya, katılmak isteyen meslektaşlarımızın en geç 15 Aralık 2021 tarihine kadar **vaskulit@hacettepe.edu.tr** veya **dogukan.okur@devent.com.tr** adreslerine e-posta ile bilgi vermelerini (ad-soyad-kurum-cep telefonu) bekliyoruz.
- Sayın meslektaşlarımız, hastalıkların spektrumunu daha iyi yansıtabilmek için, farklı tutulum gösteren Dev hücreli arterit ve Polimiyaljiya Romatika olgularınızı olgu sunumu olarak gönderebilirsiniz.
- Olgu gönderimi için: www.abstractmodule.com/2021ankararomatoloji/
- E-poster olarak sunulacak bildiriler, bildiri kitapçığında basılacaktır.

Koordinatör: Prof. Dr. Ömer Karadağ
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CONTENTS

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POSTER PRESENTATIONS

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EDITORIAL

New aspects of Giant-cell arteritis in the 21st Century

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As the most common vasculitis of the elderly with a peak age of onset over 70 years old and female predominance, giant-cell arteritis (GCA) is usually considered a rare disease in Turkey. This is partly true as it only approaches the Caucasian prevalence rates in the Trace (European) region of the country. However, as it is also reported to be one of the major causes of fever of unknown origin (FUO) or inflammation of unknown origin (IUO) in the elderly, we should approach these incidence rates with caution.

The diverse clinical spectrum of GCA, from constitutional symptoms of several months to a recent-onset headache, jaw claudication, carotidynia, or ischemic optic neuropathy leading to acute vision loss (accepted as an ophthalmologic emergency), may deceive the unexperienced physician who may not have seen a single case until that time. The high frequency of GCA in aging populations of Western countries led to '*Fast-Track*' Clinics, which aim to see any patient with suspected GCA within 24 hours. Recent guidelines also emphasize the role of these Clinics for the fast diagnosis in suspected cases with Doppler US and temporal biopsy. Although lower incidence rates in Turkey might cause the implementation of this strategy to be somewhat controversial, as clinicians who are best equipped to diagnose GCA, we, a rheumatologist, should increase education programs for the specialties such as Neurology and Opthalmology who may encounter GCA patients first-line.

In this supplement of '*Acta Medica*,' you will read the reviews prepared after the GCA symposium organized in December 2021 by the Vasculitis Center of Hacettepe University, led by Dr. Omer Karadağ. First epidemiology of GCA in Turkey is discussed by Dr. Emre Bilgin. Then clinical features are given by Dr. Fatma Alibaz-Oner with data from the first Turkish GCA Registry, which now follows over 300 patients. Polymyalgia rheumatica co-exists with GCA in up to 40% of the cases in some series and will be presented by Dr. Ediz Dalkılıç. Dr. Sibel Kadayıfçılar and Dr. Figen Bezci as ophthalmologists and Dr. Ayşe İlksen Colpak as a neurologist will approach GCA from their perspectives. A crucial part of the diagnostic process, histopathology, will be presented by Dr. Ozay Gokoz. Finally, the emerging diagnostic field, radiology, will be discussed for Doppler US by Drs. Mehmet Ruhi Onur and Ilkay İdilman, CT and MRI by Selin Ardalı and Tuncay Hazırolan and FDG-PET/CT by Murat Tuncel. Dr. Burak İnce and Murat İnanç will summarize the diagnostic and classification criteria, and management will be discussed by Dr. Omer Karadağ and Dr. Gizem Ayan.

I hope you will find this supplement on GCA educational and beneficial for your clinical practice and research activities. I would also like to thank all my co-authors for their efforts in realizing the supplement.

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INVITED REVIEW

Epidemiology of GCA in Turkey, unmet needs, and what to do?

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Giant cell arteritis (GCA) is a large-cell vasculitis involving mainly the cranial branches of the aorta. It is the most common type of primary vasculitis in Western countries. The female to male ratio is approximately 3:1. Predominantly occurs in patients older than 50 years of age; the peak age of incidence is about 80. Incidence is highly variable according to latitude, ranging from 1 to 76 per 100000 people. With increasing latitude, the risk of GCA tends to increase; Scandinavian countries and North America have the highest reported incidence rates. The incidence may vary according to case definition (biopsy-proven, imaging, or clinical). In recent years, the incidence of biopsy-proven GCA has been decreasing. Data regarding prevalence is limited, and case definition is also variable across studies. In North America and Scandinavia, the prevalence is about 200-250 per 100000 people; it is low in the far East- about 1-2 per 100,000 people. The etiology of GCA is unknown. Obesity, diabetes, respiratory system infections, smoking, and seasonal variability seem to have a role in pathogenesis.

Polymyalgia rheumatica (PMR) is characterized by pain and stiffness in proximal muscles – shoulders and pelvic girdle -and elevated acute phase response. Incidence is higher in females and increases after 50, and the peak age is about 70-80. Similar to GCA, the incidence is higher in North America and Scandinavia (50-70 per 100000 people) than in Southern Europe (12-17 per 100000 people). Parallel to incidence, prevalence is also higher in North America and Scandinavia (700-900 per 100000 people). Co-occurrence of PMR and GCA is present in about 30-40% of patients. HLA-DRB1*04 is an essential predictor of this co-occurrence.

Up to now, there is only one epidemiological study published from Turkey. This study was a hospital-based study from Edirne. Incidence of GCA and PMR was higher in females, 1.13 per 100000 people for GCA and 3.15 per 100000 people for PMR. Prevalence of GCA was reported as 20 per 100000 people, which is much lower than in North America and Scandinavia. However, this study has several limitations; it represents only one region of Turkey, hospital-based, conducted in a 3rd-step hospital, and has low generalizability. We need more precise, generalizable, population-based studies to better understand GCA and PMR in Turkey.

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Note:
This manuscript was reviewed by Ali İhsan Ertenli.

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INVITED REVIEW

The Clinical Symptoms and Signs in Giant Cell Arteritis with the Preliminary Results of Turkish Multi-Centered GCA Registry

Fatma Alibaz Öner[1]
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Giant cell arteritis (GCA) which is a granulomatous large vessel vasculitis, is characterized by the presence of ischemic signs such as headache, visual manifestations, scalp tenderness, jaw claudication, and stroke together with systemic symptoms such as weight loss or anorexia, fatigue, and fever.

GCA is the most frequent primary systemic vasculitis among patients ≥50 years of age [1], peaking in the seventh and eighth decade of life [2]. In a recent systematic review, the pooled incidence of GCA was 10 [9.22, 10.78] cases per 100,000 people over 50 years old. The incidence was threefold higher in Scandinavia relative to the rest of Europe and was 6 times higher in Scandinavia compared to East Asia. Pooled prevalence was 51.74 [42.04, 61.43] cases per 100,000 people over age 50 [3]. Mortality in GCA was found to generally decrease over time and showed no geographic variation [3].

GCA frequently begins insidiously. The severity of the symptoms gradually increases over a period of weeks or months. In some cases, the onset can be abrupt with a major complication such as losing eyesight. The spectrum of initial disease manifestations is quite broad, and physicians need to be alert to not miss subtle manifestations of vascular insufficiency or clinical symptoms. Most patients present with headaches, scalp tenderness, and polymyalgia rheumatica (PMR); fever, weight loss, malaise, and anorexia are also frequent disease manifestations. Suppose the arteritis affects the cranial vessels, headaches, and clinical findings of the eye, brain, and cranial muscles' ischemia. If extracranial arteries are involved, patients often have an aortic arch syndrome characterized by impaired blood flow to the upper extremities. If the major disease component is a systemic inflammatory syndrome, vascular complications may be subtle. Nevertheless, systemic inflammation findings are less specific but very useful for screening suspected cases.

Glucocorticoids (GC) are the mainstay of medical treatment in GCA. EULAR suggests starting with 40–60 mg/day prednisone-equivalent for induction of remission and tapering the GC dose to a target dose of 15–20 mg/day within 2–3 months and after one year to ≤5 mg/day. Slow tapering of GC with a withdrawal between 18 and 24 months is suggested to avoid relapse [4]. Tocilizumab and methotrexate, in some cases, are suggested as steroid tapering agents [5].

Recently, we assessed the clinical findings and the relapse rates of patients with GCA in the Turkish multi-centered GCA registry retrospectively. Our study included 330 (F/M: 196/134) patients with GCA. The mean age at disease onset was 68.9±9 years. The most frequent symptom was headache (Table 1). While the duration of headache was longer than one month in 57.8% of patients, the duration was shorter than one month in 42.2% of patients. Headache is mostly localized in the temporal region (82.1%). Ocular symptoms were present in 42.1% of the patients. Permanent vision loss developed in 70 (21.2%) patients. PMR was also present in 81 (24.5%) patients.

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Note:
This manuscript was reviewed by Şule Apraş Bilgen.

The median duration of PMR symptoms before GCA diagnosis was 60 (2-3240) days. PMR was started within the last three months in 51 (62.9%) of 81 patients. The Turkish cohort's distribution of clinical signs and symptoms was compatible with the literature. Temporal artery the Doppler US was performed in 132 patients. 42 (31.9%) have a "halo sign" compatible with the GCA diagnosis. Temporal artery biopsy was available in 241 (73%) patients, and 180 of them had positive histopathological findings for GCA diagnosis. Inflammation markers were normal in 25 (7.6%) patients during diagnosis. In 12 of these 25 patients, GCA diagnosis was confirmed by temporal artery biopsy. PET-CT was done in 49 patients. 28 (57.1%) had increased vasculitic FDG uptake in the aorta and its main branches. Large vessel involvement was detected in 4 patients by CT/MR angiography. While all patients received 1 mg/kg/day GC treatment for remission induction, additional GC pulses (250-1000 mg) were given to 69 (20.9%) patients. Immunosuppressives as steroid-sparing agent was used in 252 (76.4%) patients (cyclophosphamide=2, methotrexate=187, azathioprine=54, tocilizumab=9). At third month after diagnosis, 92.7% of patients achieved remission (280/302).

In conclusion, Turkish multi-centered GCA patients' clinical signs and symptoms were similar to the literature data. The relapse rate is lower than the literature, possibly due to higher conventional immunosuppressive agent usage and corticosteroids at diagnosis.

Table 1. Clinical characteristics of patients with Giant-Cell Arteritis

	Giant-Cell Arteritis (n=330)
Manifestations of systemic inflammation	
Anemia (<12 mg/dL for female,<13 mg/dL for male)(n, %)	202 (61.2)
Erythrocyte sedimentation rate (mm/hour)(n=328)	79.7 ± 29.2 (9-159)
C-reactive protein (mg/l, n=325)	84.9 ± 69.3 (0.6-403)
Malaise (n,%)	261 (81.3)
Weight loss (n,%)	137 (41.5)
Fever (n,%)	80 (24.3)
PMR	81 (25.5)
Manifestations of Vascular Ischemia	
Headache (n,%)	294 (89.1)
Scalp tenderness (n,%)	156 (47.3)
Sensitivity on temporal artery region (n,%)	177 (53.6)
Jaw claudication (n,%)	128 (38.8)
Ocular symptoms (n,%)	139 (42.1)
Extremity claudication (n,%)	18 (5.9)
Absent or asymmetric pulses (n,%)	5 (1.5)
Asymmetric blood pressure (n,%)	4 (1.2)
Vascular bruit (n, %)	25 (7.6)
Neurological manifestations (n,%)	25 (7.9)

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INVITED REVIEW

Polymyalgia rheumatica: When co-present with Giant cell arteritis, when not?

Ediz Dalkılıç[1]
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In fact, to answer this question in one sentence, we can say, "*It is not clear.*" The term interrelated diseases can be used for Polymyalgia rheumatica (PMR) and Giant cell arteritis (GCA) [1]. The relationship between GCA and PMR can be compared to the associations between Systemic lupus erythematosus/Antiphospholipid syndrome, Rheumatoid arthritis/ Sjogren's syndrome, or Psoriatic arthritis/Gut disease. Socially, I can define these PMR and GCA as "*Two diseases that will make you famous*" for young physicians.

We can evaluate these two diseases in separate categories as isolated PMR, GCA seen in PMR, isolated GCA, PMR accompanying GCA, and GCA affecting large vessels [2].

When GCA is diagnosed, 40-60% have PMR symptoms, while 15-21% of PMR patients have GCA. Subclinical GCA may be detected in some PMR cases. However, since most of those who underwent temporal artery biopsy were patients with GCA symptoms, this rate is unknown in unselected cases [1,3].

Differences and similar features between PMR and GCA are summarized in Table 1 and 2.

Is PMR a limited or early form of GCA? Is PMR a type of vasculitis? Is PMR an auto-immune disease or an autoinflammatory disease?

There is no "*it*" supplement in the name of PMR, findings such as thrombosis, ischemia, and bleeding that we see in vasculitis are very rare, and PMR is not mentioned in the Chapel Hill classification for these reasons, PMR is not considered a primary vasculitis. In terms of auto-immune diseases, the presence of advanced age, the absence of a serological marker, the background of synovitis and its inability to accompany other autoimmune diseases also distract from the classification of autoimmune diseases. In terms of autoinflammatory diseases, advanced age, lack of course in the form of attacks, and the fact that there are constantly very high acute phase reactants also take away from this group [4].

Is there a need for GCA review in all PMR cases?

A difficult question. If we consider that one of the five PMR cases may have GCA, we can say "*yes*" to this question. Still, since this rate is unknown in unselected cases, unnecessary high dose steroid usage may increase, so the patient should be evaluated and decided on a case basis. On the other hand, insufficient steroid dosage may be raised if no investigation is done in patients with symptoms. As imaging methods other than temporal artery biopsy develop, more accurate answers will be given to this question. After PMR treatment is started, close follow-up is required in terms of headache, fatigue in the jaw, tongue, persistent fever, and eye symptoms. In terms of aortitis, it is necessary to investigate GCA in back pain, leg pain, and increased acute phase reactants. PMR symptoms have been more common in recent years, especially in GCA, affecting large vessels, which affects the aorta [4,5].

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Note:
This manuscript was reviewed by Sedat Kiraz.

Table 1. Differences between PMR and GCA

PMR	GCA
Shoulder and hip pain	Headache
Movement limitation	Eye involvement
Morning stiffness	Tongue and jaw claudication
Low grade fever	Scalp tenderness
	Fever

Table 2. Common findings of PMR and GCA

Female
Advanced age
Fatique
Weight loss
Fever
Depression

The differences between the cranial form of GCA and the large vascular involvement form are summarized in Table 3.

Table 3. The differences between the predominant cranial form and large vessel involvement form

	Predominant cranial	Predominant LVV
Age at disease onset	65-85 years	50-70 years
Delay to diagnosis	+	++
Constitutional symptoms	++	+++
Cranial ischaemic manifestations	+++	+
Positive temporal artery biopsy	++	+/-
Visual ischaemic complications	+/++	+/-
Polymyalgia rheumatica	++	++/+++
Intermittent limb claudication	+/-	+
Relapses	+/++	++
Glucocorticoid therapy: longer	++	+++

LVV: Large Vessel Vasculitis

As a result, the answer to the question of when PMR is with GCA when is not clear today. Symptoms should be evaluated on a case basis. There are differences between these two diseases regarding the course, prognosis and corticosteroid dosages. Especially in cases with PMR, after treatment begins, the risk of GCA development needs close follow-up.

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INVITED REVIEW

Ocular Involvement in Giant Cell Arteritis

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Introduction

Giant cell arteritis (GCA) is a granulomatous vasculitis that affects large and medium-sized arteries [1]. GCA is the most feared ophthalmological emergency as it may cause irreversible profound vision loss [2]. Horton and Magath in 1937 and Jennings in 1938 were the first to report a visual loss in one or both eyes as an ocular complication in GCA [3,4]. GCA-associated vasculitis particularly involves the temporal, ophthalmic, and posterior ciliary arteries (PCA). The PCA are branches of the ophthalmic artery, supplying the choroid, optic nerve head, and cilioretinal artery when present. The retinal layers are supplied mainly by the central retinal artery, another branch of the ophthalmic artery [5]. The ophthalmic artery also provides blood to the extraocular muscles via its other branches. The ocular involvement reported 20-70% in GCA is primarily ischemic in nature due to thrombosis by granulomatous inflammation of one or more of the PCAs, and rarely of the ophthalmic or central retinal artery [2].

GCA - Ocular Symptoms

The most dreadful aspect of GCA is the progressive reduction and permanent loss of visual acuity. In a series of 170 consecutive predominantly Caucasian patients with temporal artery biopsy-proven GCA, the incidence of ocular involvement was 50% and visual loss 49%. Patients with ocular findings were older than the others. In the 85 patients with ocular involvement, diplopia was the leading complaint in 6% and eye pain in 8%. Amaurosis fugax - painless transient visual loss lasting for seconds to minutes - was reported in 31% [2]. Lower incidences have been reported in other series [6-9]. Bilateral visual loss in GCA, reported at differing rates in the literature (26.9-36%), was present at the initial visit in 32% in this series [2,6,8,10]. Half of the cases became aware of the visual loss when the second eye was involved. In the others, the time interval varied from 1 day to more than six months [2]. Recognition of visual symptoms due to GCA and initiation of appropriate treatment in a short time may prevent second eye involvement and thus bilateral visual loss [11]. Recognition of visual symptoms due to GCA by physicians in a short time is very valuable.

Systemic signs of GCA generally accompany the ocular symptoms, i.e., headache, jaw claudication, neck pain, scalp tenderness, fever, weight loss, increased inflammatory response parameters, and visual symptoms accompanied by systemic symptoms or present only. However, it should be kept in mind that *the absence of systemic symptoms and normal erythrocyte sedimentation rate do not rule out GCA*. GCA may be occult in up to 21.2% of the cases [12].

GCA Ocular Findings

Ocular ischemia due to GCA may manifest as amaurosis fugax, arteritic anterior ischemic optic neuropathy (A-AION) and arteritic posterior ischemic optic neuropathy (A-PION) at the optic nerve; central retinal artery occlusion, cilioretinal artery occlusion and cotton wool spots at the retina; choroidal ischemic lesions, anterior segment ischemia, pupillary disorders, ischemia and motility disorders of extraocular muscles, ocular ischemic syndrome, and inflammatory orbital syndrome.

Arteritic- anterior ischemic optic neuropathy (A-AION)

A-AION is the most common manifestation of GCA, the main reason for permanent vision loss. Most cases of A-AION occur within a few weeks after the onset of GCA. Optic disc ischemia develops after partial or total involvement of short PCAs, which provide the main blood supply of the optic disc. Although medial short PCA is frequently involved, lateral or bilateral PCA may be affected by GCA [13]. A-AION is reported in 81.2 % of patients in Hayreh's series [2]. The mean age of patients presenting with A-AION was 76.2 ±7.0 (range 57– 93 years), and it was more common in women and Caucasians [2].

Patients with A-AION present with a sudden, painless, severe visual loss [8]. This may be preceded by amaurosis fugax in 39% of the cases [2]. At ophthalmoscopy in the acute phase, the optic disc is pale, edematous, and has a chalky-white appearance with no superficial congestion of capillaries (Figure 1) [11]. Edema regresses within 6-8 weeks, optic atrophy develops, and cupping may occur. This cupping can be confused with glaucomatous optic cupping, but in glaucoma, the optic rim appears normal, whereas, in A-AION, the optic rim is pale [14]. A-AION is accompanied by occlusion of the cilioretinal artery if present.

Differentiation from nonarteritic AION depends on clinical appearance (optic disc is more hyperemic in NAION), associated systemic symptoms, and laboratory evaluation [15].

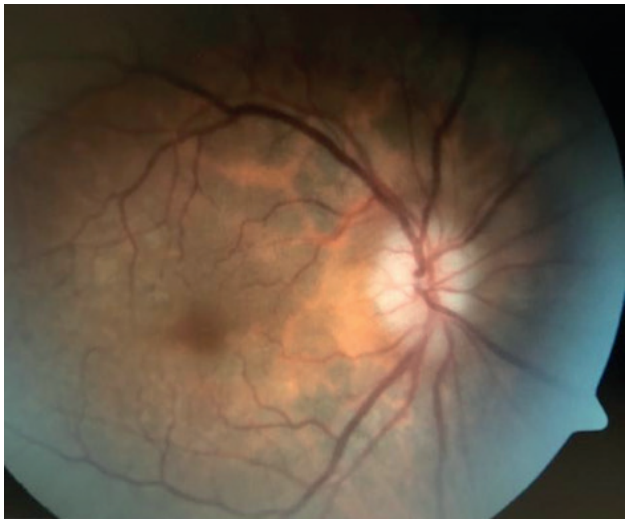

Figure 1. Chalky white optic disc edema in a patient with GCA

Arteritic- posterior ischemic optic neuropathy (A- PION)

PION is not as common as AION in GCA. It is due to occlusion of pial branches of the ophthalmic artery, which supply the retrolaminar portion of the optic nerve. In Hayreh's study, PION was reported in only 6 of 85 patients with ocular involvement [2]. A-PION presents with sudden painless loss of vision. Visual acuity is 20/200 or worse in 50% of cases. Fundus and optic disc are normal at ophthalmoscopy. Optic disc pallor appears within 6-8 weeks, especially temporally. The treatment is the same as A-AION, but there is no adequate response [14].

Central retinal artery occlusion (CRAO)

CRAO is due to GCA in 4.5% of cases. GCA should be ruled out in CRAO patients, especially in those over 50 years of age. CRAO was reported at different rates in patients with GCA; Singh et al.[16] reported 4%, while Hayreh et al. [2] reported 12%. CRAO patients usually present with sudden vision loss. It is due to the occlusion of the central retinal artery along with PCA. At ophthalmoscopy, the retina is edematous with a cherry-red spot appearance in the macula (Figure 2) [17]. But if the choroidal blood supply is significantly impaired, a cherry red appearance may not be seen. Optic disc edema may accompany. At later stages, optic atrophy, retinal attenuation, and pigmentary changes at the macula can be seen [18]. Fundus fluorescein angiography (FFA) is vital to detect whether concomitant PCA involvement could be detected. CRAO and PCA involvement are nearly almost diagnostic for GCA [1].

