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UNCOMMON AND/OR UNUSUAL HEADACHES AND SYNDROMES (J AILANI, SECTION EDITOR)

Giant Cell Arteritis: A Case-Based Narrative Review of the Literature

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Abstract

Purpose of Review Giant cell arteritis (GCA) is a chronic, inflammatory condition, primarily affecting the medium and larger arteries. The purpose of this narrative review is to describe GCA in the context of headache and facial pain, based on a case and the available current literature. Understanding the etiology, pathophysiology, the associated conditions, and the differential diagnoses is important in managing GCA.

Recent Findings In a patient presenting with unilateral facial/head pain with disturbances of vision, GCA should be considered in the differential diagnosis. There is an association of GCA with several comorbid conditions, and infections including coronavirus-19 (COVID-19) infection. Management of GCA primarily depends upon the identification of the affected artery and prompt treatment. Permanent visual loss and other serious complications are associated with GCA.

Summary GCA is characterized by robust inflammation of large- and medium-sized arteries and marked elevation of systemic mediators of inflammation. An interdisciplinary approach of management involving the pertinent specialties is strongly recommended.

Keywords Giant cell arteritis (GCA) · Halo sign · Vasculitis · Facial pain · Artery biopsy · Temporal arteritis

Introduction

Giant cell arteritis (GCA) is a chronic, inflammatory condition, primarily affecting the medium and larger arteries, usually in patients older than 50 years of age. Permanent loss of vision is one of the most serious complications of the condition. The etiology of GCA is largely unknown; however, the condition has been known to co-exist with polymyalgia rheumatica (PMR) and systemic vasculitis. Biopsy of the affected temporal artery still remains the golden standard for confirmatory diagnosis of GCA when the temporal artery is affected. This narrative review is based on a case of bilateral temporal GCA. Based on an exhaustive literature search, we elaborate on the clinical features, etiopathogenesis, investigations, and management of GCA. We compare the cardinal features present in this case, with the established literature, and also provide a thorough review to differentiate GCA from other similar vasculitis entities.

This article is part of the Topical Collection on *Uncommon and/or Unusual Headaches and Syndromes*

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Case Presentation

History of Present Illness

A 79-year-old South Asian male patient presented with the chief complaints of bilateral headaches, facial pain, bilateral neck and upper limb pain, complete loss of vision in the right eye, and acute partial loss of vision in the left eye.

Onset

The headache was of a sudden onset in the temporal region. The left-sided peri-auricular pain and the neck pain radiating to the arms were of a slow onset.

Location

The bilateral headache was in the temporal region; the facial pain sites were peri-auricular and temporomandibular joint (TMJ) areas bilaterally (right > left). The arm pains were along the entire length of both the arms. The bilateral neck pain radiated to the arms ipsilaterally. The loss of vision was complete in the right eye and partial in the left eye.

Chronicity

The temporal pain and vision loss were acute. The neck pain and the pain radiating to the arms were chronic.

Frequency and Duration

The frequency and duration of the temporal pain were continuous; TMJ and ear pain were intermittent (provoked); the neck pain and the radiating pain occurred intermittently, multiple times a day.

Intensity

The intensity of the temporal pain was 5 to 6 on a visual analog scale (VAS) of 0 to 10. The TMJ and ear pain were 4 to 5; neck pain radiating to arms was 3 to 4.

Quality

The temporal pain had a throbbing quality; the TMJ, ear, and neck pains were "dull-aching."

Temporal Characteristics

The temporal pain was chronic progressive; the TMJ, ear, and neck pain were non-progressive; the visual symptoms were rapidly progressing.

Aggravating Factors

The temporal, TMJ, and ear pain were aggravated by chewing, and the neck and arm pain by neck movements.

Relieving Factors

The temporal pain was unrelenting. The TMJ, ear, neck, and arm pain were relieved by rest.

Response to Past Treatment

None of the chief complaints was responsive to any of the past attempted therapies, the details of which were not available.

Associated Features

The patient complained of claudication upon chewing, paresthesia in the neck and arm with neck movements, complete/partial loss of vision, and scalp tenderness.

Radiation/Referral

The jaw pain radiated to the neck, arms, and the side of the head ipsilaterally. The neck pain radiated to ipsilateral arm.

Association with Sleep

The patient reported poor quality of sleep.

Medical History

He is a known diabetic, hypertensive, and hyperlipidemic, all being managed adequately by medications. Patient takes olmesartan 40 mg OD, sitagliptin 50 mg BD, and rosuvastatin 5 mg OD.

Clinical Examination Findings

All the mandibular movements were within normal limits, but with pain. Cervical range of motion was restricted by approximately 30–40% with moderate pain. Palpation of the temporalis and masseter muscles elicited intense pain, reproducing the patient's familiar pain and chief complaints of facial/jaw pain bilaterally, by approximately 70%. Temporal artery appeared tortuous on the right, and its pulse was nonpalpable on the right, and feeble on the left. Palpation of the bilateral sternocleidomastoid muscles reproduced the patient's familiar pain and chief complaints by approximately 50–60%. Fibromyalgia screening was positive. TMJ palpation elicited mild pain of 3 on VAS bilaterally. For

vision-related complaints, the patient was promptly referred to an ophthalmologist.

Laboratory Investigations

HbA1c = 7.4 (normal value: 4.0–5.6)
Erythrocyte sedimentation rate (ESR) = 94 mm/h (normal value: 0–15)
C-reactive protein (CRP) = 131.8 mg/L (normal value: 0.0– 10.0)
Total leukocyte count (TLC) and polymorphonuclear leukocyte count were markedly high with reduction in lymphocyte count.

Imaging

Color duplex ultrasonography of the temporal artery showed atherosclerotic vessel wall changes in both temporal arteries. Perivascular hypoechoic halo noted around both superficial temporal arteries, more on the right than the left. These imaging findings are highly suggestive of GCA (Fig. 1).