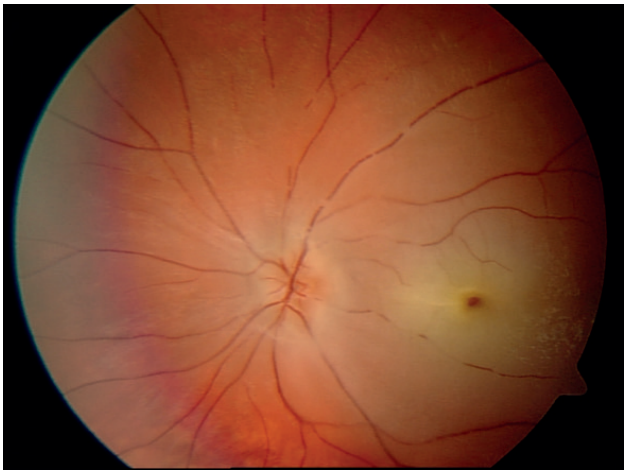

Figure 2. Central retinal artery occlusion with retinal edema and cherry red spot appearance at the macula

Cilioretinal artery occlusion (CLRAO)

The cilioretinal artery (CLRA), with a prevalence of 6.9 to 49%, is an important anatomic variation [19]. It may arise directly from the peripapillary circulation or PCA and supply the papillomacular area, where photoreceptors are concentrated. CLRA may play a role in maintaining visual acuity in CRAO [20]. In GCA patients, CLRA may also be affected along with PCA. CLRAO may accompany A-AION and CRAO in these patients or present alone [21]. In Hayreh's series, CLRAO was detected in 14 of 85 GCA patients with visual symptoms; twelve were with AION, one was accompanied by PION, and one was pure CLRAO [2]. Sudden painless vision loss is the main symptom, but transient vision loss may proceed [21]. In patients with only CLRAO, the visual prognosis may remain above 20/40 even if they do not receive any treatment. Conversely, visual acuity remains low in cases of accompanying CRAO or AION [22]. At ophthalmoscopy, the retinal area fed by the CLRA appears white and edematous. The definitive diagnosis needs FFA. It is very important to rule out GCA in a patient with CLRAO [1].

Cotton wool spots

Cotton wool spots (CWS) are focal inner retinal ischemic lesions. They are due to the axonal infarcts of the retinal nerve fiber layer, seen at an acute stage in one-third of patients with visual loss. At ophthalmoscopy, they appear as soft, fluffy white patches (Figure 3). Cotton wool spots probably develop after platelet microembolization from thrombosed arteries [1].

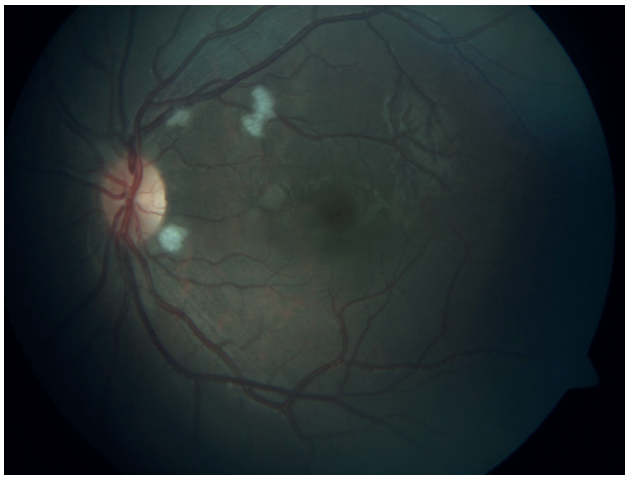

Figure 3. Cotton wool spots

Choroidal ischemic lesions

Occlusion of PCAs may create choroidal infarct areas, usually in addition to A-AION [1], but choroidal infarct alone has also been reported. Ophthalmoscopy during the acute period of visual loss may reveal white, yellow, and deep retinal lesions [23]. Approximately 2-3 weeks later, pigmented chorioretinal degeneration areas are usually seen in the midperiphery, with the apex towards the posterior pole [1].

Anterior segment ischemia

Anterior segment ischemia is rare and may develop after general ocular ischemia. Ocular hypotonia, decreased corneal sensitivity, corneal edema, iris ischemia, and scleritis may develop [24]. It may be mistaken for anterior uveitis.

Pupillary abnormalities

GCA-related tonic pupils and Horner's syndrome have been reported [25,26]. The most common pupillary defect is a relative afferent pupillary defect due to vision loss in the eye [2].

Extraocular motility disorders

Extraocular muscle involvement in GCA may be neurogenic or myogenic and presents with diplopia which is often a temporary finding [17]. Diplopia has been reported in GCA at varying rates, though not common [7,8,16]. GCA should be ruled out in patients over 50 presenting with diplopia.

Visual Prognosis

In GCA patients with ocular involvement, visual acuity often decreases to 20/200 or less, even to no light perception. Unfortunately, it may not recover [27]. Danesh-Meyer et al. reported that despite a high dose of methylprednisolone in the first six days, visual deterioration occurred in 27% of the patients. Visual acuity increased in 15% of eyes, but few had corresponding visual field improvement [28]. In another study, permanent vision loss was observed in 15.75% of patients, and 30.4% were bilateral [6]. Salvarani et al. [8] reported that 63.4% of patients with visual symptoms developed permanent vision loss, and 26.9% were bilateral. In GCA, which can result in blindness in both eyes, initiation of appropriate treatment in a short time may result in a reduction in permanent vision loss [11].

Conclusion

GCA is a potentially blinding disease. Quick recognition of visual symptoms due to GCA by physicians is essential to prevent bilateral permanent visual loss by the prompt institution of therapy.

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INVITED REVIEW

Ophthalmologic Assessment in Giant Cell Arteritis

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Note:
This manuscript was reviewed by Özlem Dikmetaş.

Introduction

Ocular examination starts with the measurement of visual acuity. In a patient with decreased vision, color vision, light reaction, and relative afferent pupillary defect should also be assessed. After evaluating ocular motility, especially in cases complaining of diplopia, a slit lamp examination should be done to determine anterior segment structures. Intraocular pressures are measured afterward. If the preliminary diagnosis necessitates a visual field exam, it should be done before pupillary dilatation for funduscopy. Possible funduscopic findings in the acute stage of giant cell arteritis (GCA) include pallid edema of the optic nerve head and signs of retinal ischemia, including cotton wool spots (Figure 1) [1]. Besides visual field testing, angiography and optical coherence tomography (OCT) is also employed in diagnosing and monitoring patients with GCA-associated ocular involvement.

Ancillary Ocular Examination

Visual field testing

In patients with GCA, evaluating the visual field is as important as measuring the central visual acuity. Visual field defects develop in GCA due to retinal, optic nerve, or cortical pathologies. Visual field exams can be done with static automated perimetry or, less commonly, with kinetic (dynamic) perimetry, which is mostly manual. In nonarteritic anterior ischemic optic neuropathy (NA-AION) patients, absolute inferior nasal defect (22%) and relative inferior altitudinal defects are more frequently detected with kinetic perimetry. If only static automated perimetry is available, patterns including central and peripheral points (e.g., FF 120, 165) should be employed to evaluate the periphery. Central scotomas are also a feature of AION. The visual field defect is usually the same type but more extensive and pronounced in arteritic-AION than NA-AION (Figure 2). In posterior ischemic optic neuropathy, central visual field defects are more frequent [2].

Fundus fluorescein angiography (FFA)

In this imaging modality, sodium fluorescein is given intravenously from an antecubital vein. Its passage into the choroidal circulation and then into the retinal circulation can be monitored by a fundus camera with special filters [3]. Suspected GCA may be evaluated with FFA, which can demonstrate delay of perfusion and hypofluorescence of either choroid, retina, or both (Figure 3) [1]. A large area of choroidal hypoperfusion is highly suggestive of GCA. Prolonged arm-to-choroid and choroidal filling times are observed in patients with A-AION, GCA's most common ocular finding [4]. The affected PCA will have peripapillary choroidal hypofluorescence on the same side. Depending on the degree of involvement, the optic disc may be stained in the late phases [5]. In NA-AION, early stages of FFA disclose filling defect or delay, usually at the prelaminar and peripapillary region and the watershed zone (the area between the medial and lateral PCA) [2].

In cases with central retinal artery occlusion, FFA is important to rule out GCA. Choroidal non-filling, in addition to the delayed retinal filling, will be a sign of accompanying PCA occlusion. In the case of cilioretinal artery (CLRA) occlusion, which may be together with A-AION, hypoperfusion is seen in the area supplied by the CLRA extending to the macula.

In GCA, FFA is an extremely important imaging modality as it shows choroidal and retinal hypoperfusion, especially in the acute phase. When collaterals develop over time, the delay in choroidal filling may not be detected [3].

Indocyanine green angiography (ICGA)

Indocyanine green angiography is a less commonly employed imaging modality in daily practice, as the dye is not widely available. The fundus camera should have specific filters according to the absorption and emission wavelengths of the dye. It shows choroidal circulation better than FFA as the molecule is highly protein-bound and does not leak from fenestrated choriocapillaris. In GCA, ICGA discloses severe ischemia of the choroid and staining of several peripheral choroidal vessels [3].

Optical Coherence Tomography (OCT)

Optical Coherence Tomography (OCT) is a non-invasive, non-contact imaging system providing high-resolution cross-sectional images of the posterior segment of the eye. It is analogous to B scan ultrasonography but uses light instead of sound.

In patients with optic neuropathies, OCT shows retinal nerve fiber layer (RNFL) edema in the acute phase [6]. With the development of optic atrophy, RNFL gets thinner (Figure 4). With OCT, it is possible to measure peripapillary RNFL thickness.

Cotton wool spots are focal hyperreflectivity in inner retinal layers (Figure 5). Deep capillary ischemia is seen as paracentral acute middle maculopathy, characterized by a hyperreflective band-like lesion in the inner nuclear layer and outer plexiform layer on OCT.

In patients with central retinal artery occlusion, OCT-A shows increased retinal thickness and reflectivity of the inner retinal layers at the acute stage. At later stages, retinal thinning becomes evident.

Optical coherence tomographic angiography (OCT-A)

OCT-A is a new, non-invasive imaging method that allows visualizing blood flow in the retina and choroid without employing a dye. With OCT-A, it is possible to evaluate the retina's superficial and deep capillary plexi separately. Peripapillary capillary plexus can also be examined (Figure 6). In cases with AION, the flow deficits in retinal capillaries were compatible with visual fields [7].

Conclusion

The ocular examination is essential in the timely diagnosis of ocular complications of GCA. Visual field testing is critical in the diagnosis of optic neuropathy. To assess ocular ischemia, fluorescein and/or indocyanine green angiography should be employed. OCT is used for detecting retinal and peripapillary changes. The role of the newest technique, OCT-A, in monitoring is currently being studied.

Figures

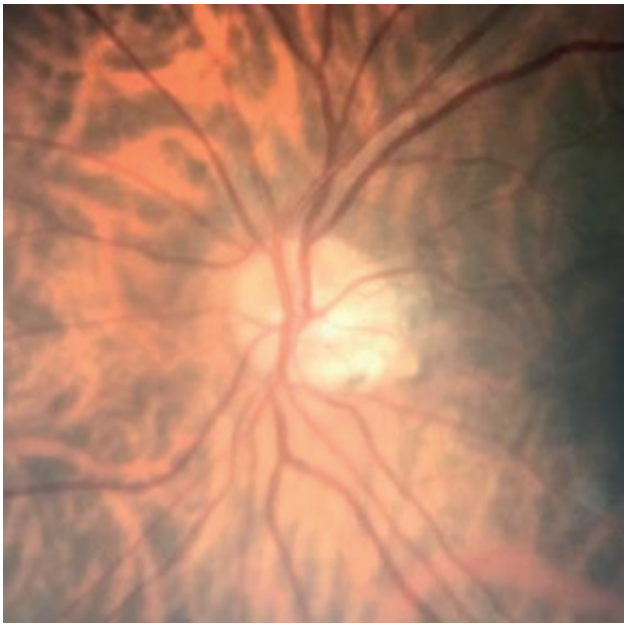

Figure 1. Left optic disc of a patient with A-AION due to GCA

Figure 2. Visual Field of the eye in Figure 1: Inferior altitudinal defect

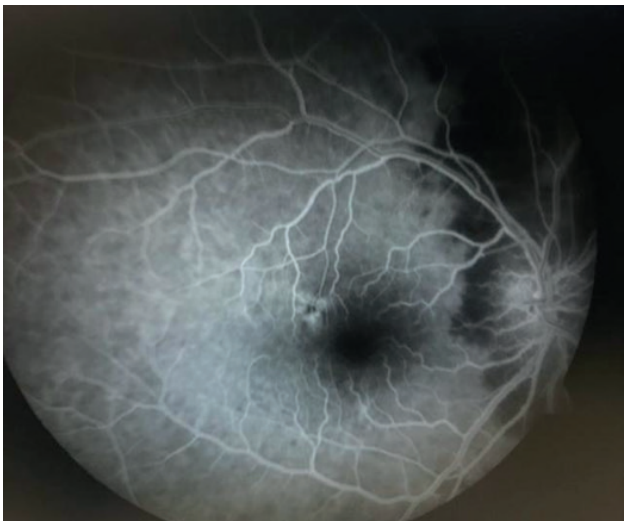

Figure 3. FFA: Peripapillary choroidal filling defect more marked superiorly in a case with A-AION

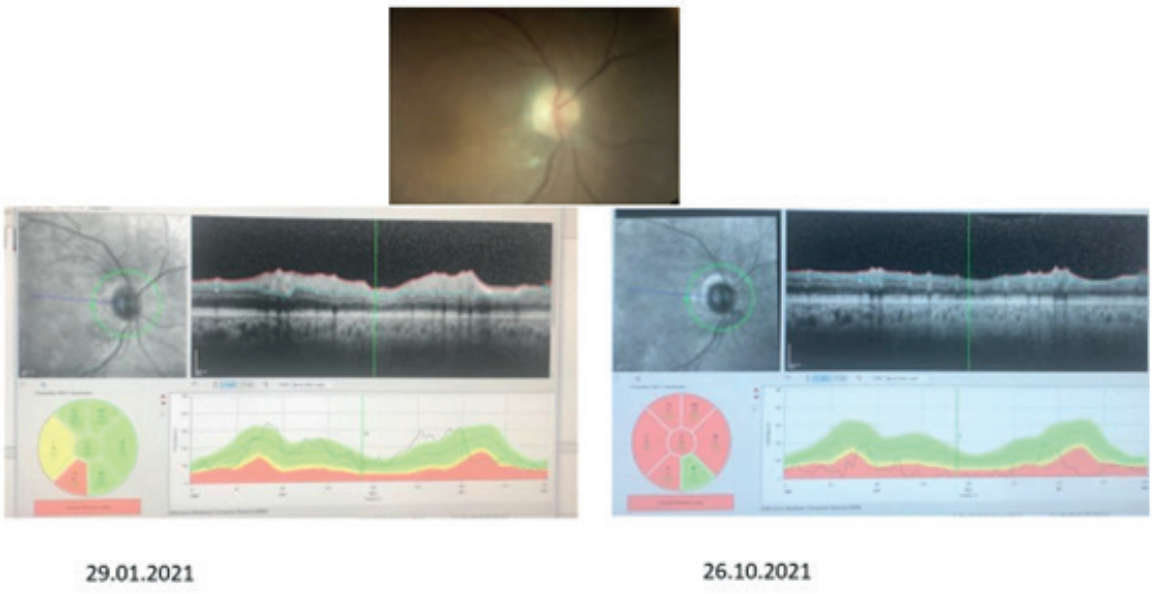

Figure 4. OCT: Development of optic atrophy and thinning of peripapillary nerve fiber layer in 9 months in a case with A-AION secondary to GCA

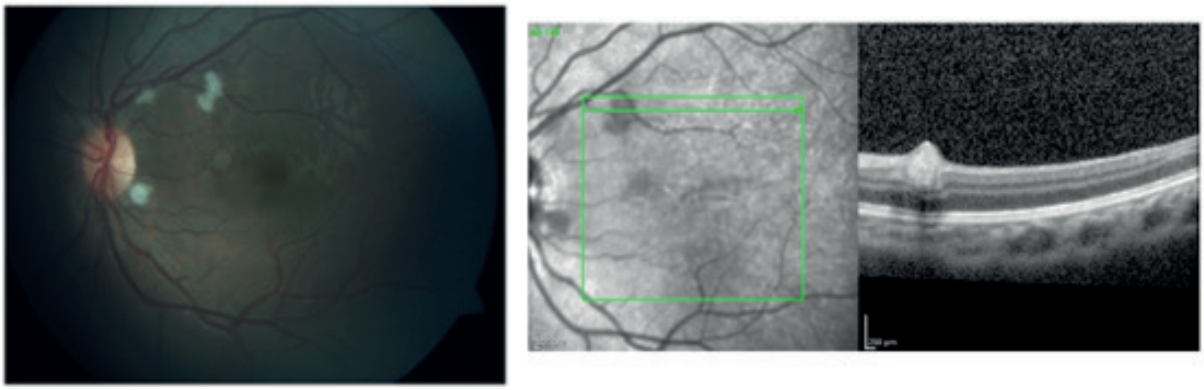

Figure 5. OCT: Increased reflectivity in inner layers of the retina corresponding to the cotton wool spots

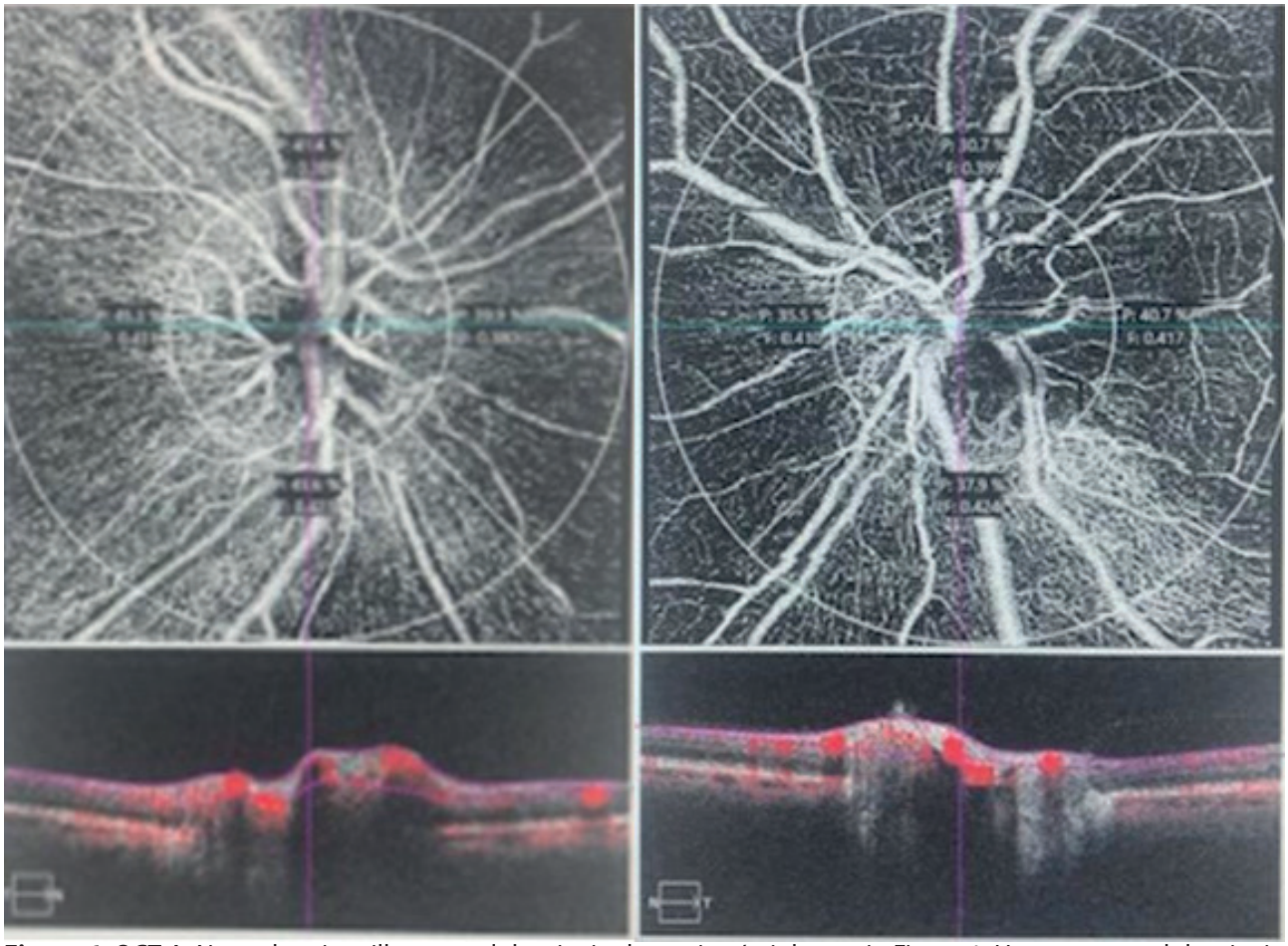

Figure 6. OCT-A: Normal peripapillary vessel density in the patient's right eye in Figure 1. However, vessel density in the left eye decreases, which has ischemic optic neuropathy

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INVITED REVIEW

Differential Diagnosis of Optic Neuritis and Neuro-Ophthalmological Assessment in Giant Cell Arteritis

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Giant cell arteritis (GCA) is the most common systemic vasculitis in individuals over 50 years old, peaking between the ages of 70 and 79. It is a chronic, granulomatous systemic vasculitis affecting large and medium-sized vessels, especially the branches of internal and external carotid arteries. Ischemia of the temporal and ophthalmic arteries is responsible for common symptoms such as; headache, vision loss, and jaw claudication.