Magnetic resonance imaging (MRI) of the brain, brain stem and neck, with and without contrast, failed to reveal any of the characteristic features associated with GCA. Magnetic resonance angiography (MRA) of the neck vessels and the circle of Willis showed no narrowing, aneurysm, malformations, dissections, or other significant abnormalities.

Histopathology

Biopsy of the right superficial temporal artery showed a narrow lumen with hyperplastic intima layer, focal disruption and fragmentation of the internal elastic lamina, marked thickening of the tunica media with multiple ill-formed granulomas, and concomitant evidence of Monckeberg's medial sclerosis (MMS). The granulomas were composed of epithelioid cells, lymphocytes, and multinucleated giant cells (Fig. 2). Multiple congested blood vessels, edema, and transmural inflammatory cell inflammation (lymphocytes, plasma cells, and neutrophils) were also seen. These histopathological findings were confirmatory of GCA.

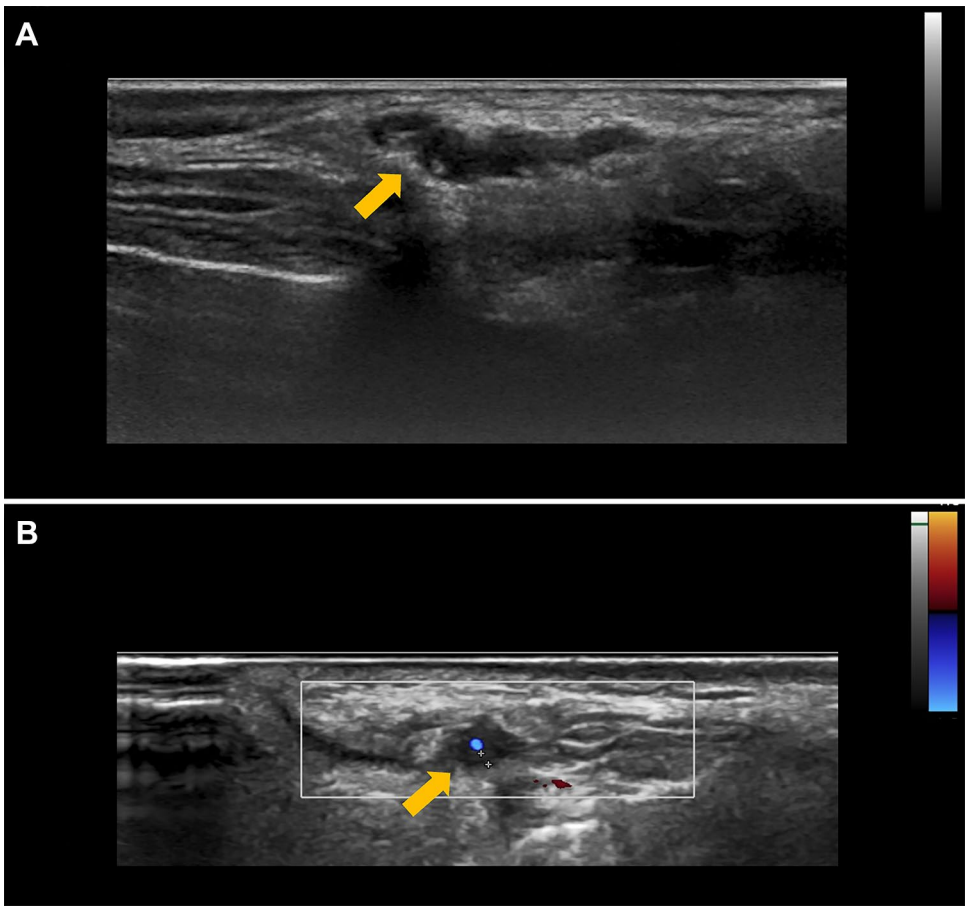

Fig. 1 **A** Longitudinal section showing perivascular hypoechoic halo. **B** Axial section showing the perivascular hypoechoic halo. The blue dot at the center designates the narrowed lumen

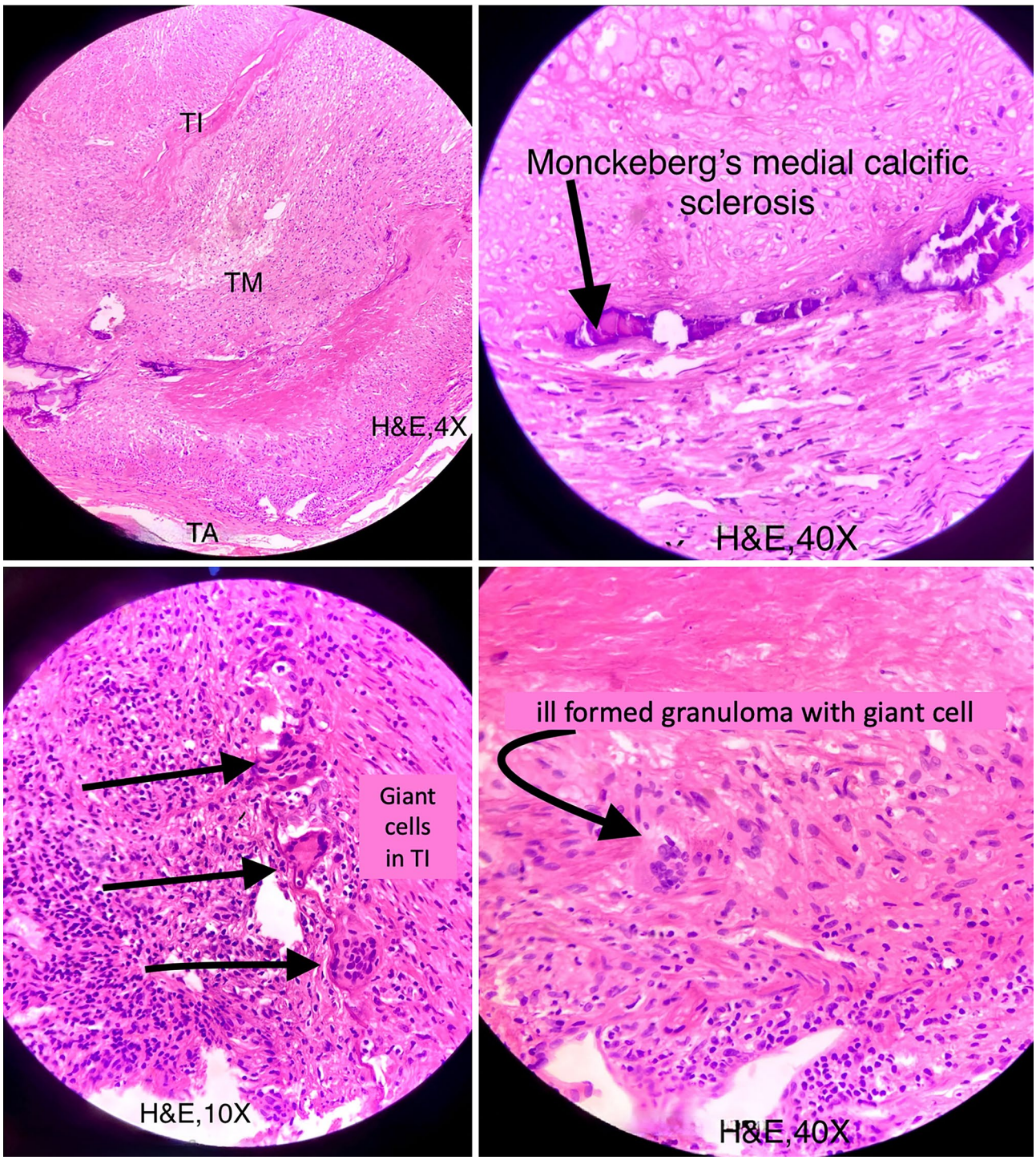

Fig. 2 Histopathological features of the biopsy specimen (TI, tunica intima; TM, tunica media; TA, tunica adventitia; H&E, hematoxylin and eosin)

Management

The patient was treated with methylprednisolone starting with 1 g intravenously (IV) once daily (OD) for 5 days, followed by tapered dose from 60 mg, reducing 10 mg weekly. Concomitantly, pantoprazole 40 mg IV and calcium 500 mg OD were administered for 5 days. Patient was scheduled for follow-up every 3 months afterwards.

Complications

This patient had significant complications including complete loss of vision in one eye and partial loss of vision in the other. The diabetic and hypertensive status of the patient posed a challenge in considering corticosteroid therapy for the management of this condition.

Discussion

Definition

Initially described by Hutchinson (1890) and Horton (1932), GCA is a form of autoimmune systemic vasculitis [1, 2]. In GCA, there is an increased incidence of involvement of the temporal arteries [3]; however, GCA is a systemic disease. GCA is defined by the American College of Rheumatology (ACR) as a type of vasculitis or arteritis a group of diseases whose main feature is inflammation of the blood vessels. The 2018 European League Against Rheumatism (EULAR) is largely in consensus with the ACR criteria [4•]. A recent international consensus describes GCA as a granulomatous arteritis [5].

Synonyms

Horton's disease [3]
Temporal arteritis [3, 6]
Large-vessel GCA [5, 7–9]
Cranial arteritis [10]
Granulomatous arteritis [6, 11]
Polymyalgia arteritica [8]
Arteritis of the aged [12]
Anarthritic rheumatoid disease, Pulseless disease [12]

Classification Criteria for GCA

The ACR 1990 criteria for GCA include age 50 years or older, a headache of new onset, and localized; reduced pulsation, and palpation-tenderness of the temporal artery, which are not attributed to arteriosclerosis of cervical arteries; elevated ESR ($\geq$ 50 mm/h), and biopsy showing characteristic features. The ACR has recommended that at least three (or more) of the five criteria, when positive, carries high sensitivity and specificity with it. Additional ACR criteria include claudication of tongue, jaw, or upon swallowing, and scalp tenderness [1]. The current ACR/EULAR criteria are for vasculitis in general, and not limited to GCA. Clinicians can expect an update from ACR/EULAR on the diagnostic criteria of vasculitis and GCA in the upcoming months.

Epidemiology

GCA has an annual incidence of approximately 10–20 and prevalence of 50 cases [13] in every 100,000 of the general population middle aged or older [13, 14]. The peak incidence is over the age of 70 years [8, 13–16]. GCA shows a racial predilection for non-Hispanic Caucasians from the northern latitudes, and there is a geographic variation in the incidence of "biopsy positive/negative" GCA cases [17]. GCA has a female gender predilection, with an approximate female to male ratio of 2:1 in the Caucasian population, with an even gender distribution in populations in Spain, India, and Turkey [14, 17, 18]. One of the comorbidities of GCA, polymyalgia rheumatica (PMR), is reported to occur in approximately 50% of patients with GCA [19••]. Conversely, the same literature shows that approximately 18% of PMR cases have a concomitant GCA. The average time elapsed between onset of symptoms and diagnosis was 6 to 9 weeks [20, 21]. The cranial arteries, primarily the temporal artery of the scalp, are most commonly involved, followed by the ophthalmic, occipital, and posterior auricular arteries [15, 18, 22].