Headache is the most likely reason for a neurologist to encounter a patient with GCA, while vision loss is the most dreadful, as it is irreversible. Early diagnosis and treatment are vital to prevent permanent visual loss, and GCA is accepted as a neuro-ophthalmological emergency. Vision loss occurs in almost 20% of GCA patients, and 79-91% are due to arteritic anterior ischemic optic neuropathy (AAION). AAION is caused by occlusion of the posterior ciliary arteries, and patients have severe monocular sudden vision loss. Examination findings are loss of visual acuity at counting fingers level, loss of color vision, relative afferent pupillary defect, altitudinal (primarily inferior) visual field defect, optic disc edema, and chalky-white pallor of the optic nerve head. The diagnosis is more likely to be considered in patients with systemic symptoms like weight loss, fever, jaw claudication, or temporary vision loss precede AAION. In 25% of patients, GCA is insidious and may present with AAION. Simultaneous optic nerve involvement is very rare, but second eye involvement in days or weeks is quite common, seen in 12-50% of GCA patients. Although the response to steroid therapy is very poor in the affected eye, second eye involvement is the main reason to start prompt steroid treatment. Non-arteritic ischemic optic neuropathy (NAION) presents similar to AAION, and it is more common compared to AAION at these ages. Differentiation is not easy just with the examination; only retinal or choroidal ischemia would support AAION. Vision loss is milder in NAION; patients have no prior transient vision loss episodes and no inflammatory changes in serum (elevated erythrocyte sedimentation rate (ESR), elevated C-reactive protein (CRP), thrombocytosis and anemia). Central retinal artery occlusion is another neuro-ophthalmological emergency and can be seen in 5 to 14% of cases in GCA patients. Stroke is not a common complication in GCA, and homonymous hemianopia due to occipital lobe ischemia is rare. Double vision is another rare complaint, mainly associated with sixth nerve palsy.

Especially in patients over 50 years of age, in the presence of new-onset headache and temporary vision loss, GCA should be considered, and diagnostic tests should be performed as soon as possible.

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Note:
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INVITED REVIEW

Histologic Assessment of Temporal Artery

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The temporal artery is classified among muscular arteries. The arterial wall is a heterogeneous, three-layered structure composed of an intima, smooth muscle-bearing media, and adventitia. Between adventitia and media, there is external elastic lamina; between media and intima, there is internal elastic lamina (IEL). (Fig.1)

Each layer exhibits specific histological, biochemical, and functional characteristics. The adventitial stroma consists of an extracellular matrix containing fibroblasts, blood and lymphatic vessels, nerves, progenitor cells, and immune cells, making the adventitia the most complex and heterogeneous compartment of the vessel wall. Adventitial cells are capable of sensing and directing responses to many stimuli through communication with other adventitial cells and with cells of the neighboring tissues. In response to hormonal, inflammatory, and environmental stresses, resident adventitial cells are often the first vascular wall cells to be activated. The fibroblast is the most abundant cell type in the vascular adventitia. Adventitial fibroblast may be a sentinel cell in the vessel wall that responds to various stimuli as the first vascular wall cell to exhibit evidence of activation [1].

Histopathology of temporal arteritis

Giant-cell arteritis (GCA) is a granulomatous vasculitis affecting arteries of medium to large size. Macrophages and lymphocytes are the main components of the inflammatory infiltrate in all layers of the artery, and multinucleated giant cells are present in about one-half of positive biopsies. Polymorphonuclear neutrophils, eosinophils, plasma cells, B-lymphocytes, and dendritic cells may be observed. Additional histological characteristics include fragmentation of IEL, intimal hyperplasia, and formation of new capillaries, particularly at the intima and intima-media junction. There is segmental involvement of the artery. Temporal arteries from GCA patients may exhibit a variable extent of inflammatory involvement, ranging from slight adventitial infiltrates to fully developed granulomatous lesions distributed along the entire vessel wall. Temporal arteritis (TA) is segmental arteritis in which inflammation starts from adventitia and concentrates around the IEL. Inflammation passes through media to the intima and causes disruption of IEL. Transmural inflammation leading to marked luminal narrowing is seen in a significant amount of cases [2]. Calcification and thrombus formation can also be present (Fig.2).

Chronic inflammation with extensive destruction of elastic lamina represents healed TA. The lymphocytes are CD3(+) with a predominance of CD4 positivity over CD8. The histiocytes are CD68 positive [3]. Disruption of elastic lamina can be well demonstrated by Verhoeff van Gieson's elastic stain. As TA is usually seen in older ages, intimal thickening due to age-related changes are frequently present in temporal artery biopsies (TAB).

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Note:
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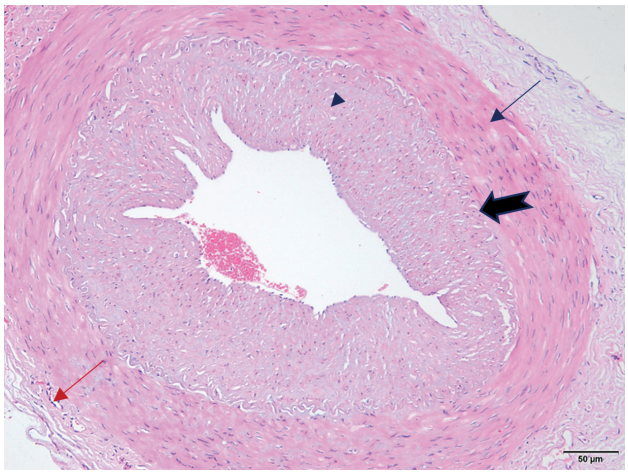

Figure 1. Normal histology of a muscular artery. Arrowhead: tunica intima, thick arrow: internal elastic lamina, thin black arrow: tunica media, red arrow: adventitia. H.E. x100

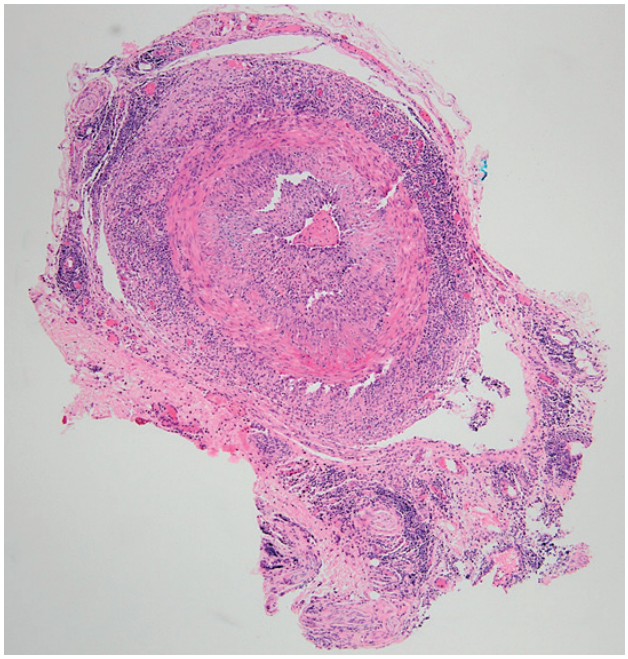

Figure 2. Transmural inflammation of temporal artery and thrombus formation in a 72 years old male patient with headache, shoulder ache and stiffness, high ESR and CRP levels, and DCVAS 12, negative for halo sign and USG findings. Treatment was given four days after the biopsy. H.E. x 40. Inlet shows an enlarged segment of temporal artery biopsy specimen with heterogeneous surface and nodular change.

Pathogenesis

In the adventitia, unknown environmental stimuli activate immature dendritic cells through toll-like receptors leading to chemokine release, which recruits CD4(+) cells with IL-6 release. Under the influence of IL-6, these cells differentiate into Th1 and Th17 cells leading to the release of INF-γ. In turn, vascular smooth muscle cells recruit monocytes that transform into macrophages or giant cells. Macrophages release reactive oxygen species and matrix metalloproteinases, leading to the destruction and necrosis of tissue. Macrophages injured vascular smooth muscle cells, and giant cells release PDGF leading to intimal hyperplasia, luminal stenosis, and thrombosis [4]. Several signaling pathways have been implicated in initiating and sustaining pathogenic CD4(+) T cell function, including the NOTCH1-Jagged1 pathway, the CD28 co-stimulatory pathway, and the PD-1/PD-L1 co-inhibitory pathway, and the JAK/STAT signaling pathway. Inadequacy of mechanisms that generally dampen immune responses, such as defective expression of the PD-L1 ligand and malfunction of immunosuppressive CD8(+) T regulatory cells, is a common theme in GCA immunopathology [3].

Differential Diagnosis

Positive TAB is 100% sensitive for TA. But the histopathological features of TA are not always diagnostic, and there are other entities with shared features. Intimal thickening without destruction but sometimes with reduplication of IEL are apt to be age-related changes. Intimal thickening is mistakenly respected as atherosclerotic changes in a significant number of cases. In fact, an intimal disease with a necrotic core defines atherosclerosis, and it is occasionally seen in the temporal artery. Unusual patterns of inflammation in patients younger than 55 years suggest other types of vasculitides like granulomatosis with polyangiitis (necrosis), PAN (fibrinoid necrosis and adventitial inflammation), or Buerger's disease (cellular thrombus). Medial calcification centered on IEL represents Monckeberg's calcification [5]. A patient with clinical features of TA who later develops renal and muscular involvement of microscopic polyangiitis can have a positive TAB with histological features similar to TA [6]. A patient with granulomatous vasculitis, few eosinophils, and occasional giant cells can be p-ANCA positive, have eosinophilia, sinusitis, and bronchial asthma leading to the diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA) [7]. Chronic inflammation of branch vessels without the involvement of the main artery is suspicious but not diagnostic for TA. Patients with chronic perivascular inflammation but no arteritis seem no more likely to have temporal arteritis on clinical grounds than similar patients without inflammation on biopsy [8,9].

Negative Biopsy

A negative TAB can be seen due to a variety of factors. Segmental distribution of the inflammation, short biopsy length, inadequate sampling, and inadequate microscopic evaluation can end with a negative biopsy. Palpation of the artery before the biopsy procedure is essential for an adequate sample. In a review of 1520 TAB datasets, the search for an optimal cut-off length suggested that the best diagnostic sensitivity might be offered for TAB of at least 0.5 cm long [10]. For pathological examination, routine sectioning may miss the diagnosis in a subset of cases, and in some cases, sectioning deeper into the paraffin block may be warranted. The vast majority (94%) of patients that were biopsy "proven" to be negative for temporal arteritis on initial examination remained negative after review of all subsequent deeper levels, but 6% of the initially "biopsy-negative" cases did turn out to be positive on deeper levels [11]. Steroid therapy does not seem to affect histologic changes. TAB performed 1–4 weeks after starting glucocorticoids still reveals changes consistent with GCA, including inflammatory infiltrates and/or giant cells in most patients with a clinically suspected diagnosis [12]. In patients with newly diagnosed GCA, the diagnostic yield of TAB within four weeks of starting high-dose steroid treatment was 74%; when the duration of therapy extended beyond this period, the TAB positivity rate fell to 40%. In patients that developed GCA on a background of a prior history of polymyalgia rheumatica, a late TAB is also generally informative despite long-term treatment with low doses of corticosteroids [13].

In short, TAB should be taken with careful palpation. The length of the biopsy can be as small as 0.5 cm if the right segment is sampled. Histopathologically, mononuclear cell infiltration of vascular wall layers with the destruction of IEL is highly diagnostic for TA. Histologic assessment can need several deep sections for the diagnosis. Histologic differential diagnosis of TA consists of microscopic polyangiitis, EGPA, and small-vessel vasculitis of several special entities for which clinical confirmation is crucial.

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INVITED REVIEW

Temporal Artery Ultrasonography in Giant Cell Arteritis

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ABSTRACT

Temporal arteries may be involved in giant cell arteritis. Ultrasonography (US) with linear transducers enabling high-resolution image acquisition has a vital role in diagnosing and following giant cell arteritis. Sonographic evaluation needs to be performed with the appropriate technique. US findings of giant cell arteritis include halo sign, compression sign, and luminal stenosis in the temporal artery. Color flow Doppler US may be used in follow-up for patients undergoing treatment of giant cell arteritis of temporal arteries.

Keywords: temporal artery (D013699), Doppler US (D018608), giant cell arteritis (D013700)

INTRODUCTION

Giant cell arteritis (GCA) is a primary systemic vasculitis characterized by the involvement of large and medium-sized arteries [1]. Although the diagnosis of GCA is usually based on clinical criteria, color flow Doppler ultrasonography (CDUS) can be used as a noninvasive, easy-to-use, and cost-effective imaging modality for diagnosis and follow-up. CDUS reveals sonographic features of the arterial wall and lumen and blood flow characteristics of the temporal artery along with its frontal and parietal branches [2].

The ability of high-resolution imaging makes the US the first-choice imaging tool in temporal artery vasculitis. Indications of US in temporal artery vasculitis include signs or symptoms of temporal arteritis (headaches, vision loss, jaw pain, fever, fatigue, and weakness), abnormal laboratory values suggesting vasculitis (e.g., increased erythrocyte sedimentation rate, liver function tests, Immunoglobulin G, complement levels), prior history of vasculitis, polymyalgia rheumatica or other rheumatologic conditions, and abnormal findings on previous imaging studies [3].

US Technique

A linear array US transducer with at least 15 MHz frequency should be used to obtain high-resolution images [4]. Scanning should be started with the gray-scale US and followed by color Doppler mode. Temporal artery Doppler US can be performed as patients lying on their lateral side or back in a recumbent or semirecumbent position [3]. CDUS examination of the temporal artery and its branches is usually started in the transverse plane. After scanning the temporal artery in the transverse plane, the probe can be rotated by 90º to obtain US images of the temporal artery in the longitudinal plane. The operators may find the first part of the temporal artery at the level of the tragus. The temporal artery and its frontal and parietal branches should be examined bilaterally as much as possible as in their entirety in transverse and longitudinal planes [5]. Proximal, mid-and distal parts of the temporal artery and its branches should be scanned in the transverse and longitudinal plane, and the findings related to each segment should be documented. The bifurcation level between frontal and parietal branches of the temporal artery is the marker point to define the proximal part of these branches [3].

The color signal representing blood flow in the vessel lumen should be obtained from the vessel lumen. Appropriate CDUS settings such as color gain and pulse repetition frequency (PRF) adjustments can avoid scattering artifacts outside the vessel wall. The PRF of color Doppler US should range between 2-3.5 kHz depending on the vessel caliber to

overcome the artifacts causing false-positive halo sign [4]. Power Doppler may be preferred in deep or tortuous vessels or cases with very low blood flow or occlusion [3]. In CDUS, at least one duplex spectral Doppler waveform should be obtained in the temporal artery along with its frontal and parietal branches.

CDUS of the temporal artery and its branches should include transducer compression to evaluate the compressibility of the vessels. To assess the compression sign, the operator should hold the transducer perpendicular to the vessel in the transverse plane and compress the temporal artery and its branches.

US operators should perform 30-50 temporal artery CDUS examinations in 30–50 people without GCA to be familiar with the normal appearance of the temporal artery [2].

US Findings

a. Halo sign

A halo sign is characterized by a rim of uniform hypoechogenicity surrounding a segment of the temporal artery and/or its branches. It represents concentric wall thickening towards the luminal side. The hypoechoic or anechoic appearance of the halo sign results from cell infiltration and edema occurring in the media layer of the vessel [5]. If a halo sign is detected in the transverse plane, the presence of a halo should also be confirmed on a longitudinal plane to determine the maximum thickness of the halo. Positivity for the halo sign is assumed to be consistent with active inflammation maximum thickness of the hypoechoic halo is defined as the measurement of intima-media layer thickness (IMT). The cut-off values of IMT to decide GCA involvement of the temporal artery and its frontal and parietal branches were reported as 0.42 mm, 0.34 mm, and 0.29 mm, respectively [5]. However, recent reports suggest that an IMT between 0.2 and 0.6 mm can be detected in normal temporal arteries. They also indicate that vascular wall swelling greater than 0.5-0.8 mm is usually associated with a positive temporal artery biopsy result [5]. The sensitivity and specificity of unilateral halo signs were reported as 68% and 91%, respectively. The specificity of the bilateral halo sign reaches 100% [6].

The operators should be aware that atherosclerotic changes and tortuosity of the vessels may cause interpretation errors in CDUS. Concentric wall thickening in GCA differs from the focal hyperechoic wall thickening in atherosclerosis. Vessel curves in temporal arteries with tortuose appearance may be wrongly interpreted as halo signs due to overlapping vessel walls in transverse and longitudinal planes [3].

b. Compression sign

Compression sign refers to the compression of the temporal artery and its branches by inserting pressure with the transducer. The tiny wall of the normal temporal artery should not be visualized as a separate anatomic structure with compression. The superficial vessels can not be compressed, and luminal narrowing does not occur in the setting of inflammatory cell infiltration. The operators should compress the temporal artery and its branches when detecting the halo sign. Halo sign does not disappear upon compression in patients with GCA [3]. The compression of the temporal artery and its branches may be recorded as cine-loop images to review after the scanning.

c. Luminal stenosis

GCA may appear as luminal narrowing of the temporal artery on transverse and longitudinal planes. Areas of stenosis in GCA may be detected with CDUS as an aliasing artifact secondary to the turbulent flow of the narrowed lumen. Chronic inflammatory changes and segmental stenosis may be manifested with a tortuous appearance. Once luminal narrowing/irregularity is identified, spectral Doppler waveform should be obtained to measure peak velocity before, at, and beyond the area of maximum stenosis [7]. Hemodynamically significant stenosis in the temporal artery presents on spectral Doppler US as two or more times higher flow velocity in the stenotic segment compared with the proximal or distal sides of the stenosis and persistent diastolic flow in the distal segments of the stenosis [8].

Acute temporal artery occlusion is demonstrated on the gray-scale US as an anechoic or hypoechoic appearance of the lumen without flow findings. Chronic occlusion appears as severe luminal narrowing and hyperechoic luminal appearance. Differentiating occlusion and pre-occlusive stenosis

may be accomplished using low PRF values and high color gain settings. The absence of blood flow in the temporal artery in these CDUS settings indicates an occlusion [9].

Utility of US Findings

The sensitivity and specificity of CDUS differ in various studies. However, recent studies report higher sensitivity and specificity values as a possible indication of improvement in the acquisition of high-resolution images and increased experience of operators. A recent report comparing US findings with the final clinical diagnosis noted that the US could diagnose with 91.6% sensitivity and 95.8% specificity [10]. Most studies revealed that the US is more sensitive than temporal artery biopsy since biopsy evaluates only a small anatomical region in a systemic disease while the US enables to visualize whole temporal artery and its branches [5].

US Assessment in Follow-up

Assessment with the US at the early phase may be necessary to evaluate GCA before treatment. CDUS should also be performed immediately in patients with suspected GCA and ophthalmic artery involvement to reduce the visual loss [9]. The sensitivity of US may be decreased in patients under steroid treatment due to the disappearance of findings as halo sign [11]. A recent report found that the halo sign may disappear after only two days of treatment [11]. US findings of GCA in temporal artery following the beginning of medical treatment may resolve after 16-22 days of the treatment [12]. The sensitivity of CDUS was reported as 88% within the first day of treatment, reduced to 50 % after more than four days of treatment [13]. Resolution of halo finding was found to occur in a long period, such as 11 weeks which was attributed to intimal proliferation with fibrosis that is often histologically reported as healed arteritis [14].

CONCLUSION

CDUS should be used as first-line diagnostic imaging for patients with suspected GCA. Characteristic findings of GCA are helpful in the diagnosis and follow-up of the disease after treatment. A fast-track US evaluation provides timely diagnosis and treatment initiation in suspected cases and prevents permanent vision loss.

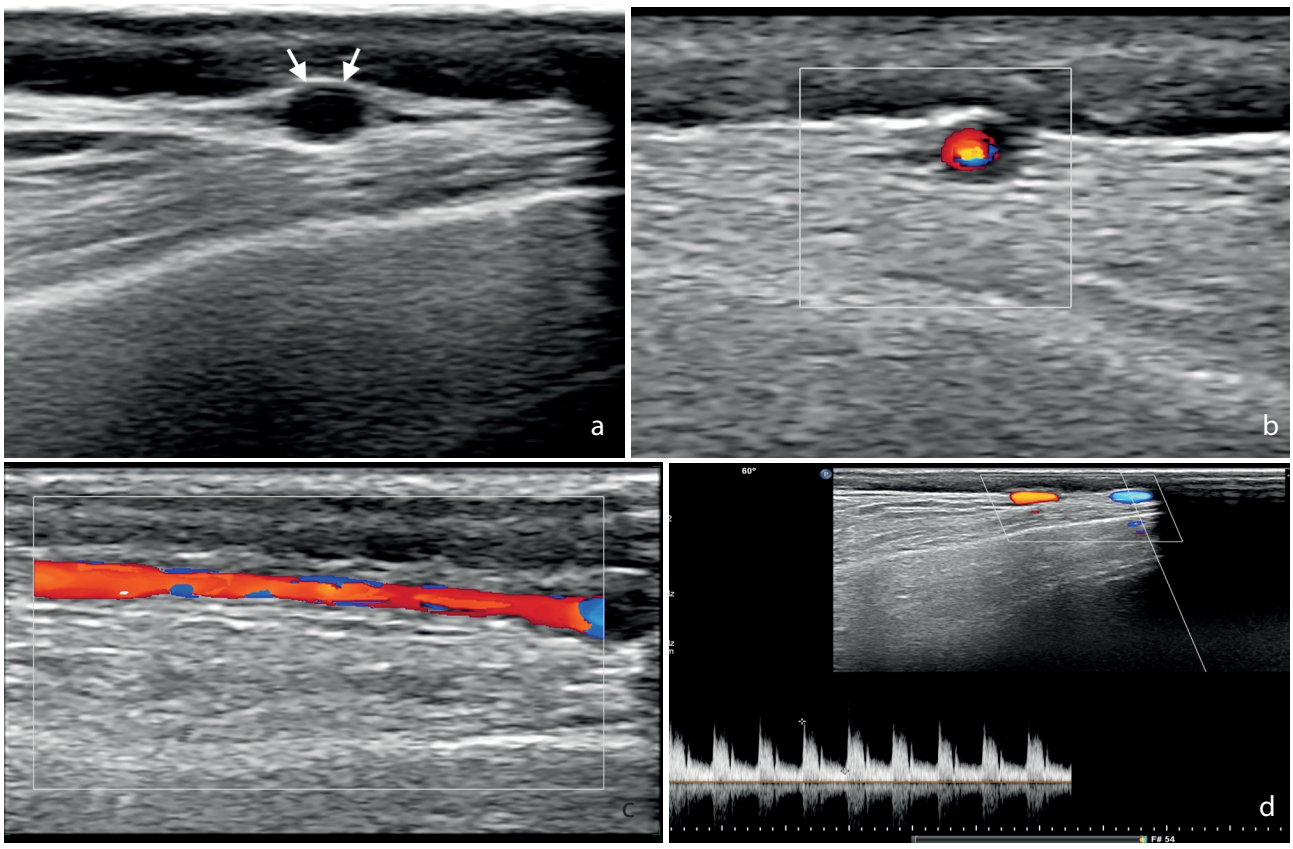

Figure 1. Gray-scale US image at the transverse view **(a)** demonstrates STA with a normal vessel wall appearance. CDUS images at transverse **(b)** and longitudinal **(c)** views reveal color filling in the STA lumen.