Etiology and Pathophysiology/Pathogenesis

The pathophysiology of GCA is complex and largely unknown; however, the role of age, genetics, and infections has been proposed amongst others [15]. The role of age in the pathogenesis of GCA has been linked to age-related degenerative changes [16, 23•], oxidative damage, protein abnormalities, mutations, mitochondrial defect, and age-related vascular inflammation [16, 24]. A possible role of sex hormones in the pathophysiology of GCA explains the female predilection [17, 25]. The role of infections has been proposed in the pathogenesis of GCA [26]. Due to the cyclical and seasonal nature of GCA manifestations, a role of sun exposure and seasonal infections has been suggested [26]. A hypothesis of increased "infectious load" and consequent activation of vascular dendritic cells has also been proposed. Infectious agents like *Chlamydia pneumoniae*, parvovirus B19, Epstein-Barr virus, varicella-zoster virus, and most recently COVID-19 have shown an association with GCA [26]. GCA is often described in the literature as a "T-cell mediated disease" [27]. The pathogenesis of GCA is thought to be brought about by an unknown antigen triggering a cascade of immunological events, culminating in the characteristic blood vessel and target tissue changes as observed in tissue histopathology [27, 28] (Fig. 3).

Genetics

A strong association of GCA with certain human leukocyte antigens (HLA) such as HLA-DR4 and HLA-DRB1*04 alleles has been reported [16, 25, 29••, 30]. The HLA-DRB1*04

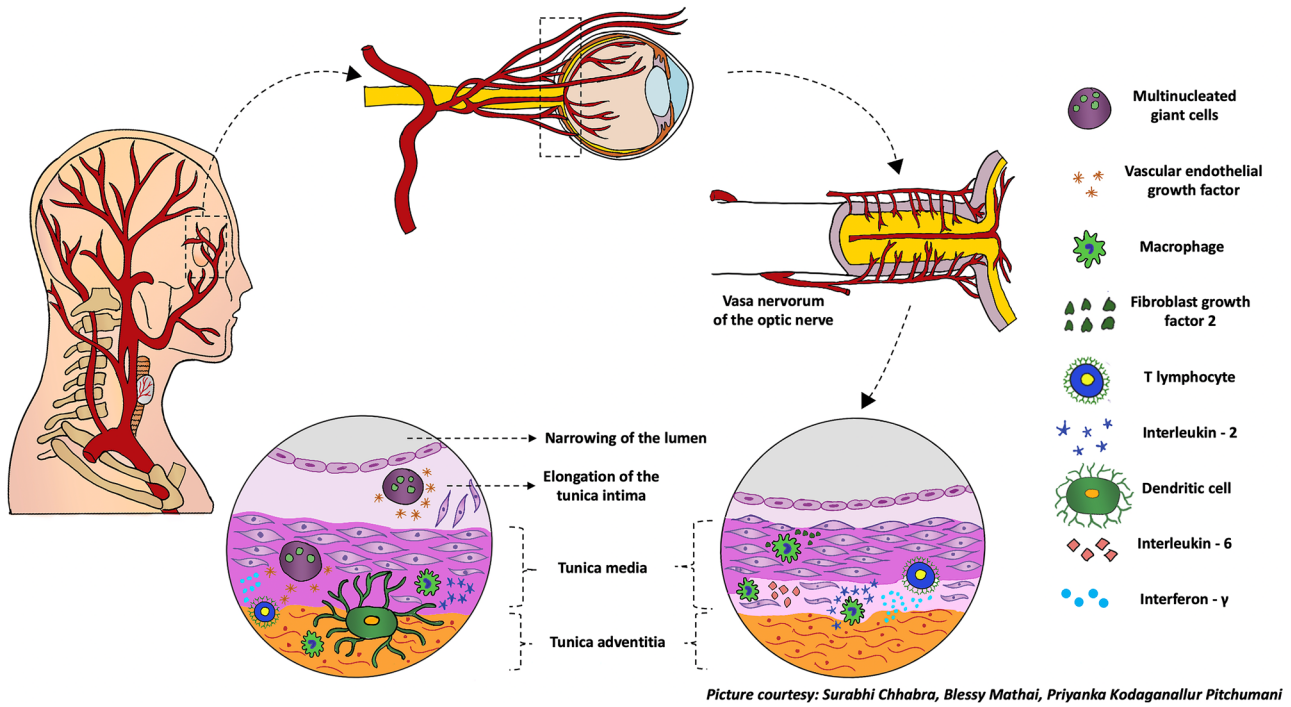

Fig. 3 Schematic representation of the macro- and micro-anatomy of giant cell arteritis

allele is associated with the resistance of the disease to corticosteroid therapy [29••, 30] and loss of vision secondary to GCA [29••]. Other non-HLA genes related with GCA include PTPN22, LRRC32, IL17A, and IL33 [25].

Clinical Manifestations

Extracranial Manifestations The constitutional symptoms include low-grade fever, fatigue, weight loss, night sweats, unexplained dry cough [31], backache, abdominal pain or dyspnea, anemia, and depression [14, 18]. Due to its strong association with GCA, all patients with a diagnosis of PMR should be tested for the presence of GCA and vice versa [32]. The extracranial blood vessels mainly involved with GCA include the aorta [33], abdominal aorta [33], the carotid arteries, the vertebral and basilar arteries [34]; the subclavian, axillary, iliac [33], femoral, renal [34], mesenteric [34] and others [33]. The extracranial features include limb claudication, limb vascular bruits, giant cell aortitis, and reduced or absent pulse [35]. Arthritis and arthralgia frequently involve the knees, wrists, and the metacarpophalangeal joints in an asymmetric, nonerosive pattern [36].

Craniofacial Manifestations The most common/cardinal symptom of GCA is a new onset headache in the temporal region [6, 7, 14, 15, 37] with tenderness and allodynia upon palpation of the temporal artery [18]. Palpation of the artery may reveal irregular contour, beading, thickening, and induration. The onset, duration, frequency, and intensity are reported in widely variable patterns [21, 25, 32, 37, 38]. Scalp tenderness and allodynia are also reported [14, 32]. The involvement of the internal maxillary artery and facial artery results in jaw claudication [6, 14], which is defined as pain and fatigue in the facial and masticatory muscles upon prolonged function and may be relieved with rest [18, 39]. Temporal headache and jaw claudication are the initial symptoms for which the patient seeks relief; hence, their identification is crucial [6].

Approximately 20% of GCA patients present with visual symptoms [15, 18]. Blurred vision, amaurosis fugax, and loss of vision are the most frequent symptoms. Amaurosis fugax along with jaw claudication are symptoms most often related to permanent vision loss [17, 18, 40]. Anterior ischemic optic neuropathy (AION) is reported to be the cause of permanent loss of vision in majority of the cases of GCA [39, 41]. Vision loss usually begins unilaterally, and can simultaneously or, in a short period of time, sequentially involve the other eye [15, 17, 40]. Diplopia can be transient or permanent, unilateral, or bilateral depending on the artery involved, and is experienced before vision loss, by 20% of patients due to ophthalmoparesis [17, 42, 43]. One of the rare signs is visual blurring with heat or exercise (Uhthoff's sign) and marked reduction of the visual field [39, 41].

Oral Manifestations GCA affecting the lingual artery can show signs of ischemia of the tongue such as loss of taste, unilateral/bilateral pallor, cyanosis, and necrosis. Tongue claudication and pain at rest or on function can be a symptom [8, 18, 32, 38]. The involvement of the ascending pharyngeal artery can result in throat pain and dysphagia. Toothache and gingival pain can also occur secondary to GCA [15, 31, 32, 38, 44].

Atypical Manifestations These include fever of unknown origin, cough, hearing loss [31], glossitis [15], Raynaud's phenomenon, minor/major stroke limb claudication [31], and lesions in the breast and ovaries [15]. In addition, systemic associated comorbidities include hypertension, diabetes, thyroid dysfunction, cardiovascular disease, and glaucoma [18]. The various comorbidities reported in the literature are presented in Fig. 4.

Histopathology

The cardinal findings in the histopathology of GCA include arterial wall inflammation, destruction of the internal elastic lamina, thickening of the tunica intima, and the presence of multinucleated giant cells at the junction of the tunica media and tunica intima [7, 18]. Half of the temporal artery biopsy specimens may be negative for giant cells [7]. One-third of the biopsied arteries are shown to be negative for GCA [18, 25]. In addition to giant cells, the inflammatory response includes mononuclear lymphocytes, histiocytes, neutrophils, and eosinophils [18]. Inflammation of the vasa vasorum may also be seen. "Skip lesions" where there may be unaffected segments of normal looking arterial tissue interspersed between the lesions along the course of the affected artery are characteristic of GCA [7, 18]. This necessitates the process of multiple punch biopsies to enhance the chances of capturing the lesional areas. Some authors and organizations (including EULAR) recommend temporal artery biopsy (when involvement of temporal artery is suspected from clinical features) earlier than late, due to the fact that the histopathological features may not be as robust later in the disease [18].

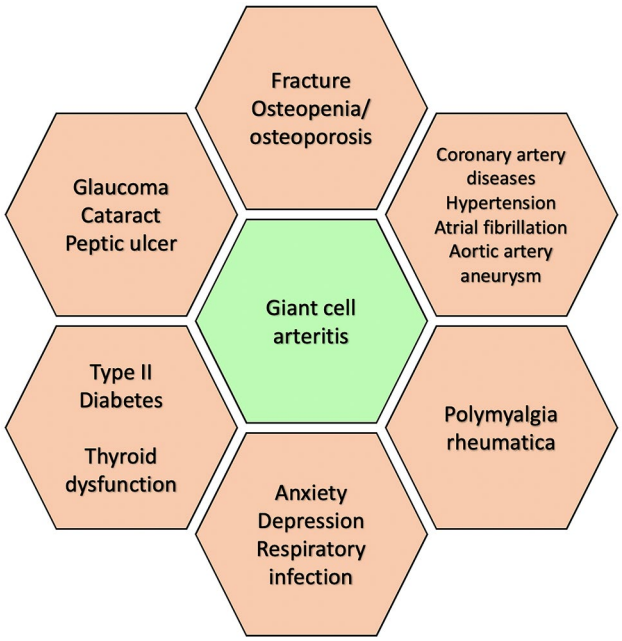

Fig. 4 Comorbidities in giant cell arteritis

The diagnosis of GCA has traditionally been by the histopathology features subsequent to biopsy of the affected temporal artery. The 1990 ACR criteria require histopathology for diagnosis. However, the preference to include or avoid temporal artery biopsy has not been without some controversy. Factors such as biopsy length and site, presence of skip lesions, the experience of the surgeon, quality of the biopsy sample, and phenotypic characteristics of the GCA are reasons affecting sensitivity [45]. Though considered a safe procedure, TAB is an invasive technique with associated complications including facial nerve injury, brow ptosis, scalp necrosis, infection, bleeding, and hematoma [17, 46]. Accidental nerve and vein biopsies, incisional alopecia, widening of the scar, and foreign body reaction to entrapped hair have also been reported [46]. A negative biopsy is instrumental in avoiding the long-term risks of corticosteroid therapy [7]. Longer TAB segments are preferred for demonstrating inflammatory changes in artery segments, thereby minimizing the risk of missed diagnosis secondary to skip lesions [46]. Skip lesions are considered when features of arteritis were absent in single or multiple segments of the same artery that showed characteristic features of arteritis in other sections [46].

Laboratory Investigations

Since there are no specific blood biomarkers for GCA, multiple laboratory values are employed for diagnosis. The ACR criteria require the ESR to be > 50 mm/h. Increase in CRP (> 20 mg/L) is another feature [42]. These two values are non-specific yet are sensitive enough in correlation with clinical features of GCA. A complete blood count may reveal anemia, leukocytosis, thrombocytosis, and an increase in acute-phase proteins in serum albumin electrophoresis [7]. Thrombocytosis is considered as an adjunct marker that may aid in the differentiation of AION from other types of optic neuropathy. When a complete metabolic panel is ordered, there may be findings of mild abnormalities in the liver function tests, including an increased alkaline phosphatase, increased aspartate transaminase, and prolonged prothrombin time. Elevated von Willebrand factor is another feature in GCA patients.