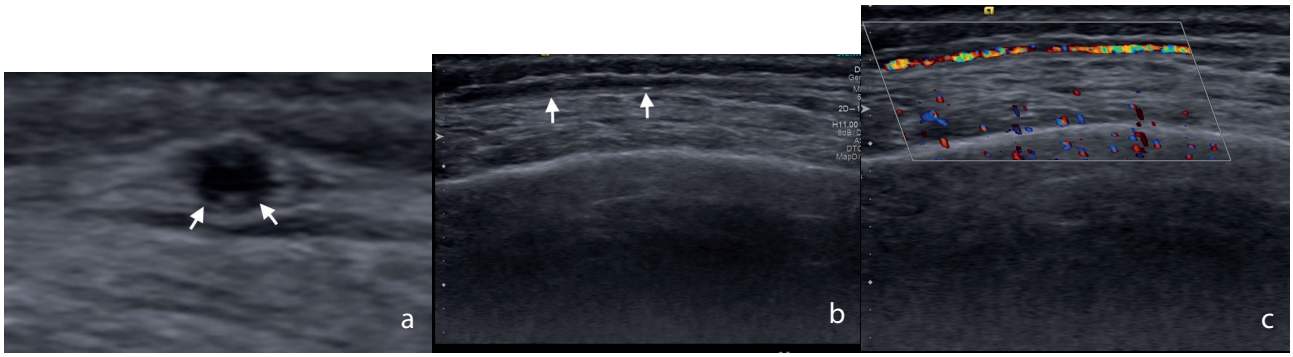

Figure 2. (a) Transverse view of gray-scale US image demonstrates halo sign which is concentric wall thickening of the temporal artery with hypoechoic appearance (arrows). **(b)** A longitudinal view of the gray-scale US image reveals wall thickening and luminal narrowing (arrows) in the temporal artery. **(c)** Color flow Doppler US shows an aliasing artifact representing the temporal artery's turbulent flow.

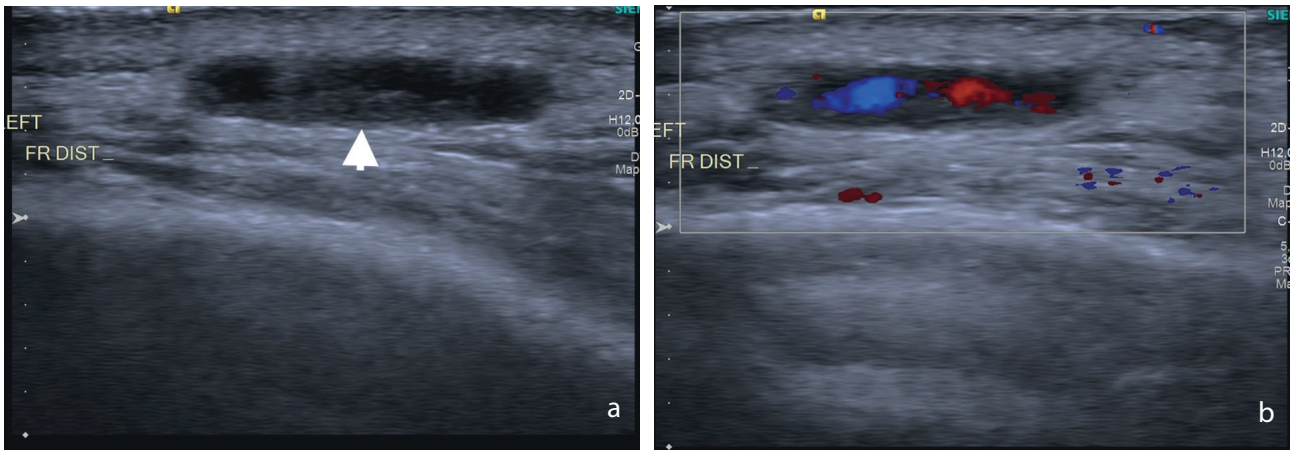

Figure 3. (a) Gray-scale US demonstrates a hypoechoic atheroma plaque (arrow) with an eccentric luminal narrowing in the temporal artery. **(b)** Color flow Doppler US reveals a filling defect in the temporal artery due to atheroma plaque.

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INVITED REVIEW

Doppler Ultrasonography of Axillary and Subclavian Artery in Giant Cell Arteritis

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Giant cell arteritis (GCA) is a systemic vasculitis characterized by immune-mediated inflammation of the large arteries [1]. GCA usually affects the aorta and/or its major branches and often involves the temporal artery [2]. The gold standard for the diagnosis of GCA is temporal artery biopsy which is an invasive procedure with limited sensitivity [3,4]. Ultrasound (US) with color Doppler US is the preferred first-step imaging modality in patients with suspected GCA because of its low cost, accessibility, and safety. The main US and color Doppler US findings in patients with GCA are thicker vessel walls with decreased lumen caliper and velocity changes in the affected vessel [5]. Schmidt et al. also defined a concentric "halo" sign in all patients with suspected GCA, which disappears two weeks after glucocorticoid therapy [5].

A normal intima-media complex (IMC) should have a hypo-anechoic homogeneous appearance limited by two linear parallel echogenicities on US examination called "double line pattern." A typical vessel should be compressible with pressure (Figure 1). The inflammation in GCA generally starts in media and progresses to intima and adventitia, which causes US findings that are defined for GCA [6]. The early finding; the "halo" sign is the concentric hypoechoic thickening in the vessel wall. The suggested upper limit for IMC thickness for the axillary artery is 0.6 mm with 1.5-2 mm in GCA [7]. The inflammation in the vessel wall also causes non-compressible arteries [6]. Stenosis and occlusions generally occur in the setting of critical vessel wall inflammation that can be diagnosed as increased peak systolic velocities and absence of color-coding with color Doppler US, respectively [6]. Halo sign is generally seen in the acute phase. Loss of double line pattern with concentric wall thickening and findings such as stenosis, occlusion, and collateral vessels are usually seen in the chronic phase [10].

It is shown that the axillary artery should also be included in the US evaluation as the temporal artery may not be involved in some GCA cases [8,9]. Both arteries should be evaluated in routine GCA examination, and other large arteries should also be assessed in the setting of insufficient findings [6]. Supra-aortic vessels such as subclavian arteries, carotid arteries, and vertebral arteries may be evaluated with US and color Doppler US. The term large-vessel GCA (LV-GCA) is used in extra-cranial involvement [11] (Figure 2). The aortic arch and proximal third of the left subclavian arteries can be evaluated with low-frequency probes due to the deep location that causes lower resolution. However, the right subclavian artery, middle and distal part of the left subclavian artery can be examined with high-frequency probes, as well as the axillary artery, carotid artery, and vertebral arteries.

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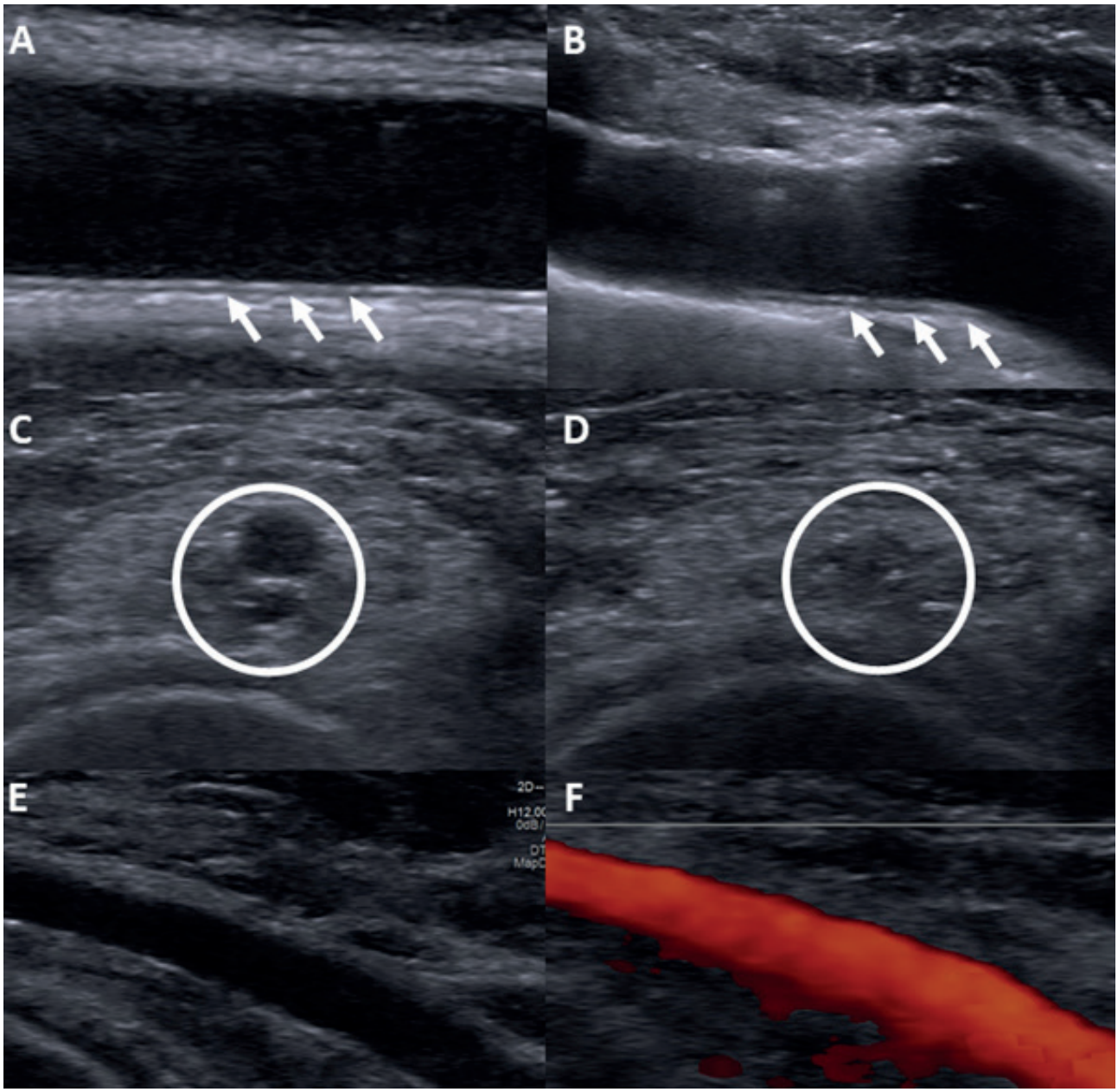

Figure 1. US and color Doppler US images of a 47-year-old female patient with normal findings. US images demonstrate normal intima-media thickness of the right carotid artery (A) and the right subclavian artery (B) with a "double line pattern" (arrows). Normal compressibility of the right axillary artery is demonstrated in the axial US images; before (C) and after compression (D). US (E) and color Doppler US (F) of the right axillary artery are demonstrated in the longitudinal US images.

In the follow-up evaluation, regression of the halo sign is defined mainly for temporal arteries after glucocorticoid therapy [12,13]. Aschwanden et al. evaluated LV-GCA and observed that regression of wall thickening is less common than in the temporal artery in LV, irrespective of clinical remission [14]. Sebastian et al. also demonstrated a stable axillary artery halo score after tocilizumab therapy in contrast with a significant decrease in median temporal artery halo score [15]. Seitz et al. evaluated IMT in temporal arteries, axillar arteries, and subclavian arteries and observed that glucocorticoid pulse therapy resulted in a transient decrease in all arteries IMT [16]. However, tocilizumab monotherapy resulted in a slower and steady decrease in just temporal arteries IMT [16].

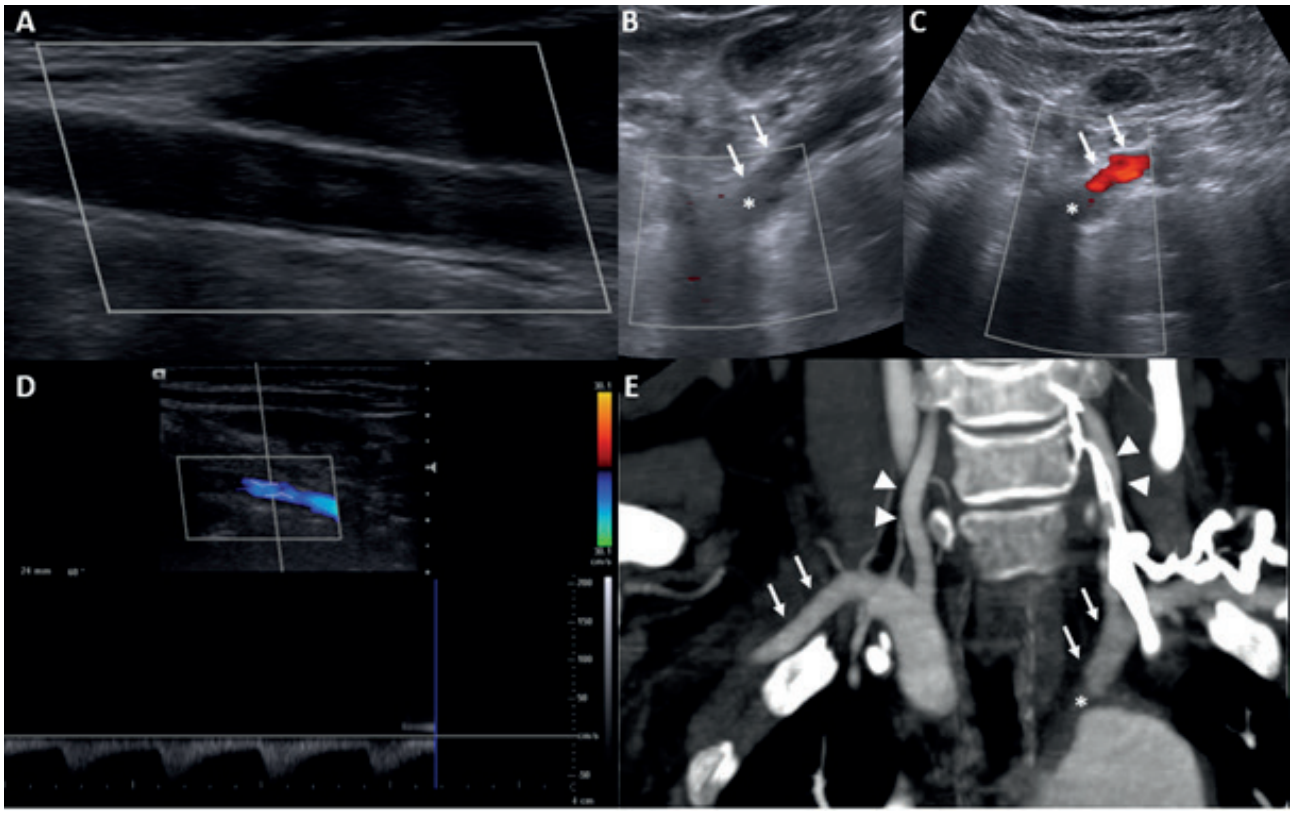

Figure 2. US and color Doppler US images of a 48-year-old female patient with known large vessel vasculitis. Color Doppler US demonstrates left main carotid artery occlusion (A) with left subclavian artery origin occlusion (B). In the proximal part of the left subclavian artery (arrows), the color Doppler US demonstrates the blood flow. Completely retrograde flow is observed in the left vertebral artery on color Doppler US (D), confirming subclavian steal syndrome. Please also note lower iodine concentration in the left subclavian artery (arrows) and vertebral artery (arrowheads) in contrast with the right ones in the coronal MPR computed tomography image (E). The left subclavian artery origin occlusion is also evident (*)

In conclusion, US and color Doppler US should be used as a first-step imaging modality in patients with GCA. The findings in GCA are halo sign, non-compressibility, stenosis, and occlusion in the involved vessel. The axillary artery should also be included in the routine US evaluation, as well as temporal arteries. The physician should be aware of US and follow-up imaging characteristics in specific vessels in GCA.

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INVITED REVIEW

CT and MR Angiography of Aorta and Aortic Branches in Giant Cell Arteritis

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Giant cell arteritis (GCA) is a granulomatous systemic vasculitis of large and medium-sized arteries predominantly affecting patients older than 50 years [1]. The external cranial arteries, such as the temporal artery, are commonly involved in GCA (cranial GCA). However, with the advances in imaging technology and more widespread use of cross-sectional imaging, frequent involvement of the aorta and its branches were also seen and referred to as extracranial large-vessel GCA (LV-GCA) [2,3].

While temporal artery ultrasound (US) and biopsy are commonly used as diagnostic methods, GCA may present without temporal artery involvement. Schmidt et al. reported negative US and histology findings of temporal arteries in 38% and 33% of LV-GCA patients, respectively, [4]. Also, in extracranial LV-GCA, the clinical presentation is often more subtle than temporal arteritis, ranging from non-specific constitutional symptoms to extremity claudication depending on the affected vessels [3,5]. Based on these, imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), and 18F-fluorodeoxyglucose positron-emission tomography/computed tomography (FDG-PET/CT) have been increasingly used in the diagnosis of LV-GCA.

Using imaging, aortic involvement is reported in 45-65% of GCA patients, and the most commonly affected part of the aorta is the thoracic aorta (aortic arch and descending aorta) [6,7]. If abdominal aorta involvement is present, the thoracic aorta is also usually affected. Apart from the aorta, the supra-aortic branches- particularly subclavian and axillary arteries- are frequently involved. Carotid and vertebral artery involvement may be less often observed. Less commonly, visceral branches of the abdominal aorta and iliofemoral arteries may be affected [5,7–9].

To standardize imaging in large vessel vasculitis, European League against Rheumatism (EULAR) published some recommendations in 2018. According to these, early imaging before the treatment or as soon as possible after the therapy initiation is recommended to support the clinical and laboratory criteria in suspected GCA cases [3]. Because therapy with glucocorticoids reduces the sensitivity of the imaging [10], if there is a high clinical probability, the diagnosis of GCA can be made with positive imaging findings, eliminating the need for further investigations such as temporal artery biopsy. While in cranial GCA, first-line imaging should be temporal and axillary artery Doppler ultrasound, in extracranial LV-GCA, ultrasound, CT, MRI, or FDG-PET/CT is recommended to support the diagnosis. Conventional angiography is no longer recommended for diagnosis, considering significant disadvantages such as invasiveness, procedural risks, and the disability to show the vessel wall changes [3]. On the other hand, CT and MR angiography allows the evaluation of the aorta and its branches in a larger area in a single acquisition and the simultaneous assessment of the vessel wall and lumen.

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Therefore, the use of CT and MR angiography gained importance to address the involvement of the aorta and its main branches for diagnosis and disease monitoring in LV-GCA. Moreover, since GCA is seen in the elderly, findings of atherosclerosis such as wall thickening may interfere with imaging findings of large vessel vasculitis [11]. This review aims to describe CT and MR angiography findings of the aorta and its main branches' involvement in LV-GCA and focus on differentiating LV-GCA from atherosclerosis by imaging findings.

CT angiography in LV-GCA

CT angiography (CTA) is widely used in diagnosing large vessel vasculitis with a shorter acquisition time and superior spatial resolution. Multislice CT should obtain CTA with thin slices reconstructed with a thickness of 0.5-1 mm [12]. Besides the arterial phase, venous phase imaging should be performed to assess wall enhancement. The major disadvantage of CT is ionizing radiation exposure. Although the ongoing advances in radiation reduction algorithms partly overcome this, it is still a significant consideration in repetitive imaging during the follow-up [3,13,14].

The main imaging findings of LV-GCA are circumferential wall thickening and vessel wall enhancement depicted in the delayed/venous phase. Berthod et al. reported a wall thickness threshold of 2.2 mm, presenting the best sensitivity and specificity combination for GCA [15]. The wall enhancement on the venous phase exhibits a "double-ring" appearance characterized by a hypodense inner ring representing edematous intima surrounded by the hyperdense enhancing outer ring (Figure 1). Also, stenosis, occlusion, dilatation, and aneurysms may be observed in affected vessels [7,13,16,17] (Figure 2).