Imaging

An ultrasound (US) can be used along with the ACR criteria for GCA diagnosis [47]. This may preclude the necessity for the biopsy and avoid delay in prompt initiation of treatment. The EULAR recommends the use of US as the first imaging modality when a diagnosis of GCA is suspected. US abnormalities in GCA are described as "halo" sign, "compression sign," stenosis, and occlusion. In a transverse scan, the halo is visible as concentric, homogenous, and hypoechoic arterial wall thickening which is well delineated towards the luminal side [48]. "Compression" sign is positive when the hypoechogenic thickened wall demonstrating vasculitis remains visible against the mid-echogenic to hyperechogenic surrounding tissue wall even upon compression [49]. Some studies suggest a 96% specificity for US in the diagnosis of GCA [50]. However, "halo" is also seen in conditions such as amyloidosis and atherosclerosis, hence the added significance of a thorough history and clinical examination [48]. EULAR recommends the use of high-resolution MRI to visualize artery thickness in cranial arteries when US imaging is not available [43], and to monitor long-term structural damage. Detailed information about the arterial lumen and wall can be obtained by MRA and can be used to support the diagnosis of large vessel vasculitis [43], with a relatively high sensitivity and specificity.

Positron emission tomography (PET) and computed tomography angiography can be useful in suspected vasculitis such as GCA [34, 48]. EULAR only recommends the use of PET to detect mural inflammation in extracranial arteries and does not recommend it for cranial arteritis [43]. A combination of symptoms, clinical findings, laboratory data, and imaging is used to diagnose GCA. The ACR's GCA criteria were formulated to differentiate GCA from other vasculitides and should not be confused with clinical diagnostic criteria [51].

Differential Diagnosis

Due to considerable overlap in the clinical features and investigations, the three entities considered in the differential diagnosis of GCA are PMR, MMS, and Takayasu arteritis. A summary of the comparisons of these four entities is given in Table 1.

Management

Corticosteroid therapy is the treatment of choice for GCA, due to its long-term success, although newer drugs are being currently studied. One of the main goals of steroid therapy is to prevent blindness [78]. Some studies have shown that hypoechoic halo disappears within 3 weeks with tapered doses of corticosteroids [44, 47], while others show evidence of continuing arteritis after a long course of steroid therapy [79, 80]. Daily dosage of 40–60 mg of prednisone is prescribed as a single or divided dose for 2–4 weeks [41, 67], with the progress being evaluated with subsequent ESR and CRP levels. However, a better assessment can be made with the level of interleukin-6 after 4 weeks, following which the dosage can be titrated [67, 81–83]. Abrupt exacerbation of the symptoms of GCA is seen in 30 to 50% of the cases even with corticosteroid therapy [39, 67, 81, 84]. Recently, tocilizumab has been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to be used in combination with a tapered dose of corticosteroids, and not as a monotherapy [85]. There is no established treatment protocol regarding the dosage, route of drug administration, and period of the drug therapy; however, preventing blindness and stroke should be the primary objective [10, 86].

Complications

Stroke and blindness are the most common and serious complications of GCA [41, 70, 74, 87], along with thoracic aortic aneurysm and cardiovascular complications [88, 89]. Other significant complications of GCA include cranial aneurysm, posterior stroke, cognitive impairment, seizures, and mood fluctuations [34, 90, 91]. Life-threatening extracranial manifestations of GCA are intestinal infarction, pulmonary embolism, renal insufficiency, transient ischemic attacks, and carotid artery dissection [34, 38, 92–99]. Aortic complications reported are aortic aneurysm or dissection (mainly the ascending aorta), and aortic arch syndrome [34, 35, 100–104]. Lingual artery ischemia can cause tongue claudication which results in tongue blanching and bluish hue and may even lead to necrosis and gangrene formation [39, 44, 105]. More rare complications of GCA include lip necrosis [106]. Complications of GCA secondary to treatment with drugs such as steroids including methyl prednisone include ischemic cerebrovascular accidents [90, 92, 107], cardiac arrhythmias, infection, epileptic attacks, tissue necrosis, anaphylaxis, hyperglycemia, and gastric disturbances [40, 108–110]. Flaring up of the GCA can also occur due to low doses of corticosteroids [39]. Drugs such as tocilizumab used to treat GCA may cause adverse effects including myocardial infarction, stroke, organ failure, and infections [111].

Case Discussion in the Context of the Literature

Onset

The sudden onset of headache reported in this patient is consistent with the literature [18, 19••, 22, 24, 25]. Recently published reviews have mentioned the new onset or changed