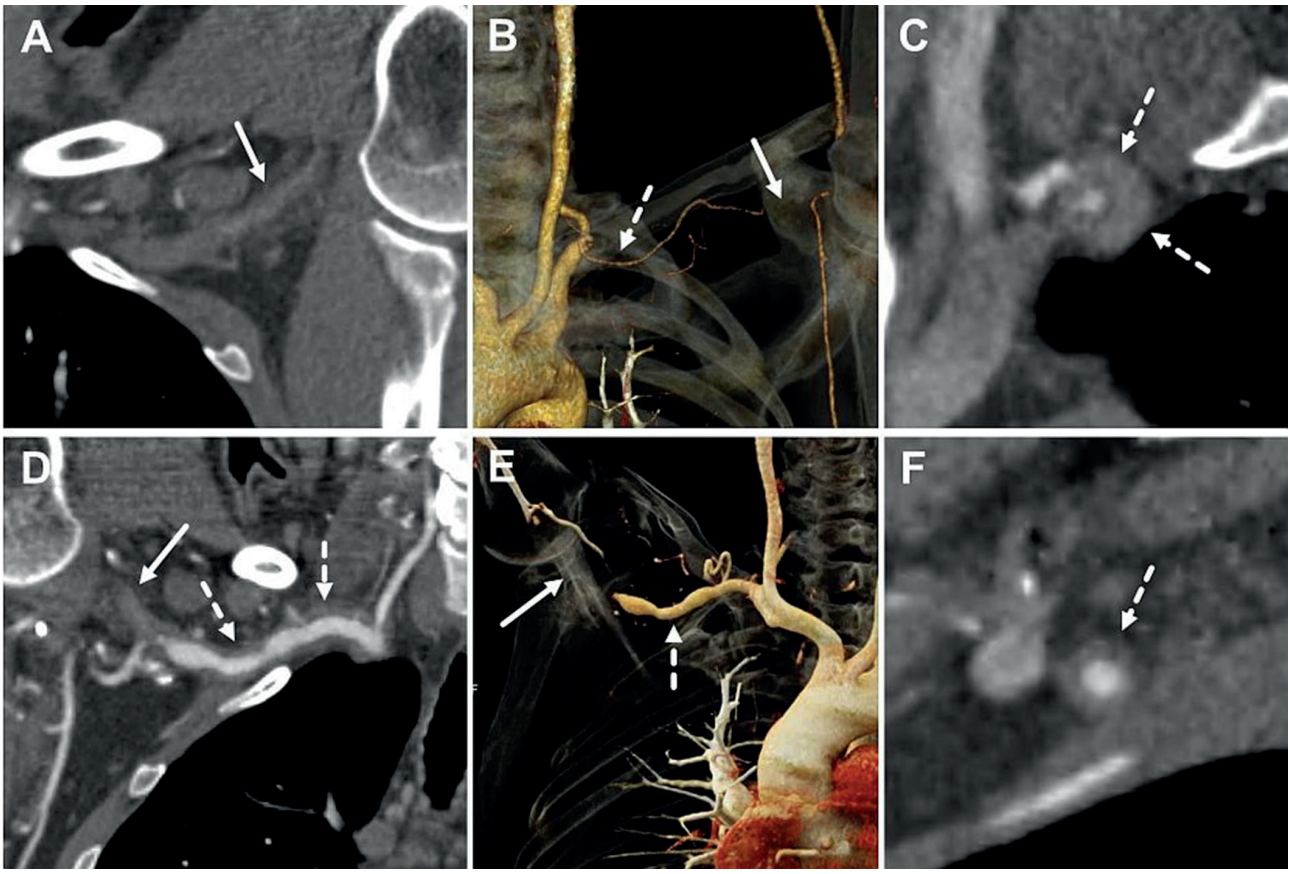

Figure 1. CT angiography images of a 65-year-old male patient with left upper extremity claudication. Coronal MPR (multiplanar reformat) image shows left axillary artery occlusion (arrow) (A), which is better delineated in the coronal VRT (volume-rendered technique) image (arrow)(B). Also, long segment severe stenosis of the left subclavian artery is seen (dashed arrow)(B). Circumferential wall thickening with a "double-ring" sign causing severe stenosis in the left subclavian artery is shown (dashed arrows)(C). Coronal MPR image (D) and cinematic VRT image (E) demonstrate wall irregularities, focal ectatic areas, and concentric wall thickening of the right subclavian artery (dashed arrows). Also, note that the right axillary artery is occluded (arrow). Circumferential wall thickening of the right subclavian artery is observed (dashed arrow)(F).

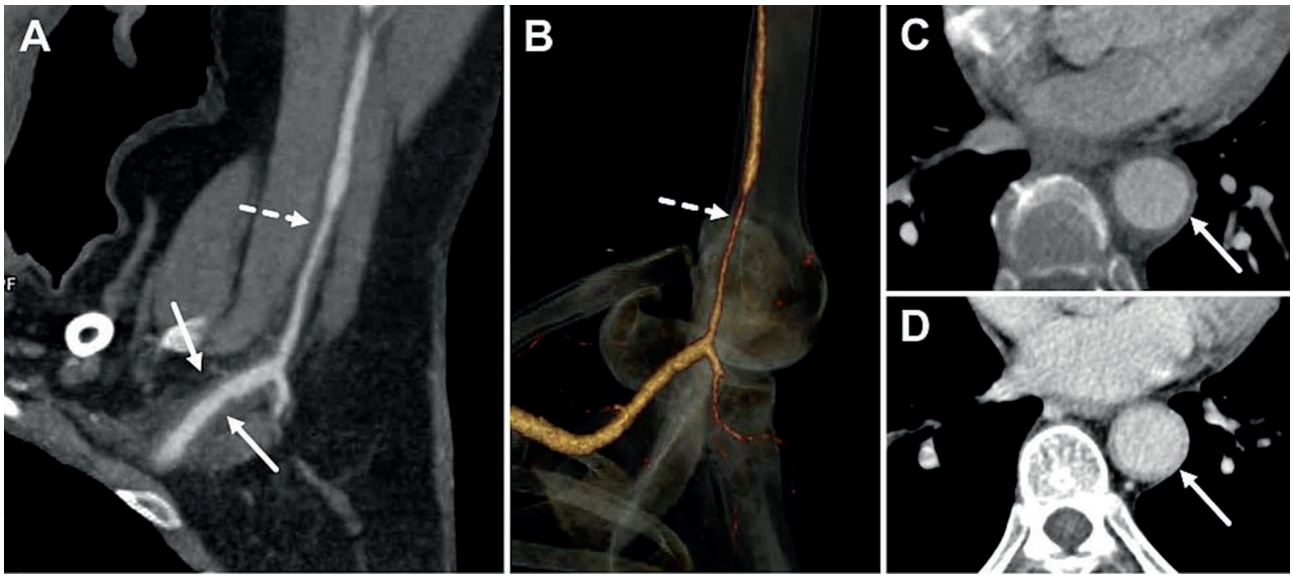

Figure 2. CT angiography of a 67-year-old female patient with temporal arteritis. Coronal MPR (A) image shows concentric wall thickening of left axillary artery (arrows). Also, concentric wall thickening causing severe stenosis in the proximal brachial artery is seen in coronal MPR (A) and VRT (B) images (dashed arrow). Axial arterial phase CT image demonstrates wall thickening of the thoracic aorta (arrow, C) and wall enhancement in venous phase image (arrow, D).

Aortic dilatation- mainly in the thoracic aorta- is reported in nearly 15% of GCA patients at the time of diagnosis [7].

Lariviere et al. compared CTA and FGD-PET/CT for the diagnosis of GCA and reported sensitivity rates of 73% and 66.7%, respectively. Although sensitivity rates were similar, CTA had a lower specificity (84.6%) compared to the uptake on FDG-PET/CT (100%) [17]. In De Boysson et al.'s study, CTA has a sensitivity of 95% and a specificity of 100% in a per-patient analysis when FDG-PET/CT is accepted as a reference [18]. In both studies, FDG-PET/CT had a higher performance in per-segment analysis, especially for the aorta branches [17,18].

MR angiography in LV-GCA

MR angiography (MRA) is increasingly preferred in diagnosing and following large-vessel vasculitis due to the lack of ionizing radiation. MRA should be obtained covering the entire area between carotid bifurcations and iliac arteries, including axillary and brachial arteries [3]. Multiplanar dark blood (HASTE) and bright blood (single shot true-FISP) images can be acquired for the morphological assessment of vessel walls. Also, short-tau inversion-recovery (STIR) and T2 weighted fast spin-echo images allow the identification of vessel wall edema without using contrast material. After administering gadolinium-based contrast agents, three-dimensional (3D), MR angiography for the detection of luminal changes and post-contrast T1 weighted imaging for the assessment of wall enhancement should be performed [13,14,19].

MRA has a reported sensitivity of 79% and specificity of 96% for the GCA diagnosis [20]. Similar to CTA, imaging findings of LV-GCA are concentric wall thickening, wall edema, wall enhancement, and luminal changes such as stenosis, occlusion, and aneurysms [21,22](Figure 3). Although the wall edema on T2-weighted sequences has been attributed to disease activity, there are controversial observations in the literature stating the persistency of edema despite clinical remission [22–24]. Also, EULAR said that T2-weighted imaging for edema is more prone to artifacts and, therefore, less sensitive [3].

MRA has disadvantages such as longer acquisition time and lower spatial resolution compared to CTA. Also, patient cooperation, examination protocol, and operator dependence affect the examination's quality [25].

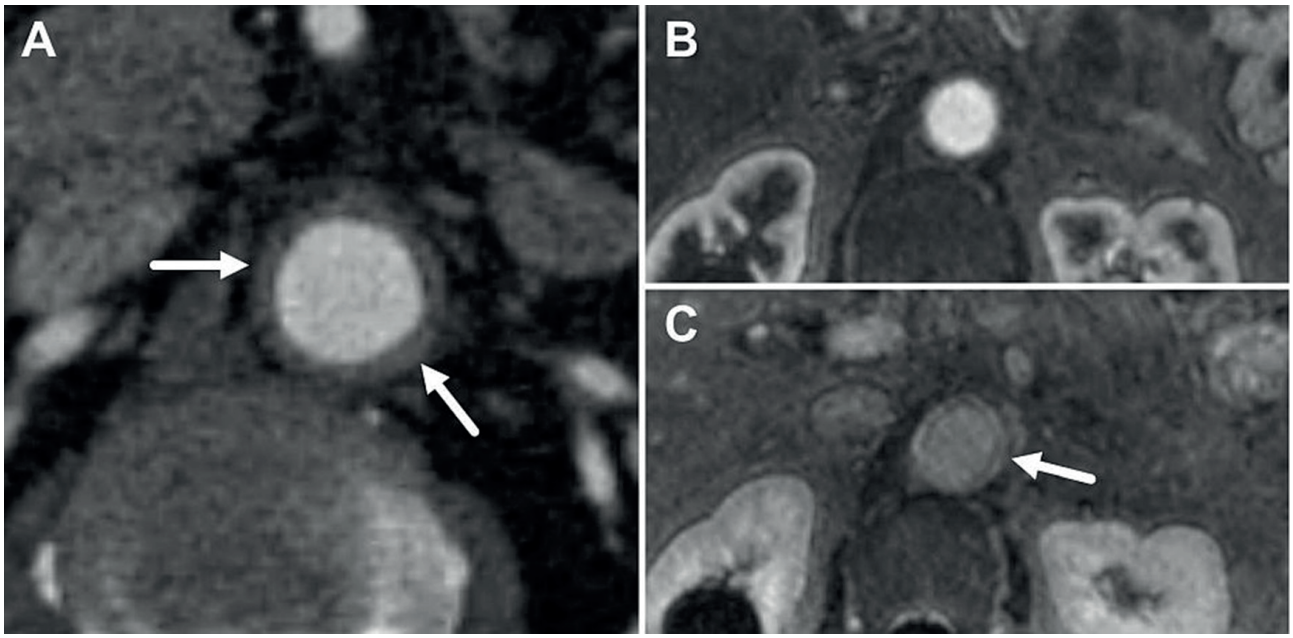

Figure 3. CT and MR angiography images of the same patient as in Figure 1. Axial CT image in the arterial phase shows circumferential wall thickening of the abdominal aorta (arrows). The thickened abdominal aorta wall demonstrates enhancement in the delayed phase MRA image (arrow, C), which is better depicted when compared to the arterial phase image (B).

Differentiation of LV-GCA from atherosclerosis based on imaging

Since GCA typically affects the elderly, atherosclerosis is an important differential diagnosis that should be considered in this patient group. Moreover, atherosclerosis may accompany LV-GCA, and imaging findings may be confusing.

Vessel wall changes are also observed in atherosclerosis, mainly affecting intima. In contrast to circumferential and rather long segment wall thickening of GCA, atherosclerosis mainly presents with focal/patchy, eccentric wall thickening resulting in plaque formations [8,11]. Vessel wall calcifications on CTA are commonly associated with atherosclerosis. Still, calcifications do not rule out vasculitis as they may also occur in large-vessel vasculitis in the long-term [26] (Figure 4).

The affected vascular structures may aid in differentiating atherosclerosis from LV-GCA. LV-GCA most commonly affects the supra-aortic branches of the aorta, such as the axillary - subclavian artery and thoracic segment of the aorta. In contrast, atherosclerosis favors carotid arteries at the supra-aortic level, abdominal aorta, and iliofemoral arteries [27]. Contrast enhancement in the vessel wall is generally not expected in atherosclerotic lesions. However, as atherosclerosis is also an inflammatory condition, contrast enhancement, and FDG uptake may be observed in inflamed plaques [11,28,29].

Follow-up imaging in LV-GCA

According to EULAR recommendations, imaging can monitor long-term results and complications of GCA, such as vessel occlusions, stenoses, or aneurysm formation. There is no clear recommendation regarding which modality should be used in the follow-up process. As the modality selection depends on the availability and local expertise, the choice of imaging frequency and modality in follow-up should be decided on a patient basis. When a flare is suspected, imaging findings may help confirm disease activity. On the other hand, imaging is not recommended in the case of clinical and biochemical remission [3]. Although the wall enhancement mostly disappears after treatment, this may occur later than clinical

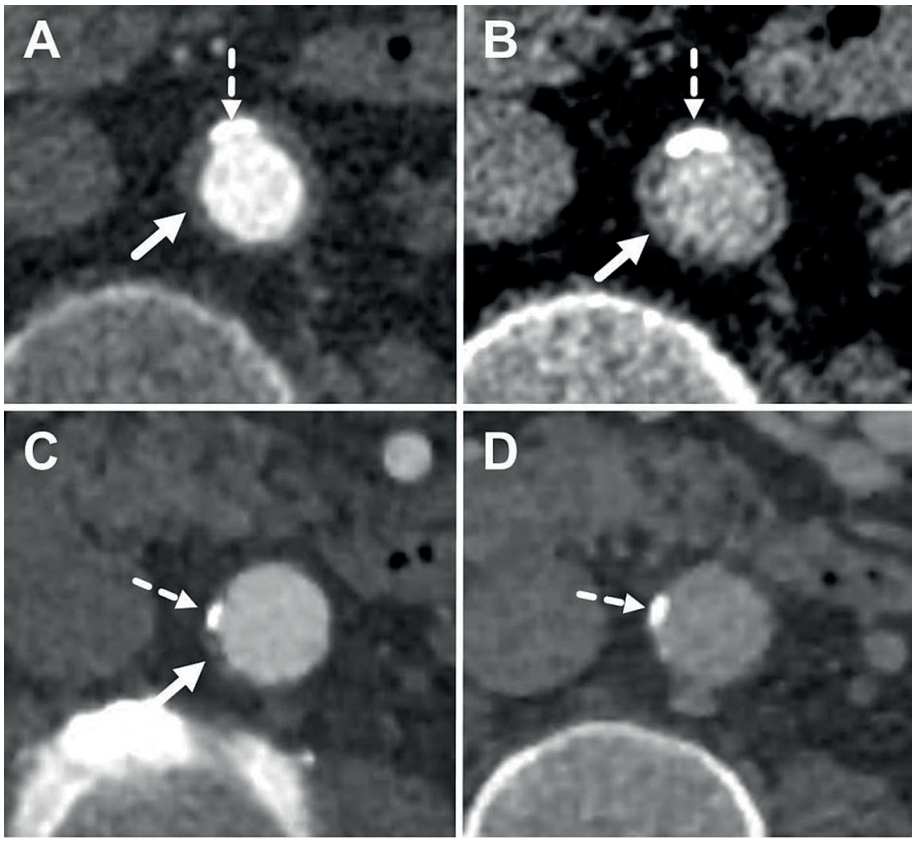

Figure 4. Differentiation of GCA from atherosclerosis. Axial arterial (A) and venous phase (B) CT images of a patient with GCA show concentric wall thickening of the abdominal aorta with contrast enhancement in the venous phase (arrows). Calcifications may also occur with large vessel vasculitis (dashed arrows, A-B). Axial arterial (C) and venous phase (D) CT images of a patient with atherosclerosis show eccentric wall thickening without enhancement in atherosclerosis, contrary to vasculitis (arrows). Plaque calcification is also seen (dashed arrows, C-D).

and biochemical remission. Also, even though the number of affected segments and wall thickness decreases, wall thickening may persist in two-thirds of LV-GCA patients [14,30].

Imaging in the follow-up period is vital in assessing potential complications of structural vessel damage. Increased incidence of aortic aneurysms predominantly in the thoracic aorta and aortic dissections were reported in GCA patients in the literature [31]. In Garcia- Martinez et al.'s study, aortic structural damage such as dilatation and aneurysm more commonly in thoracic aorta is observed in 22% of the patients after a median of 5.4 years regardless of clinical activity [32]. These patients were further monitored over a median follow-up for 10.3 years, and significant increases in aortic diameters were observed [33].

Conclusion

The role of CT and MR angiography in the diagnosis of extracranial large-vessel type GCA has gradually increased. By demonstrating the luminal and vessel wall changes of the aorta and aortic branches, imaging may provide important information to support the diagnosis in the presence of clinical suspicion and reveal possible complications in the follow-up. Although the imaging findings may overlap with atherosclerotic changes, type of wall thickening (concentric or eccentric), presence of calcifications or wall enhancement, and distribution of the affected vessels may aid in the differential diagnosis.

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INVITED REVIEW

FDG-PET/CT Imaging of Large Vessel Vasculitis

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ABSTRACT

Large vessel vasculitis (LVV) is a heterogeneous group of disorders characterized by inflammation of large and medium-sized blood vessels. When not properly diagnosed and treated, it may lead to severe morbidity due to ischemic events. ^{18}F-florodeoxyglucose (FDG) PET/CT can be helpful in the assessment of disease activity before treatment as well as monitor therapeutic effect or detect relapse of the disease. Proper preparation of the patients before FDG-PET scan and standart interpretation methods are crucial part of the evaluation. New technologies like whole body and digital PET or new PET radiotracers may further increase the clinical value of PET imaging.

INTRODUCTION

Large vessel vasculitis (LVV) is defined as inflammation of large arteries. It usually involves the internal and external carotid arteries, aorta, and its main branches more centrally in the thorax [1]. Takayasu arteritis (TA) and giant cell arteritis (GCA) are the two main forms of vasculitis. Although they share some common features, TA and GCA are different diseases with different ages of onset, ethnic distribution, immunogenic background, distribution, and therapy response. TA generally affects the aorta and its branches, but GCA affects cranial arteries[2] as well as the aorta. These vasculitides may also co-exist with other rheumatological diseases. GCA and polymyalgia rheumatica (PMR) often coexist in the same patient. PMR can be seen in half of the patients with GCA, while approximately 20% of patients with PMR have concomitant GCA [3]. These vasculitides have important outcomes that lead to severe morbidity and mortality, therefore, appropriate treatment is necessary [4]. Optimal vasculitis imaging is critical to solve clinical dilemmas and avoid disease-related complications. Imaging with ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) are routinely used to identify the source of inflammation. However, these modalities lack enough specificity and accuracy. Metabolic imaging of LVV with ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) combined with CT or MRI helps in the diagnosis and follow-up of inflammation [5]. It acts as a clinical problem-solving tool in the difficult scenarios of inflammation and is recommended by several organizations like the American College of Radiology [6-8].

In this paper, imaging of large vessel vasculitis is described in the following topics; FDG-PET imaging procedure, patient preparation, mechanism of action, imaging features and clinical value of FDG on disease course, and future aspects.

^{18}F-FDG Imaging

FDG is a positron-emitting radiotracer that behaves similarly to the human body's glucose. The radiotracer enters the cell via glucose transporters (GLUTs); it is phosphorylated and no longer metabolized [9,10]. Positron emission of trapped FDG in the cell enables PET imaging, thus leading to visualization of tissues' glucose metabolism [10]. Active inflammatory cells, especially macrophages, in inflamed arterial walls and synovia/bursa show increased glucose metabolism and FDG uptake [11].

Table 1. Patient preparation for FDG-PET/CT

Dietary preparation	Fast for at least six hours before FDG administration
Blood glucose levels	Preferably <126 mg/dL for non-diabetic and <200 mg/dL) for diabetic patients
Drugs	Glucocorticoids: Withdraw or delay therapy until after PET unless there is a risk of ischemic complications. FDG-PET within three days after the start of GC is optional as a possible alternative
PET acquisition	Patient positioning: Supine, arms next to the body Scan range: Whole body (Head down to the feet) Scan duration 3D: 2–3 min/bed position Dose of FDG injection: 3-5 MBq/kg body weight Incubation time after FDG injection: Standard 60 min PET/CT: Low-dose non-contrast CT for attenuation correction and anatomical reference.

FDG uptake of tissues is directly related to glucose metabolism and some patient characteristics also interfere with FDG uptake, so optimal patient preparation is crucial (Table 1). The optimal biodistribution of FDG depends on blood insulin and glucose levels. Patients must be fasting for at least 6 hours before FDG injection, and measured blood glucose levels should be <126 mg/dL for non-diabetic patients and <200 mg/dL for diabetic patients. In addition, strenuous physical activities should be avoided within 24 h before FDG administration to avoid muscle uptake. After administration of FDG, patients should relax in an adequately temperature-controlled room to minimize physiologic uptake in muscles and brown fat [11]. In some cases, FDG uptake in brown fat can be reduced by beta-blocking drugs, e.g., orally administered 20 mg propranolol one h before FDG injection.

Glucocorticoids (GC) may reduce vascular wall uptake of FDG; the available data regarding the effect of GC withdrawal on FDG uptake are scarce. Nielsen et al. recently confirmed that diagnostic accuracy of LVV with FDG-PET remained for three days after initiation of GC. After three days, a significant decrease in radiotracer uptake was detected. If active LVV is suspected, FDG-PET/CT should be performed before GCs are started in case of no ischemic complication risk or within the first three days of treatment [12].

Before PET scan, patients wait for 60-90 min. to get enough uptake and reduce the background blood pool activity after the injection. The patient must be well hydrated and void before scan.

The PET scan from vertex to feet takes around 15 to 20 minutes. At the same time, CT or MRI sections are also obtained. After the scan, no isolation for radiation protection is required [11,13-16].

For FDG-PET/CT imaging, a low-dose non-contrast CT must be performed for attenuation correction and anatomical localization. Alternatively, a diagnostic contrast-enhanced CT may be performed according to applicable local protocols and guidelines. If intravenous contrast is going to be used, renal function tests must be checked to avoid toxicity.

Special imaging techniques could be performed to increase the accuracy of FDG-PET. The detection of smaller vascular structures in the head and neck region can be improved by increasing the acquisition time and matrix size per bed position [17].

Imaging inflammation

The pathophysiology of inflammation is quite complex. In theory, there are many molecular pathways to target for imaging. At inflammatory focus, inflammatory cells like macrophages, neutrophils, and monocytes upregulate in their GLUT transporters, thus showing increased glucose metabolism. FDG-PET can non-invasively detect this increased population of inflammatory cells with increased glucose metabolism [6,7,9,10].

FDG-PET has been used for several etiologies of inflammation. Infective endocarditis, IgG4 related disease, osteomyelitis, and large vessel vasculitis are major indications of FDG-PET. Two forms of large vessel vasculitis, TA and GCA, can be imaged by FDG-PET scan [7,8,11,18-20].

Large Vessel Vasculitis and ^{18}F-FDG PET/CT

TA and GCA generally affect medium-large vessels like the aorta and its branches, referred to as large

Table 2. Main findings of available meta-analyses on the diagnostic accuracy of FDG-PET in patients with large-vessel vasculitis

LVV	Publication	Studies included	Number of patients	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive likelihood ratio	Negative likelihood ratio	AUC
GCA	Lee et al. [24] 2016	3	66	83.3 (72–91)	89.6(80–96)	7.10(2.91–17.36)	0.2(0.11–0.34)	0.88
	Soussan et al. [23] 2015	4	57	90 (79–96)	98(94–99)	28.7(11.5–71.6)	0.15(0.07–0.29)	0.98
	Besson et al. [46] 2011	6	101	80 (63–91)	89(78–94)	6.73(3.55–12.77)	0.25(0.13–0.46)	0.84
TA	Soussan et al. [23] 2015	7	191	87 (78–93)	73(63–81)	4.2(1.5–12)	0.2(0.1–0.5)	0.91
	Cheng et al. [25] 2013	6	76	70.1(58.6–80)	77.2(64.2–87.3)	2.31(1.11–4.83)	0.34(0.14–0.82)	0.805
LVV	Lee et al. [24] 2016	8	170	75.9(68.7–82.1)	93(88.9–96)	7.27(3.71–14.24)	0.3(0.23–0.4)	0.86

vessel vasculitis [2]. On conventional imaging with MRI or contrast-enhanced computed tomography (CECT), thickening of the vessel wall or aneurism formation can be seen [21]. Anatomic imaging can not give adequate functional data about disease activity [8]. Molecular and functional imaging helps in these clinical situations. One of the recent meta-analyses showed FDG-PET/CT has a sensitivity and specificity of 88% (95% CI: 79–93) and 81% (95% CI: 64–91)[22] (Table 2). The diagnostic performance of FDG-PET was higher for the detection of GCA than TA (87% vs. 58%, respectively; $p < 0.0001$)[23,24] Similarly, in a meta-analysis of four pooled studies, for the diagnosis of patients with GCA, FDG-PET demonstrated high pooled sensitivity (90%) and specificity (98%), without significant heterogeneity [23].

In TA, FDG-PET demonstrated pooled sensitivity of 87% and specificity of 73% for the assessment of disease activity in a recent meta-analysis of seven studies including 191 patients with TA, with significant heterogeneity [23]. These findings are in line with a previous meta-analysis including TA patients evaluated by FDG-PET, showing pooled sensitivity and specificity of 70% and 77%, respectively [25]. The specificity of FDG-PET increased to 84% when considering studies using National Institutes of Health (NIH) criteria [26] as the disease activity assessment scale [23]. Visual analysis showed that high FDG uptake correlated well with the presence of markers of disease activity in TA, but vascular uptake was observed in up to 67% of TA patients without markers of activity [23]. Another meta-analysis showed FDG performance is related to serum acute phase reactants (APR) like C-reactive protein and also FDG uptake is an independent biomarker [27,28]. However the sensitivity and accuracy of the FDG-PET are impaired in patients under GC and/or immunosuppressive treatment at the time of imaging [23].

Imaging Features of LVV

A standardized evaluation and a common language between disciplines were created for the interpretation of FDG-PET images. These are qualitative and semiquantitative, but a combination of them by nuclear medicine physicians makes interpretation more accurate (Table 3). Slart et al. proposed using 0-to-3 grading system as follows "0 = no uptake (≤ mediastinum); 1 = low-grade uptake (< liver); 2 = intermediate-grade uptake (= liver), 3 = high-grade uptake (> liver), with grade 2 possibly indicative and grade 3 considered positive for active LVV" [29].

Also, a total vascular score can be calculated from seven different locations: thoracic aorta, abdominal aorta, subclavian arteries, axillary arteries, carotid arteries, iliac arteries, and femoral arteries. Scoring of these regions from 0-to-3 is: 0 for negative, 1(mild), 2 (moderate), and 3 (high) for positive (see Figure 1-2) [29]. Additionally several semiquantitative methods have also been proposed, from simple standard uptake value (SUV) metrics to target-to-background ratios (TBR) (Table 3). The clinical utility of SUV or TBR for the initial diagnosis of LVVor PMR is currently unvalidated and not routinely recommended. However, their relevance for recurrence or follow-up evaluation may be a matter of further research [30].

Table 3. Recommended PET interpretation criteria

For clinical use	Grade 0: No vascular uptake (≤ mediastinum) Grade 1: Vascular uptake < liver uptake Grade 2: Vascular uptake = liver uptake, may be PET-positive Grade 3: Vascular uptake > liver uptake, considered PET-positive
PET semiquantitative analysis*	Target: Average SUVmax artery of the vascular ROIs Blood pool: Average SUVmean of several vein ROIs TBR = average SUVmax artery / average SUVmean vein Liver: SUVmax of a liver region, preferably the right lobe TBR = average SUVmax artery / SUVmax of a liver region
Vascular targets:	- Carotid arteries - Subclavian arteries - Axillary arteries - Vertebral arteries - Ascending aorta - Aortic arch - Pulmonary arteries - Descending aorta - Abdominal aorta
Joints:	Scapulae and pelvic girdles, knees, cervical and lumbar interspinous bursae, trochanteric and ischial bursae

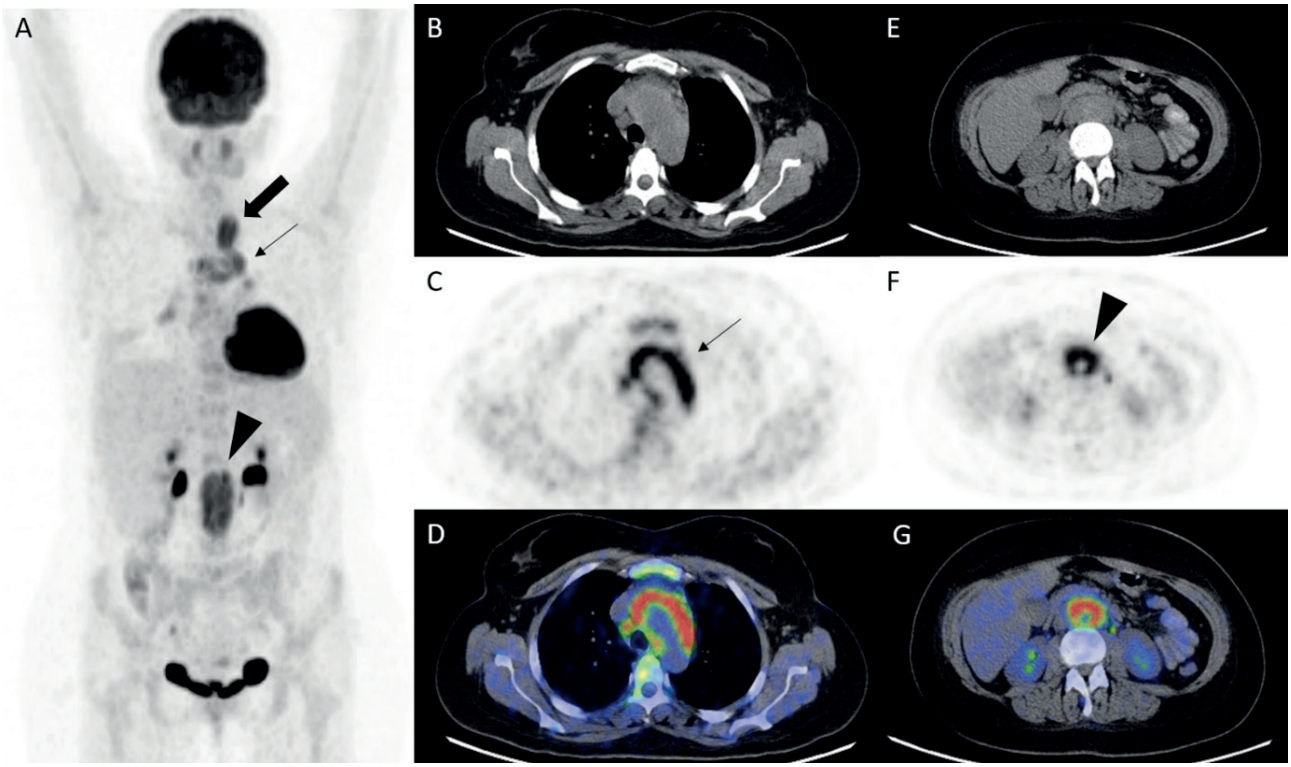

Figure 1. The maximum intensity image(a) and axial CT, PET and PET/CT fusion images showing FDG uptake of left subclavian artery (a, thick arrow), arcus aorta (a, b, c, d thin arrow) and abdominal aorta (a, e, f, g arrowhead). Grade 3 LVV with marked vessel wall FDG uptake greater than liver; total vascular score of this patient is 9 (left subclavian artery, 3 points; thoracic aorta, 3 points; abdominal aorta, 3 points). Ratio of SUVmax(thoracic aorta/liver) is 3.2.

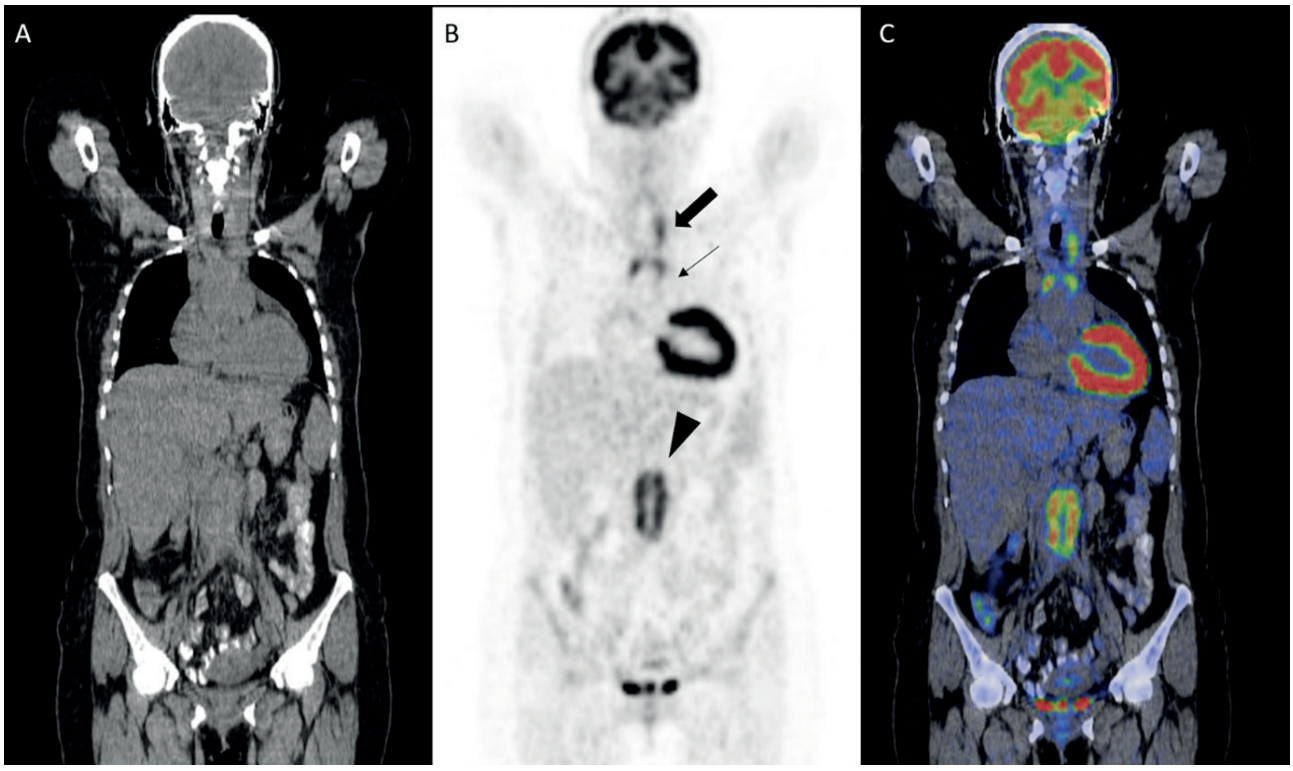

Figure 2. The coronal CT(a), PET(b) and PET/CT fusion(c) images showing FDG uptake of subclavian artery (thick arrow), thoracic aorta (thin arrow) and abdominal aorta (arrowhead).

In general, FDG-PET classically appears as a smooth linear pattern involving the aorta and its main branches (subclavian, carotid or vertebral arteries, pulmonary arteries specifically in TA), but not all main branches have to be involved. Arterial wall uptake must be higher than venous blood pool activity [31,32].

Frequencies of affected vessels detected with FDG-PET/CT are subclavian artery, aorta, iliac and femoral artery, decreasing order 74%, 50%, and 37%, respectively [33].

Special care must be taken for the atheromatous vessel walls, which might be a source of false-positive findings. Despite a classical patchy uptake pattern, atherosclerotic vascular uptake which is frequent with aging may be a source of false positivity for LVV evaluation. Uptake in iliofemoral arteries should be interpreted cautiously because this is a frequent site of atherosclerosis [34]. Generally, intraabdominal and pelvic vessels are affected by atherosclerosis, and supradiaphragmatic vessel uptake is more specific for LVV [35-37]. As stated above, GCA may also co-occur with other rheumatological diseases. As PMR and GCA frequently overlap, typical FDG joint uptake patterns, especially in pelvic and scapular girdles should be reported [29,38].

Follow up and Prognosis

Generally, there is certain decrease in FDG uptake of arterial walls in correlation with patient symptomatology and signs of disease activity. With the data from RIGA study, Schonau et al. showed that follow up of LVV with FDG-PET/CT is valuable. Symptoms and AFRs sometimes can be non-specific but FDG-PET/CT correlates with disease activity [39]. It is reported that complete normalization of vessel walls after treatment occurs [40]. And also, high uptake after initial therapy is related with refractory and/or relapsing vasculitis [37]. But 25% of the patients showed residual mild FDG uptake on the vessel walls which may be related with vascular wall remodeling or smoldering vasculitis [37,41].

Since PET is a whole-body modality, despite its cost, using it for diagnosis and follow-up helps clinicians to control the disease activity in all main vessels simultaneously. This may lead to changes in clinical management that, hopefully, result in patients' benefit.

Future Perspectives

As technology improves logarithmically, new devices and new tracers come into use. Long axial field-of-view total-body PET/CT systems are

changing the paradigm nowadays. Total-body PET is a cutting-edge device that increases the sensitivity of scan around 40-fold while reducing scan time, allowing whole-body dynamic imaging that offer simultaneous angiography [42,43]. New PET/MRI systems use digital PET technology, which increases the resolution and sensitivity of the PET scan. Combined MR angiography and digital FDG-PET data may decrease equivocal cases [21,44].

New tracers also may take place in inflammation imaging. Fibroblast-activation-protein inhibitors (FAPI) are a member of the serine proteinase family that bind cancer-associated fibroblast, which is also found in chronic inflammation sites. Wu et al. showed a patient whose FDG scan was normal but overt FAPI positive vessel walls diagnosed as TA. FAPI PET is promising for imaging inflammation as well as malignancy [45].

CONCLUSION

FDG-PET/CT has an important role in diagnosing and following patients with large vessel vasculitis. Optimal preparation of patient and standard interpretation of FDG-PET-CT are crucial. Further prospective studies involving large cohorts of vasculitis are needed to investigate and validate the role of PET.

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INVITED REVIEW

Diagnosis of Giant Cell Arteritis and Classification Criteria

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Giant cell arteritis (GCA) is a systemic granulomatous vasculitis of the aorta and its large branches. It frequently affects patients older than 50, and a female predominance has been observed in [1]. Although increased mortality has not been reported in population-based cohort studies on GCA, the development of permanent organ damage is a major concern. Vision loss due to ischemic optic neuropathy is one of the main findings in GCA and can be prevented with early diagnosis and treatment [2].

The 1990 American College of Rheumatology (ACR) Classification Criteria for GCA are widely used for classification and consist of 5 items. Patients meeting 3 out of 5 five items are classified as GCA (Table 1) [3]. The presence of fragmentation of the internal elastic lamina, in addition to arterial wall inflammation and mononuclear cell infiltration in temporal artery biopsy, is considered the gold standard for diagnosing GCA [4]. These criteria have significant drawbacks, including their limitation to cranial findings and development before the modern imaging methods.

A decrease in the sensitivity of the 1990 criteria is observed in recent cohort studies. This finding could be explained by the enrolment of patients with different clinical features in the cohorts depending on the improvement in the clinician's perspective over the years [5]. Implementing cross-sectional imaging methods, including Positron Emission Tomography – Computed Tomography (PET-CT), improved the diagnosis of GCA and facilitated the recognition of disease patterns without cranial manifestations.

Patients with isolated extra-cranial involvement reported a diagnostic delay of 2 to 5 months compared to classical DHA patients [6]. Late recognition of large-vessel involvement could cause permanent organ damage. Thoracic aorta dilatation/aneurysm has been reported in 15% and large artery stenosis in 30% of patients with proven aortic inflammation [7].

New classification criteria for giant cell arteritis have been planned based on the scope of DCVAS (The Diagnostic and Classification Criteria for Vasculitis) study data. They are expected to be published in 2022. Sudden vision loss, tongue or jaw claudication, C-reactive protein level, temporal artery ultrasound (US), PET-CT, and angiographic findings were the new items set by [8].

In the last decade, there have been significant advances regarding the role of imaging in diagnosing GCA. "EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice," published in 2018, emphasized the importance of early imaging but stated that imaging should not delay the initiation of treatment. The US of temporal and axillary arteries was recommended as the initial imaging modality of suspected cranial GCA [9]. In patients with a high probability of GCA (jaw claudication and increased acute phase reactants), positive findings in the temporal artery in the US were sufficient for diagnosis without an additional test (biopsy or further imaging) [10].

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Note:
This manuscript was reviewed by Ali İhsan Ertenli.

Magnetic resonance imaging (MRI) may be used as an alternative to the US, but the main limitations of using MRI are high costs and restricted availability. The negative predictive value of MRI in combination with normal findings in temporal artery biopsy was found to be 98% [11].

PET-CT is a technique that can show inflammation in large vessels that we cannot investigate, and its sensitivity is higher than in MRI and CT field [12]. PET-CT may also be useful in the diagnosis of polymyalgia rheumatica and in distinguishing GCA from systemic diseases such as malignancies and chronic infections.

In conclusion, GCA should be at the top differential diagnosis list in patients with certain findings and a high probability of diagnosis (sudden vision loss, typical headache, jaw claudication, and increased acute phase reactants) due to the risk of permanent organ damage and treatment should be initiated as soon as possible. Even if treatment is started, early imaging methods and biopsy can be applied to confirm the diagnosis. The ACR 1990 Classification Criteria are insufficient to identify patients who are resistant to first-line agents and would participate in clinical trials evaluating the efficacy of further treatment options such as biologics. The new criteria to be published this year are expected to fill this gap. It should be kept in mind that these criteria were created for classification purposes and treatment should be decided individually based on clinical features.

Table 1. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis

1- Patient age > 50 years
2- New onset of localized headache
3- Abnormality of temporal artery (temporal artery tenderness, reduced pulsation)
4- Elevated erythrocyte sedimentation rate > 50 mm/1st hour
5- Abnormal temporal artery biopsy

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INVITED REVIEW

Management of Giant Cell Arteritis

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Giant cell arteritis (GCA) is the most common primary vasculitis in people aged 50 years and older. Although there are names such as Horton's disease and temporal arteritis among the first names of the disease, GCA; is evaluated in two groups as cranial giant cell arteritis and large vessel giant cell arteritis [1]. Polymyalgia rheumatica may accompany both subtypes (Figure 1). There may be differences in subgroups between countries and clinics. Distribution of patients from France and Turkey is shown in Figure 1 [2].

In recent years, the concept of disease management is used for many chronic diseases such as diabetes mellitus, asthma. In this review, we prefer to use the disease management strategy to indicate multiple steps of patient care of GCA.

When the treatment strategy is planned, at the time the evaluation of the patient is completed, the patient and their relatives should be informed about the disease and prognosis. Furthermore, their views and expectations about the disease also should be taken into account during the decision of medical treatments. The web page of our vasculitis center can be visited for patient information recommendations http://www.vaskulit.hacettepe.edu.tr/hastalar.shtml [3].
It is very important to prevent our patients from obtaining information from unsafe sources. Additionally, since there is not enough information about the use of herbal products, the use of these products is not recommended in terms of possible side effects.

Multidisciplinary approach and Fast-track clinics in GCA

As in many rheumatological diseases and different types of vasculitis, multidisciplinary collaboration is vital in the differential diagnosis of patients suspected of GCA; not only for the evaluation of symptoms and signs, but also for follow-up of treatment efficacy and adverse events. Rheumatology, Ophthalmology, Neurology, and Internal Medicine clinics are the main clinics that patients frequently apply first. Due to the fact that constitutional symptoms such as weight loss and fever can be evident, the opinions of the infectious diseases and medical oncology departments of the patients can be obtained, especially during the first presentation periods.

Radiology (Doppler Ultrasonography of the temporal and axillary arteries, Computerized tomography/Magnetic resonance imaging angiography of the great vessels, and Nuclear Medicine (Positron Emission Tomography) help in the diagnosis and understanding the extent of the disease. Additionally, interventional angiography is helpful in case of indication. Evaluation of temporal artery biopsy samples taken by neurosurgery or plastic surgery departments is the current standard approach.

Several strategies have been introduced to reduce the rate of morbidity mainly from sudden vision loss. Fast-track clinic gives opportunity for a multidisciplinary approach. Using temporal artery US and confirmation by biopsy as a fast-track clinic is related to better prognosis [4].