Table 1 Comparison of the differential diagnoses of GCA

Feature	GCA	PMR	MMS	Takayasu arteritis
Etiology	- Unknown [18, 42] - Autoimmune?	- Idiopathic [19••]	- Unknown - Prolonged corticosteroid treatment? - The role of systemic conditions such as CKD? [22]	- Unknown etiology [52]
Histopathology	- Multinucleated giant cells - Inflammatory infiltration of layers of vessel wall - Thickening of tunica intima - Changes in the elastic laminae [18]	- N/A (diagnosed clinically) - Histopathology of the synovium shows macrophages and CD4 T cells	-Tunica media calcifications - Atherosclerosis - Changes in the internal elastic lamina - Elastic fiber destruction - Giant cells - Hyper mineralization of internal elastic lamina - Calcium deposits in elastic lamina [53]	- Micro-abscess, artery fibrosis, multinucleated giant cells, granulomas - Changes in tunica media: lymphoplasmacytic infiltration [54]
Pathogenesis	- Abnormal T cell activation - Unknown trigger - Abnormal repair and subsequent thickening of the tunica media - Activation of macrophages to become giant cells - Macrophage infiltration of tunica media [18, 28, 42, 55]	- Unknown - Age-related immune alterations? [56]	- Pathological stimulation of osteogenesis - Protein CD73 deficiency - Significant reduction in inhibitors of mineralization [53]	- Autoimmune - Activation of dendritic cells T cells recruitment to the vessel wall: granuloma formation [52]
Age prevalence	-> 50 years	-> 50 years [57]	- Middle age	- 18–40 years [14, 15, 25, 58]
Gender ratio (female:male)	- 2:1 [14, 17, 18]	- 2:1 [57]	- 3:2 [53]	- 9:1 [58]
Site predilection	- Branches of the vertebral and carotid arteries; temporal artery [58]	- Shoulders, hip girdles, neck, and torso [15, 24]	- Lower extremities, viscera, muscles, heart, and the orofacial areas - Medium-sized arteries including cerebral, visceral, femoral, coronary, infraorbital, and facial artery	- Aorta and its major branches [58]
Racial predilection	- Northern European descent [37]	- Caucasians [57]	- None reported	- Asian [59]
Genetic predilection	- HLA class II genes, PLG and P4HA2 genes [18]	- HLA-DRB1 [56, 57] - HLA-DRB1*04:01 allele [57]	- VKORC1, NT5E, ABCC6 [53]	- HLA-B*52 allele [60]
Associated diseases/comorbidities	- PMR - Diabetes mellitus - Hypertension - Cataract - Aortic aneurysm/dissection - Peptic ulcer disease - Cardiovascular disease - Glaucoma - Osteoporosis [18, 22]	- GCA [56] - Cardiovascular disease/ cardiovascular events, osteoporosis	- Coronary artery disease - Hyperparathyroidism - Cardiovascular disease - Systemic lupus erythematosus - End-stage renal disease and hemodialysis - Type II diabetes mellitus - Atherosclerosis - Hypervitaminosis D - Kawasaki disease [22]	- Inflammatory bowel disease - Ankylosing spondylitis [52] - Behcet's syndrome [61]

Table 1 (continued)

Feature	GCA	PMR	MMS	Takayasu arteritis
Clinical features	- Headache - Jaw claudication - Facial pain - Scalp tenderness - Local and systemic myalgia - Loss of vision - Constitutional symptoms (fever, fatigue, malaise, weight loss) [18, 22, 25]	- Malaise - Muscle pain - Stiffness of neck, shoulders, upper arms, and pelvic girdle predominantly in morning [32, 55]	- Jaw claudication with chewing - Feeble pulse - Visual changes - Headache - Hard consistency of artery - Scalp tenderness - Photophobia, phonophobia [22, 53]	- Headache - Hypertension - Aortic stenosis - Aneurysm - Epilepsy, stroke - Visual loss - Gastrointestinal bleeding - Renal arterial stenosis - Claudication of extremities [52, 62]
Radiographic features/imaging	- Color Doppler ultrasound "halo sign" [42, 47]	- Ultrasonography; PET scan subdeltoid bursitis, biceps tenosynovitis, trochanteric bursitis, glenohumeral, and coxofemoral synovitis [19••, 57]	- Ultrasound Echogenic granules in the layers of the arterial walls - Orthopantomogram - Temporal artery calcification - Railroad track, pipeline, tram track, rail tracking, tram line patterns - Calcified facial, internal carotid, lingual, and infraorbital arteries [22, 53]	- Color Doppler ultrasound "macaroni sign" [63] - CT angiography "ring enhancement" - MRA string sign [64]
Management	- Immunosuppressants - Steroids [65]	Glucocorticoids DMARD [66] Supportive therapy: calcium, vitamin D [67]	- Phosphate binders - Treatment of associated conditions - Calcimimetics - Surgical management of calciphylaxis - Magnesium - Vitamin K - Aldosterone antagonists - Vitamin D [53]	Corticosteroids, immunosuppressive agents [68] Anti-TNF inhibitors (etanercept and infliximab) DMARDs [69] Angioplasty or stent graft replacement, bypass surgery [68]
Complications	- Vision loss - Aortic aneurysms - Stroke [70]	- Cardiovascular disease [71] 29,589,402 GCA [72]	- Coronary artery disease - Stroke - Thrombus formation - Amputation - Increased pulse pressure - Cardiovascular mortality - Systolic hypertension - Left ventricular hypertrophy - Ischemic bowel - Loss of vision [53]	Stroke, cardiovascular diseases, atherosclerosis osteoporosis [73] (complications of the treatment or disease itself)
Prognosis	Predictors of poor prognosis: - Cerebrovascular and cardiovascular involvement - Infection - Aortic complications [74]	- Active disease without serious complications [75]	Factors predicting poor prognosis: - Chronic kidney disease - Diabetic nephropathy - Patients undergoing hemodialysis [76]	Predictors of poor prognosis: Cardiovascular complications, retinopathy, renovascular hypertension [77]

pattern of the headache in a middle-aged individual as "prompting concern" for GCA [15, 94]. The periauricular pain has been variably reported as slow or acute [112, 113]. Similar to this patient's slow onset neck pain, case reports have previously been published [7, 41, 114]. Jaw claudication has also been reported in previous cases [6, 14, 19••, 24].

Location

Temporal pain reported by our patient has been consistent with location in the existing GCA literature [114]. However, the bilaterality of the headache is rather unusual [114]. Similar to our patient case, there have been reports of relatively rapid loss of vision in the second eye following the first. The patient also complains of peri-auricular and temporomandibular joint pain, which is also in accordance with previously published reports [7, 18, 22, 25]. The neck and arm pain experienced by our patient was found in other articles [11, 62, 114, 115].

Chronicity

The bilateral temporal pain reported as acute, and the neck and arm pain perceived as chronic, is consistent with established literature [55, 116].