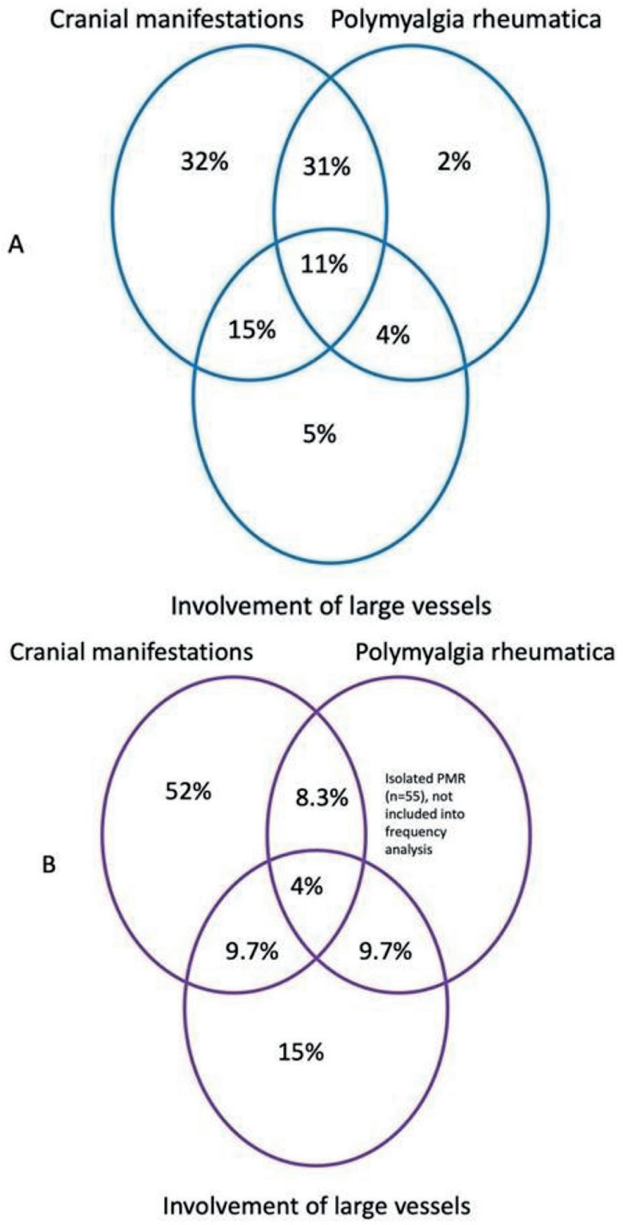

Figure 1. The distribution of GCA subtypes in Artemis study (n=360) (A) and Hacettepe Vasculitis Prospective Database (n=72) (B)

We established our fast-track clinic including radiology, ophthalmology, surgeons, and pathology departments and rheumatology as the team leader at Hacettepe University Vasculitis Center in 2016 and still have been working as a collaborative team.

Detailed evaluation of patients with suspected diagnosis of GCA

The distribution and severity of the disease should be clearly defined using a systemic approach. Questioning the patient regarding the symptoms and performing optimal physical examination using a checklist is recommended which is being done at Hacettepe University Vasculitis Center (Table 1) [3].

Table 1. Visit checklist including signs and symptoms of GCA [6]

Constitutional	Fever >38° C
	Fatigue
	Unintentional weight loss
Neurologic	Transient ischemic attacks
	Syncope
	Cerebrovascular accident
	New/worse headache
	Hemiparesis/paraparesis
Ocular	Amarozis fugax
	Blurred vision
	Retinal vasculitis (thrombosis or aneurysm)
	Sudden vision loss
	Scotom/diplopia
Cutaneous	Scalp tenderness/necrosis in scalp
Musculoskeletal	Arthralgia
	Myalgia
	Morning stiffness
	Shoulder/neck/hip pain
Cardiovascular	Carotidynia
	Chest pain, pericardial or angina
	New onset hypertension
	Other symptoms related to vascular insufficiency
Gastrointestinal	Abdominal pain (vasculitis)
Vascular parameters	New murmurs
	New loss of pulses
	New weak pulses
	Asymmetric blood pressure
	Pulse discordance
	Extremity claudication
	Increase in blood pressure
Laboratory abnormalities	Erythrocyte sedimentation rate
	C-reactive protein
	Hemoglobin/Hematocrit
Patient based assessments	General health measures
	SF-36
	Pain Visual analogue scale (VAS, 0-100)
Clinician based assessments	Physician global scale (0-100)
	Relapse
	Vascular Damage Index
	Increase in glucocorticoid dose
	New/increased immunosuppressive treatment

EULAR definitions of active disease, remission, relapse and refractory disease for GCA

Recommendations of national/international organizations should be taken into account in ensuring homogenization in disease activity assessments and reviewing treatment responses. Definitions for disease activity/damage such as flare, remission, sustained remission could be a part of routine daily practice in patients with GCA. Additionally, these definitions are helpful for better understanding of the literature. In this context, the criteria developed under the leadership of EULAR are frequently used and recommended by our center [5].

According to EULAR definitions [5] active disease, is defined as the presence of typical signs/ symptoms of active LVV and at least one additional item from;

i. Current disease activity on imaging/ biopsy.
ii. Ischaemic complications that are linked to LVV.
iii. Persistently elevated inflammatory markers not attributed to other causes

Remission state is defined as no sign/symptoms and normal acute -phase reactants under standard therapy. If the remission state is achieved for 6 months and individual target doses were reached, it is possible to mention from **sustained remission** and when all the glucocorticoids were stopped in this scenario, then it is called as **glucocorticoid-free remission**.

Instead of flare, **relapse** is the preferred term and divided into two: major and minor relapse. Recurrence of active disease with either clinical features of ischaemia or evidence of active aortic inflammation (causing aortic or large vessel dilatation, stenosis or dissection) is accepted as major relapse. If there is disease recurrence without fulfilling major relapse criteria, then it is called minor relapse. In a minority of patients, it is not possible to reach a remission state under standard therapy; it is called refractory disease.

Medical Treatments

Randomized studies are not feasible given that the GCA is rare in terms of medical treatments especially in the acute phase. Just after the diagnosis, high dose glucocorticoid (GC) therapy equivalent to 40–60 mg/day prednisolone is suggested for remission induction. A tapering strategy is also suggested when the disease is under control to a target dose of 15–20 mg/day within 2–3 months. Targeting a dose of≤5 mg/day after 1 year is suggested.

Patients with sudden vision loss are suggested to be treated by IV 1000 mg methylprednisolone for 3 days with tapering with oral treatment. GC treatment is necessary for both to prevent irreversible vision loss and all ischemic complications and to protect the other eye.

Even EULAR recommends the use of corticosteroids as solo, relapse is observed in 49-68% of patients during steroid tapering [6]. Thus, our vasculitis centre's approach is generally use of any conventional DMARD as a steroid-sparing agent [2].

Treatment can be tailored according to subphenotypes and responses might change among them. For example, de Boysson et al. showed that there is a significantly higher GC dependence in symptomatic large vessel GCA subgroup [7].

In Artemis study, 90/306 patients had at least one adjunctive treatment [8]. Hacettepe University Vasculitis Center results also showed that 87.5% of the patients had at least one adjunct treatment. In both cohorts, MTX is the most common agent used.

In a meta-analysis of 3 randomized placebo-controlled trials adjunctive MTX (7.5–15 mg/week) reduces the risk of first relapse by 35% and the risk of second relapse by 51%. In addition, this regimen had a steroid sparing effect more prominent in 24 months compared to 12 month [9].

In an-open label study, Hocevar et al. investigated the steroid sparing role of leflunomide 10 mg in GCA [10].Relapse was observed in 4 (13.3%) of leflunomide group vs. 18 (39.1%) of steroid-only group (p=0.02). Number needed to treat was found as 3.9. Further data is required to better understanding of the place of conventional DMARDS in GCA.

In refractory/ relapsing cases or when there is or an increased risk for GC side effects, adjunctive treatment with methotrexate (MTX) or tocilizumab (TOC) as an alternative were recommended.

IL-6 is a key mediator in the pathogenesis of GCA and PMR. Treatment with TOC was proven to induce prompt clinical, serologic, and radiologic

improvement in refractory/relapsing disease [11]. In Phase 2 study 85% patients in the tocilizumab group and 20% in the placebo group reached a relapse-free survival by week 52 (p=0·0010) with a cumulative prednisolone dose difference of 67 mg/kg (p=0·0005) after 52 weeks [12].

After Phase III study, TOC was approved as steroid sparing agent in GCA [13]. This study showed that 1862 mg of cumulative median dose of tocilizumab in each group, as compared with 3296/3818 mg in the placebo group that underwent the 26 and 52-week taper, respectively (P<0.001 for both comparisons).

Current approach in Turkey provides the use of TOC in patients resistant to csDMARDs after application to Ministry of Health to get approval for the usage.

Several points should be kept in mind before starting TOC, as acute-phase reactants will not be a disease marker anymore. There is a perforation risk particularly in cases with diverticuli (can be seen commonly in old population). Even additional cardiovascular burden is not proven, fasting cholesterol levels increases with the treatment. After 4-8 weeks of initiation, a control is suggested to understand any side effects and disease activity in short-term and then 6-month interval controls is recommended.

However, there are still some questions to be answered such as how long the treatment should be given [11]. Another point is, there are several reports of presence of biopsy proven arteritis in cases with clinically controlled disease raising suspicion of uncontrolled disease status in patients with palliated symptoms [11].

There are several other biologic agents in the pipeline with promising results such as abatacept, ustekinumab, updacitinib [14]. However, TNF-inhibitors do not seem to be efficacious in GCA. A case series reported the results of anakinra in 6 patients and showed steroid-sparing effect in refractory GCA [15].

Antiplatelet or anticoagulant therapy is not recommended routinely when there is no other indication such as cardiovascular disorders. However, it is suggested to considered individually for the cases with high risk of ischemic complications.

Elective vascular interventions were recommended to be left when a remission state is stable. However, in urgent situations such as arterial vessel dissection or life/organ threatening vascular ischaemia immediate referral to the vascular team is suggested.

Comorbidities

Life-style modifications to reduce cardiovascular risk and complications related to the treatment are prerequisites.

It should be noted that patients might have concomitant diabetes, hypertension, osteoporosis; It should be reminded that age-specific malignancy screening should be done. If necessary, the opinions of the Endocrinology department should be sought, as the drug treatments to be started may aggravate the accompanying diseases.

Relapse and Prognosis

Patients with major relapse was recommended to either initiate or increase the dose of GC therapy as recommended for new onset disease. In case of minor relapses an increase in GC dose at least to the last effective dose was suggested.

Mortality

A recent report, showed an increased all-cause mortality particularly occurring within the first year of diagnosis. Glucocorticoid-related complications are mostly responsible from the deaths [16].

Conflict of interest

Dr. Karadag received research grants from Novartis, Roche, Viela-Bio and a member of advisory Board, speaker of educational programmes for Amgen, Celltrion, Farmanova, UCB-Pharma.

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POSTER PRESENTATION

A Rare Manifestation of Giant Cell Arteritis: Bilateral Scalp Necrosis

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Giant cell arteritis (GCA) is a granulomatous vasculitis of medium and large vessels seen in the elderly. Superficial temporal, vertebral, ophthalmic, and posterior ciliary arteries are commonly involved. It may present with jaw claudication, headache, constitutional symptoms, or scalp tenderness. Rarely, ischemic complications due to intense inflammation and thrombosis may occur [1]. Here, we present a case of GCA presenting with severe scalp necrosis.

CASE REPORT

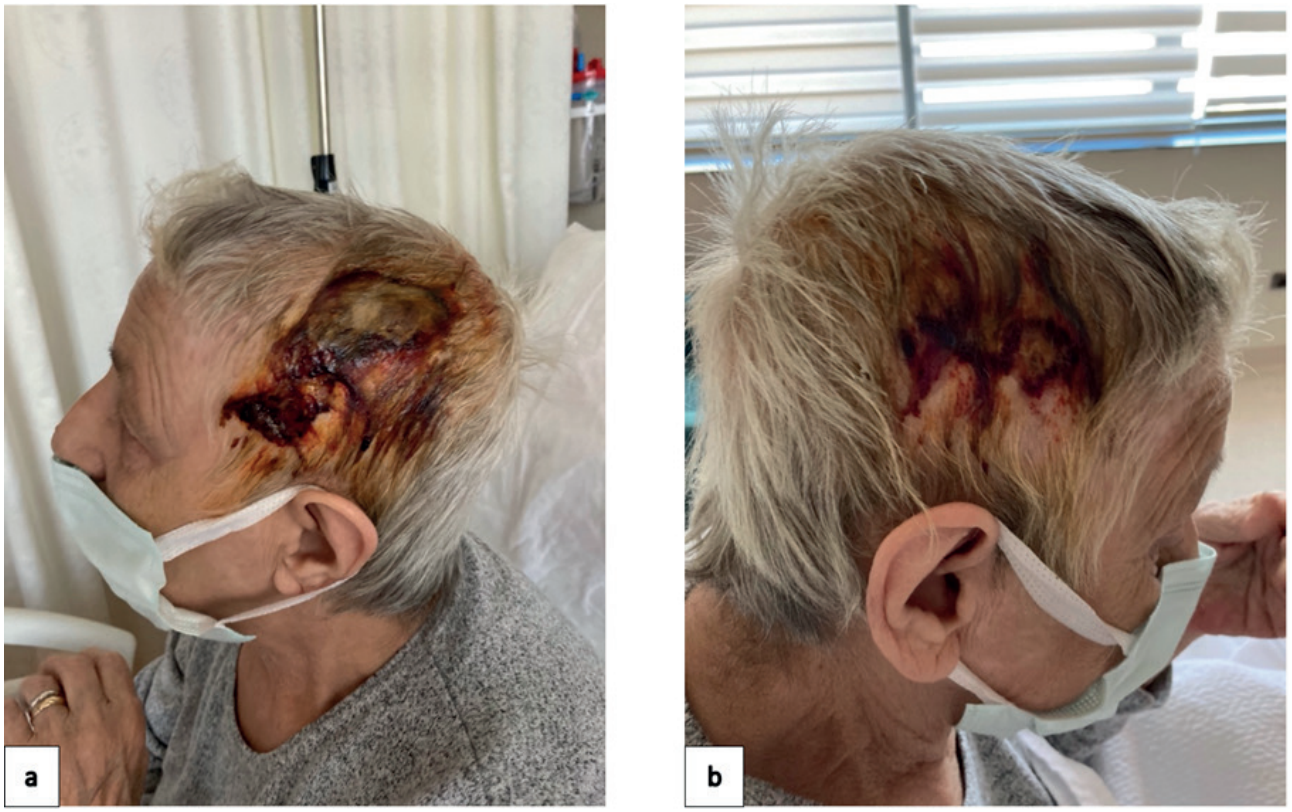
A 73-year-old female patient presented to the Dermatology department with gradually increasing painful lesions on the scalp for about three months and was referred to the Rheumatology department. She also complained of headaches that started simultaneously with skin lesions. The patient did not have symptoms such as vision loss, jaw claudication, and polymyalgia rheumatica. Physical examination revealed diffuse necrotic ulcerations extending to the parietal and temporal regions of the scalp (Picture 1 (a-b)). Temporal arteries were tender bilaterally on palpation, and the left superficial temporal artery pulse was absent. Laboratory tests showed an erythrocyte sedimentation rate of 85 mm/hr and a C-reactive protein level of 44 mg/L. A preliminary diagnosis of GCA was considered, and the patient was transferred to our clinic. Her ophthalmologic examination was unremarkable. Doppler ultrasonography examination of temporal arteries showed hypoechoic thickening, i.e., bilateral halo sign, and mild to moderate luminal narrowing on the left. A biopsy was not considered appropriate due to possible expansion of the ischemic area. Based on the clinical history, physical findings, and pathognomonic sonographic findings, the patient was diagnosed with GCA. Prednisolone treatment at a dose of 1 mg/kg was initiated. Azathioprine 2.5 mg/kg was added to the treatment one week later, and the glucocorticoid dose was tapered over follow-up. A rapid shrinkage was observed in the necrotic lesions within the following days. (Pictures 2 a/b and 3 a/b).

DISCUSSION

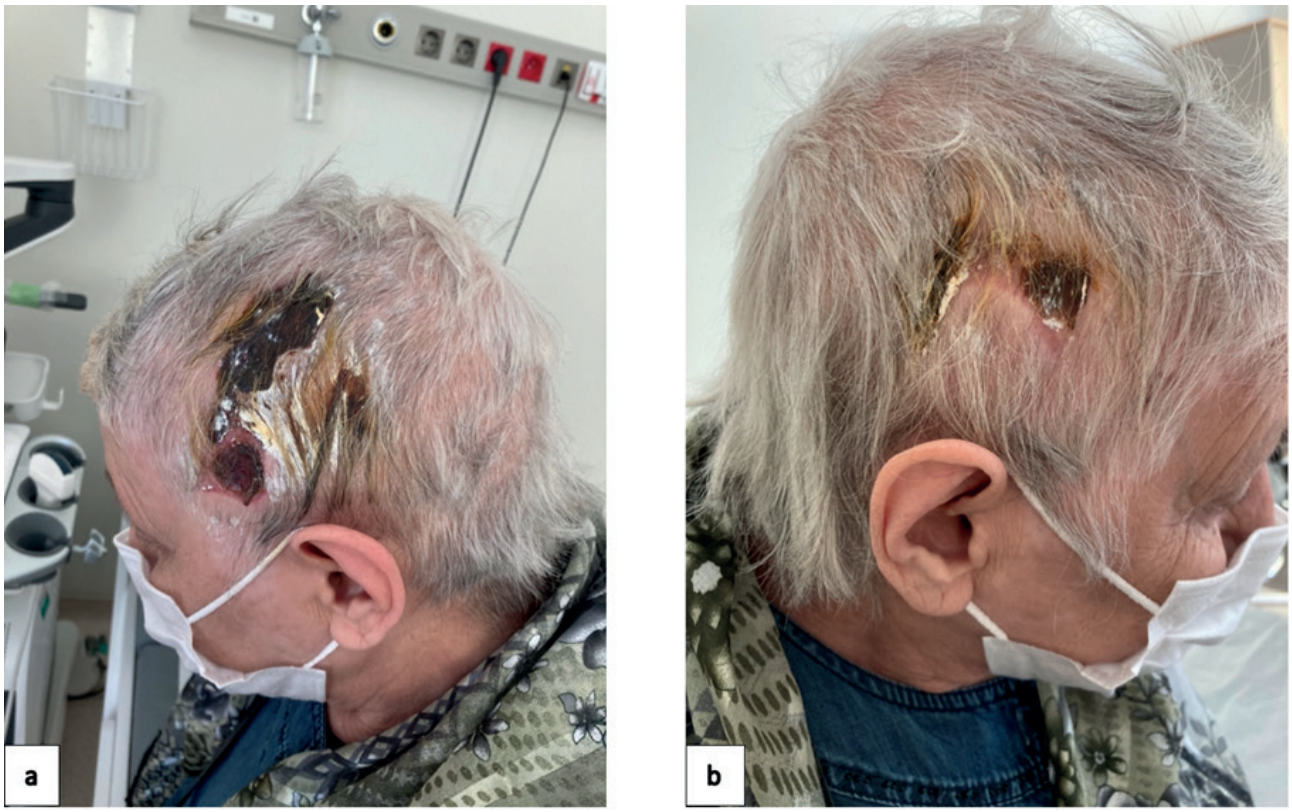
GCA-related scalp necrosis was first described in 1946, and more than 100 cases have been reported since then [1-3]. It is a well-known but rare complication of GCA. Early recognition and early initiation of treatment are significant. The onset is usually insidious, with progression in weeks to months, or acute, within days in up to 20% of cases [4]. Delays in treatment may cause inflammation to spread to all temporal artery branches and more profound tissue loss in the scalp. Lack of early diagnosis and effective treatment may result in skin necrosis, irreversible vision loss, and severe tongue necrosis.

KEY MESSAGES

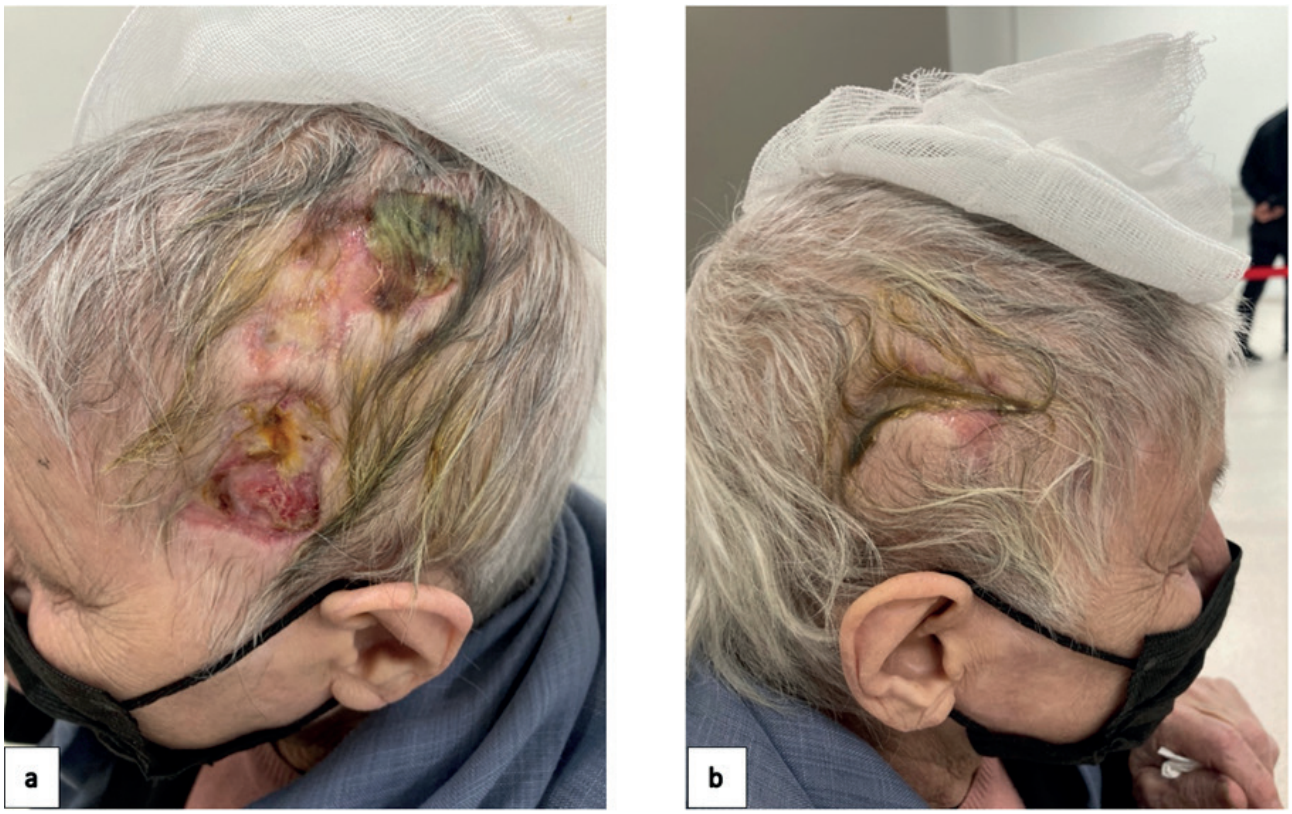
GCA can cause severe tissue and vision loss; early disease recognition is essential. Scalp necrosis is a rare but severe complication of GCA.



Picture 1 a-b. Necrotic ulcerated areas in both temporoparietal regions



Picture 2 a-b. Appearance of the lesions in the 4th week of treatment



Picture 3 a-b. Appearance of the lesions in the 8th week of treatment

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POSTER PRESENTATION

A Case with Giant Cell Arteritis: Disease Exacerbation or Atherosclerosis?

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Giant cell arteritis (GCA) is a vasculitis of large and middle-sized arteries that affects patients aged over 50 years. Patients diagnosed with GCA are usually elderly with age >55 years and thus can have underlying atherosclerosis. Atherosclerosis and GCA are two distinct medical conditions with an overlapping clinical spectrum of vascular symptoms such as limb claudication and cardiovascular events. We present a patient in whom the presence of diffuse atherosclerosis is an important pitfall in distinguishing exacerbation of GCA.

CASE PRESENTATION

In December 2013, a 66-year-old male was admitted to our outpatient clinic with a 2-month history of fever and constitutional symptoms such as weakness, fatigue, and weight loss. In his past medical history, he had diabetes mellitus and peripheral vascular disease for five years. He was an ex-smoker and smoked 43 packages/year. He also had a left-sided headache along with difficulty in chewing food for three months and experienced transient visual loss in his left eye one month ago. He was hospitalized with a preliminary diagnosis of GCA. At hospitalization, acute phase reactants were remarkably high (erythrocyte sedimentation rate:60 mm/h and C-reactive protein:7.5 mg/dL). He underwent a color-duplex ultrasound for the evaluation of his symptoms, but it was not showed significant wall thickening of the temporal artery. Computed tomography (CT) angiography examination revealed that wall thickening and irregularity starting from the aortic arch and extending through the suprarenal abdominal aorta, focal dissection at the exit of the left subclavian artery, total occlusion in the celiac trunk, and superior mesenteric artery, moderate stenosis in the inferior mesenteric artery, and atherosclerotic involvement in the bilateral common iliac artery and its branches. To confirm the diagnosis, a left temporal biopsy was done but it resulted in internal lamina calcification. He was examined by an experienced ophthalmologist for ischemic optic changes of GCA and any findings could not be seen. GCA was diagnosed and he was discharged with 60 mg/day of prednisolone with a dose reduction scheme and methotrexate (MTX) 15 mg/week. For the following 8 years, under MTX and 2.5 mg/day prednisolone, ESR and CRP were completely normal and he had no GCA-related complaints/findings.

In July 2021, he presented to the cardiologist with claudication of his legs, especially on left, and effort-induced chest pain for three months. Coronary angiography was performed on the patient because the ejection fraction was 55% and hypokinesis of the anterior septum in echocardiography. Medical treatment was planned for him due to severe stenosis or occlusion of the coronary arteries was not detected. For lower limb claudication, CT angiography examination reported total occlusion starting from the left superficial femoral artery origin, severe stenosis of the right superficial femoral artery, atherosclerotic wall thickening/irregularities, and fusiform aneurysmatic enlargement in bilateral common iliac arteries was revealed (Figure 1). The cardiologist consulted the patient with us to discuss if this condition was due to GCA. He had no fever, headache, jaw/tongue claudication, and vision loss. ESR and CRP were not high and hemoglobulin level was normal.

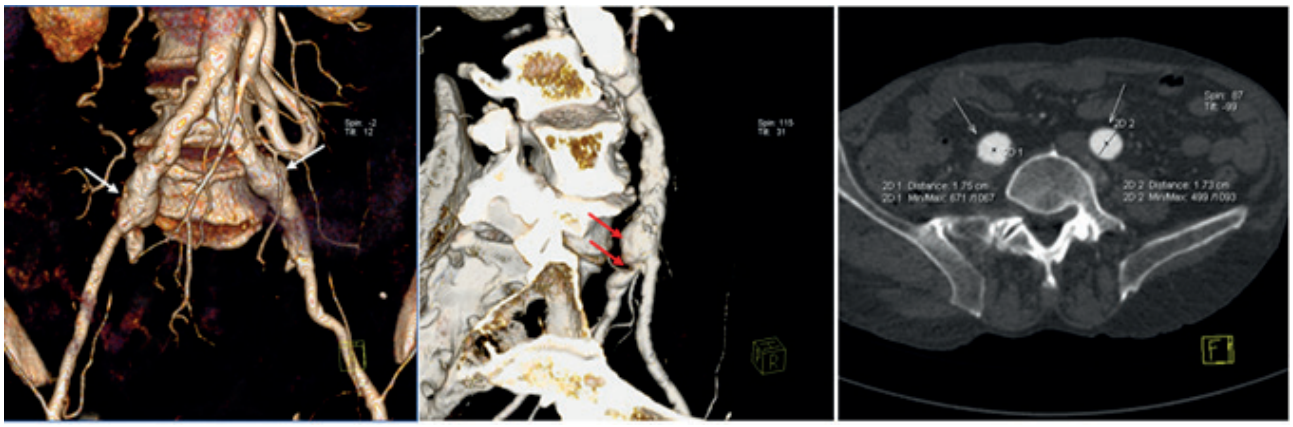

Figure 1. Bilateral common iliac artery aneurysm (anterior view), right common iliac artery aneurysm and subtotal occlusion of the internal iliac artery (lateral view), and vessel wall irregularities and diameter of aneurysms of the common iliac artery (axial view)

After the discussion with the cardiovascular radiologist, MTX and low-dose steroid treatment were continued, considering the lower extremity claudication was due to atherosclerosis. The patient was consulted for vascular surgery and vascular interventional radiology.

DISCUSSION

GCA causes arterial wall inflammation with subsequent arterial stenosis and/or occlusion-induced ischemia leading to similar symptoms as the atherosclerotic vascular disease [1]. A major diagnostic challenge is to differentiate GCA from atherosclerotic disease, which is far more prevalent among patients of a similar age [2]. GCA rarely manifests in the lower limbs and can cause ischemic symptoms [3]. Lower extremity arterial stenosis secondary to atherosclerosis is a common medical condition [4]. In some cases, it may be difficult to distinguish the atherosclerotic disease from vasculitis. Our patient's history of diabetes mellitus and peripheral vascular disease, normal inflammatory marker levels, and CT angiography views led to a diagnosis of lower limb arterial stenosis secondary to diffuse atherosclerosis. In the presence of rapidly deteriorating symptoms, elevated inflammatory markers, paucity of conventional cardiovascular risk factors, or atypical radiological findings for atherosclerosis, the exacerbation of GCA should be carefully considered.

KEY MESSAGES

The patients who are diagnosed with GCA are usually elderly aged>55 years with high-vascular risk and thus can have underlying atherosclerosis.

A careful medical history, measurement of biomarkers of inflammation, and appropriate imaging studies can be helpful in distinguishing atherosclerotic disease from vasculitis.

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POSTER PRESENTATION

A Case of Giant Cell Arteritis with Anterior Ischemic Optic Neuropathy Resistant to Corticosteroid Therapy

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Giant cell arteritis (GCA) is the most common primary systemic vasculitis in adults 50 years or older. GCA is an immune-mediated vasculitis of medium to large-sized arteries. It predicates the aorta and its major branches, including the carotid and vertebral arteries. Symptoms of GCA commonly include headache, fever, scalp tenderness, vision loss, and jaw claudication. Severe unilateral or bilateral loss of vision is the most common and feared complication of GCA related to occlusion of the short posterior ciliary arteries with resulting ischemia to the optic nerve. We know this condition as arteritic anterior ischemic optic neuropathy. In addition, there are other ophthalmic manifestations such as amaurosis fugax, diplopia, ptosis, and eye pain. The cornerstone of GCA treatment is glucocorticoids, which must be initiated immediately after diagnosis at a high dose. Nevertheless, glucocorticoids in aging people frequently lead to side effects, and some patients are refractory to this therapy.

CASE PRESENTATION

A 71-year-old male patient has known diagnoses of cured bladder cancer, early-stage Alzheimer's, and previous right leg deep vein thrombosis. He was under apixaban 2x2.5 mg and acetylsalicylic acid 1x100 mg. The patient complained of fatigue, headache, and jaw pain that started one month ago. One week later, vision loss and diplopia occurred in the right eye. In the examination of the patient at the emergency service, with the diagnosis of pharyngitis, antibiotic (amoxicillin and levofloxacin) treatment was applied for two weeks. Jaw claudication and vision loss continued after antibiotic therapy. When his symptoms did not regress, the patient was admitted to the Hacettepe University Hospital. In laboratory evaluation; Hemoglobin: 11.1 gr/dl, leukocyte:5500 x 10^3 / µL, thrombocyte:224000 x 10^3 /µL, erythrocyte sedimentation rate: 112 mm/hour, CRP: 2.5 mg/dL, procalcitonin: 0.029 ng/mL. Temporal Doppler USG resulted in atherosclerotic involvement. Brain MRI showed peripheral contrast enhancement and thickening of the arterial wall in the right temporal artery in favor of giant cell arteritis. No ischemic pathology was found in brain diffusion MRI, brain CT angiography, or carotid vertebral Doppler USG examinations. As a result of the ophthalmology consultation, extensive cotton wool spots were observed in the right retinal evaluation of the patient, and it was evaluated as giant cell arteritis. A biopsy sample containing a 1.5 cm section of the right temporal artery was taken, and giant cell arteritis was detected. The treatment was started urgently without waiting for the biopsy result. 1 g of pulse steroid therapy was given for three days. 48 mg metilprednizolon (MPZ) treatment was given as maintenance steroid treatment. The vision loss in the patient's right eye decreased. After the biopsy result, weekly subcutaneous tocilizumab 162 mg treatment was started. New onset of vision loss occurred in the patient's left eye ten days after the start of pulse steroid treatment. Giant cell arteritis was considered in the ophthalmologic re-evaluation. One gram pulse steroid treatment was applied again for three days. The patient's vision improved after three pulse steroid therapy. After that, maintenance steroid therapy was continued. On the 15th day of the treatment, vision loss occurred again in the left eye. Pulse steroid therapy for five days was planned for resistant giant cell arthritis eye involvement. The patient's vision

partially improved after five pulse steroid therapy. It was planned to take 80 mg mpz as a maintenance treatment. The patient's treatment is still ongoing.

DISCUSSION

The case is remarkable for different aspects, particularly for the dramatic aggressiveness of the disease despite intravenous MPZ, manifesting by A-AION progression in the first eye and rapid second eye involvement. There is no consensus in the literature concerning the optimal therapeutic approach in GCA patients with corticosteroid-resistant A-AION. Methotrexate could provide a long-term, but modest CS is sparing effect. However, this treatment is not an option for rapid control of the refractory disease. Cyclophosphamide may represent an option for patients with the resistant disease despite high doses of CS or requiring prolonged medium- to high-dose CS therapy. Data are nevertheless limited. We did not plan cyclophosphamide treatment because of bladder cancer.

Recently, it has been shown that TCZ can rapidly induce and maintain GCA remission in a prospective study, several case reports, and some retrospective studies. A phase III trial of tocilizumab showed sustained GC-free remission in 56% of patients receiving weekly subcutaneous tocilizumab alongside the 52-week tapered course of GC, compared with 18% in the 52-week GC taper placebo arm, respectively. Patients treated with tocilizumab required over 40% lower cumulative doses of GC and experienced fewer GC-related adverse events than the placebo group. These results led to the approval of subcutaneous tocilizumab (162mg/week) by NICE for relapsing and refractory GCA.

TCZ was given subcutaneously to all patients included in the GiACTA trial, whereas it was administered intravenously to 79.1% of the clinical practice series. Despite these differences in the route of administration, the number of patients achieving sustained remission was almost similar in both groups (54.6% in the GiACTA trial and 70.4% in the clinical practice group (iv tocilizumab every four weeks); p=0.42) [1].

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POSTER PRESENTATION

How Long Will Tocilizumab Treatment Continue?

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Giant cell arteritis is the most common large vessel vasculitis. The disease occurs as three major clinical phenotypes, cranial GCA, supra-aortic large-vessel GCA, and PMR overlapping with GCA [1]. Classic symptoms include headaches, vision loss, and scalp tenderness. First-line treatment is with high-dose steroids, but methotrexate may be of some help in decreasing steroid use. Tocilizumab (TCZ) has been shown to significantly reduce relapse rate and lower steroid cumulative dose [2].

CASE PRESENTATION

A 79- year old female patient applied to the rheumatology department with complaints of headache, visual loss, and constitutional symptoms. Her laboratory parameters; C-reactive protein: 10.3 mg/dl(0-0.8 range), erythrocyte sedimentation rate: 120 mm/hour (0-25) hemoglobin:8.8 g/dL(11.7-15.5), leukocyte: 4600/ mm^3 (4100-11200), liver and kidney function test were normal. Temporal artery Doppler ultrasonography showed findings consistent with giant cell arteritis in both temporal arteries. Mural cell reaction, lymphomononuclear cell infiltration, dystrophic calcification, and elastic tissue destruction were present in temporal artery biopsy. Imaging studies were normal. The patient was treated with deltacortil 1*15 mg/day and methotrexate 15 mg/week. She was in remission until March 2018. The patient had a headache, scalp tenderness, and acute phase elevation; the relapse did not improve despite the pulse steroids. In April 2018, tocilizumab 8 mg /kg was started, and remission was achieved. The patient is currently on tocilizumab therapy.

DISCUSSION

Tocilizumab is an effective and safe steroid-sparing therapy in relapsing giant cell arteritis. In randomized controlled trials, the certainty of the evidence for sustained remission at 12 months or greater for comparing tocilizumab versus placebo. At the same time, relapse-free survival was higher in favor of participants who received tocilizumab versus placebo: 85% versus 10% at 12 months of follow-up [2]. Although there were a few studies about TCZ treatment, there was no common consensus about treatment duration. Recent research shows that TCZ not only affects acute phase response but also profoundly affects pathogenic cellular events. Younger age and widespread involvement of inflamed vessel wall associated with relapse [3]. Although there is no laboratory and imaging method to predict recurrence, before stopping TCZ, relapse status of the disease with MRA may be helpful.

KEY MESSAGE

Tocilizumab is an effective therapy, but there is not enough information about the duration of treatment.

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POSTER PRESENTATION

A Case of Giant Cell Arteritis Diagnosed Before 50 Years of Age

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Fever of unknown origin (FUO) refers to a prolonged febrile illness without an established etiology despite intensive evaluation and diagnostic testing. FUO may be caused by over 200 malignant/neoplastic, infectious, rheumatic/inflammatory, and miscellaneous disorders [1]. Systemic symptoms associated with giant cell arteritis (GCA) include fever, fatigue, and weight loss. Fevers occur in up to one-half of patients with GCA and are usually low-grade [2]. The most significant risk factor for developing GCA is aging. The disease rarely occurs before the age of 50 years, and its incidence rises steadily after that, peaking between the ages of 70 to 79 [3]. In this case report, we wanted to present a patient under the age of <50 years, diagnosed with giant cell arteritis while being investigated with a fever of unknown etiology.

CASE PRESENTATION

A 43-year-old female patient with no known internal disease was admitted to the rheumatology outpatient clinic with a fever that had increased in the afternoon for one year and lost 18 kilograms. At the same time, pain accompanied the fever, starting from the hip and spreading to the ankles. There was also headache that started from the neck and spread to the face, felt in the bilateral temporal region, and flashes of light in the eyes. Her rheumatological examination was unremarkable except for these complaints. Before the patient was admitted to our clinic, no infection or malignancy was detected in the external center investigation for the etiology of fever of unknown origin. On physical examination, fever was 37.2 °C, bilateral upper extremity blood pressure was 120/75 mmHg, bilateral temporal and carotid artery pulses were palpable, and other system examinations were normal. In the examinations performed when the patient applied to our clinic, PPD 17 mm, sedimentation 72 mm/hr, CRP 5.6 mg/dl, hemoglobin 9.5 g/dL, WBC 16.8 x10^3 µL, neutrophil 12.1 x10^3 µL, albumin 3.25 g/dL was detected. Temporal artery Doppler USG "left temporal artery diameter 1 mm, thickening of the temporal artery wall (halo sign), stenotic foci along the artery trace; right temporal artery diameter of 0.6 mm, stenotic foci along the artery tracing" were reported. Giant cell arteritis was diagnosed with the patient's current findings, and 48 mg of methylprednisolone (to be reduced by 4 mg per week), methotrexate six tablets per week, folbiol 1 per week, ASA 1x100 mg, and calcium-D vitamin were started. In the patient, who benefited from this treatment in a 3-month follow-up, a temporal artery biopsy was performed because they had a fever twice and the headache persisted even though it decreased. The biopsy result was "artery section with medial calcinosis."

Concurrent sedimentation and CRP with biopsy were respectively 45 mm/hr and 2.58 mg/dL. Vasculitis CT angiography was normal. In this period, methotrexate eight tablets/week and methylprednisolone 12mg were administered. PET CT was planned because she had a fever again in the follow-up. Due to diffusely increased FDG (SUVmax: 5.4) in the bone marrow in PET CT, she was referred to hematology. Bone marrow biopsy was performed. It was found normal. According to these results, tocilizumab was started once a week s.c. Methotrexate was adjusted five tablets/week, methylprednisolone 1x4 mg. The patient who responded to this treatment was followed up without complications and was fever-free.

DISCUSSION

Fever of unknown origin, defined as fever ≥38.3°C (101°F) for >3 weeks that remains undiagnosed after a hospital work-up. Fever of unknown origin work-ups may be done as an outpatient. FUO can be classified as infectious, malignant/neoplastic, rheumatic/inflammatory, and miscellaneous disorders. The most common causes of rheumatic diseases in the etiology of FUO are adult still's disease, juvenile rheumatoid arthritis (JRA), and giant cell arteritis (GCA). The fever-of-unknown-origin work-up should be a symptom (history) and sign (physical examination) driven. Based on history and physical clues, determine the appropriate category for the fever. Testing should be selective and based on diagnostic probabilities, not possibilities [1].

Giant cell arteritis (GCA, also known as Horton disease, cranial arteritis, and temporal arteritis) is categorized as a vasculitis of large- and medium-sized vessels because it can involve the aorta and great vessels. It causes stenosis and aneurysm of affected vessels. Fevers occur in up to one-half of patients with GCA and are usually low-grade. However, in approximately 15 percent of patients, fevers exceed 39ºC [2]. A characteristic laboratory abnormality in many patients with GCA is a high ESR, which can reach 100 mm/hour, and high CRP. Normochromic anemia is often present before therapy, moderately decreased serum albumin, also have a reactive thrombocytosis [4].

USG, MRI, CT, and PET CT can be used as imaging modalities for diagnosing GCA. Ultrasound sensitivity is 87%, and specificity is 96%. The temporal arteries are localized superficially, about 4 mm below the skin surface. Although they are small, with lumen and wall diameters of about 0.7 mm, they are easily accessible with ultrasound. Colour Doppler ultrasound of temporal arteries shows hypoechoic (dark) oedematous wall swelling in acute temporal arteritis. This tissue is not compressible. It disappears with glucocorticoid treatment after 2–3 weeks in most patients. In some patients, detecting a characteristic wall swelling becomes difficult after only three days of treatment [5].

KEY MESSAGES

In the etiology of fever of unknown origin, rheumatological diseases should always be included in the differential diagnosis.

Giant cell arteritis should be kept in mind in patients who present with fever, headache, and vision changes at a young age, even though it is a low probability.

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POSTER PRESENTATION

A Case of Temporal Arteritis Presenting with Sudden Loss of Vision

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Giant cell arteritis (GCA) is a chronic vasculitis involving large and medium-sized vessels. Patients may present fatigue, weight loss, fever, headache, jaw claudication, scalp tenderness, and vision loss [1]. Involvement of the external branches of the carotid artery and the temporal artery is detected most frequently. The most feared complication is vision loss [2].

CASE PRESENTATION

A 76-year-old female patient revealed retinal vascular occlusion in the examinations for sudden vision loss in the right eye. While her examinations continue, she is referred to our center due to the development of blurred vision in her other eye. On ophthalmological examination, the disc is pale in the right eye, with a cotton wool spot around it, and drusen in the peripheral retina. In the left eye, the disc was slightly hyperemic, and drusen were detected in the peripheral retina. Light reflex was obtained in both eyes. In addition to the patient's eye complaint, a knife-like headache that increased with jaw movements and temporal region tenderness were detected. The patient, who had lost 15 pounds in the last five months, complained of weakness and fatigue. On physical examination, there was no temporal pulse besides temporal tenderness on the right side. In the temporal Doppler ultrasonography, there was an increase in the right temporal artery wall thickness and no flow to the distal artery. The findings were indicative of GCA. C-reactive protein was 5.71 mg/dL, and sedimentation was 41 mm/hour. The patient was treated with 1000 mg methylprednisolone/day for three days without waiting for a temporal artery biopsy result. The biopsy result was compatible with temporal arteritis. Methotrexate (15 mg/week weekly) was started. After the treatment, the visual loss improved almost completely.

DISCUSSION

The most feared complication of DHA is vision loss. If treatment is delayed, 10-20% of patients may develop permanent vision loss. DHA should be considered in differential diagnoses of patients with sudden vision loss [1,2].

KEY MESSAGE

As in our case, possible visual damage can be prevented by initiating aggressive treatment in the early period in patients who are thought to have vision loss due to GCA.

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