Frequency

The reported "continuous" frequency of temporal pain, "intermittent" TMJ and ear pain, and "multiple episodes" of neck and arm pain have appeared in the published literature [24, 37, 113].

Duration

The long duration of the temporal pain, the shorter nature of the TMJ and ear pain, and the varied nature of neck and arm pain reported in this case were also reported previously [15, 37, 116].

Intensity

The temporal pain intensity of five to six, TMJ and ear pain intensity of four to five, and neck pain of three to four on a VAS scale are consistent with the literature [21].

Quality

The "throbbing and pulsating" quality of the temporal pain [117, 118] and "aching nature" of TMJ, neck, and arm pain have been reported [117, 119].

Temporal Characteristics

The chronic progressively worsening nature of the bilateral temporal pain, the non-progressive nature of the neck, arm, TMJ, and ear pain has been described previously [119].

Associated Features

The sudden loss of vision observed in this patient (both complete and partial) has been reported in the literature [120].

Radiation/Referral

Pain radiating from head and neck to the arm and shoulders has been reported in GCA cases [121].

Time Elapsed from Symptom Onset to Diagnosis

The time elapsed between the first appearance of symptoms to diagnosis in our current case (2 months) is consistent with the literature [20, 21, 122]. The time elapsed of approximately 2 to 3 months from onset of symptoms to the first vision loss, and the second episode of acute loss of vision within 2 weeks of the first episode, is consistent with the known literature [15, 17, 40].

Response to Past Treatment

The response of the patient's condition to high doses of systemic corticosteroids (non-progression of further vision loss) goes along with the known literature [44, 47, 78].

Aggravating Factors

Jaw claudication and neck pain aggravated with function have been reported [18, 39].

Relieving Factors

The TMJ, ear, and the neck and radiating arm pain relieved by rest have been reported in previous literature [18, 39]. The unrelenting nature of the temporal pain has also been reported [118].

Table 2 Comparison of the literature with the current case of GCA

Features	References	Literature	Current case
Constitutional symptoms: malaise, anorexia, fever, night sweats, depression, weight loss		Present	Absent
Local and systemic myalgia	[119]	Present	Present
Headache in the temporal area	[18, 62]	Present	Present
Scalp tenderness	[14, 18]	Present	Present
Pain in the TMJ and associated structures/ "jaw claudication"	[119, 126]	Present	Present
Facial pain	[112]	Present	Present
Pathologic changes (pain/claudication, color changes, gangrene) in the tongue secondary to the involvement of lingual artery	[18]	Present	Absent
Pain in the gingiva and teeth	[31]	Present	Absent
Throat pain and dysphagia	[31]	Present	Absent
Loss of vision	[126]	Present	Present
Features secondary to involvement of specific artery (redness, pain, swelling, tenderness to palpation, neck pain)	[4•, 41]	Present	Present
Ischemia and subsequent necrosis of the anatomic structures perfused by the affected artery	[127]	Present	Absent
Shoulder pain	[115]	Present	Present
Intermittent limb claudication	[4•, 127]	Present	Present
Other artery involvement	[122]	Present	Absent
High C-reactive protein (CRP)	[65, 98, 125]	Present	Present
High erythrocyte sedimentation rate (ESR)	[65, 98, 125]	Present	Present
MRA "beaded appearance" of the artery	[18]	Present	Absent
Halo sign on an ultrasound	[42]	Present	Present

Association with Sleep

Association of GCA with disturbed sleep, reduced quality of sleep, and waking patient from sleep, observed in our current patient is consistent with existing literature [7, 123, 124]. An interesting feature noted by certain authors is the discovery of the loss of vision when patients wake up in the morning, and this has been proposed to be attributed to the sleep-related reduction in the blood pressure and the ensuing optic ischemia [124].

Other Features

The laboratory test features in the patient, of leukocytosis, neutrophilia, thrombocytosis, elevated ESR, and CRP, appear in the known literature [42, 55, 65, 98, 125]. The comorbidity of type II diabetes and symptoms of PMR that appeared in this patient have been previously described [18, 88].

A comparison of the features of the current case with those that appear in the literature is summarized in Table 2.

Conclusion and Clinical Pearls

GCA is a chronic inflammatory disease characterized by vasculitis of the large and medium arteries. Headache, jaw claudication, and visual symptoms may be few of the earlier presenting symptoms of GCA. To prevent life-altering complications such as permanent blindness, prompt aggressive therapy is necessary once the differential diagnosis of GCA is established. Guidelines such as ACR and EULAR should be adhered in the management of the condition.

Author Contribution Davis C Thomas and Priyanka Kodaganallur Pitchumani are first and last authors respectively, who are responsible for inception of the project, literature search, major write-up, and supervising the project. Blessy C Mathai, Anjali Ravi, Surabhi Chhabra, and Upasana Lingaiah performed literature search, contributed to case work-up and write-up, and aided in manuscript type up. Blessy C Mathai, Surabhi Chhabra, Priyanka Kodaganallur Pitchumani, and Davis C Thomas contributed to the custom diagrams. Prisly Thomas and Deep P Pillai are responsible for case work-up, management of the patient (treating physicians), literature search, processing and sharing of biopsy, and imaging reports. Dahlia Joseph contributed to case work-up, literature search, and analysis of biopsy reports.

Data Availability Data including the patient's history, test results, and clinical notes is available within the article.

Declarations

Ethics Approval N/A; critical literature review.

Consent to Participate Informed consent was obtained from the patient for participation in this case report and for submission to the journal. No patient identifiers appear on any section of the manuscript.

Consent to Publish Written informed consent was obtained from the patient for publication of this case report.

Conflict of Interest Davis C Thomas, Prisly Thomas, Deep P Pillai, Dahlia Joseph, Upasana Lingaiah, Blessy C Mathai, Anjali Ravi, Surabhi Chhabra, and Priyanka Kodaganallur Pitchumani declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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• Of importance
•• Of major importance

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