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Giant-Cell Arteritis: unusual presentations

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Abstract

Introduction: Giant Cell arteritis (GCA) is a vasculitis that may present itself with a large range of symptoms and clinical signs. In order to better understand how to promptly recognize and treat this illness, which may lead to complications, we present three cases with unusual symptoms.

Cases: The first case is an 81-year-old man with short daily nocturnal headache that awoke him from sleep between 3 and 5 AM, with no autonomic symptoms. A doppler study and a temporal artery biopsy were compatible with GCA. This appears to be the first reported case of a Giant Cell Arteritis patient presenting with a hypnic headache. The second case is of a 63-year-old woman presenting with right sided ptosis and diplopia following the start of an intense headache. Although the headache subsided with initiation of steroids, the incomplete third nerve palsy became permanent. This case illustrates the importance of investigating ophthalmic symptoms for the possibility of Giant Cell Arteritis even when that symptom is not loss of visual acuity. The third case is a 77-year-old man presenting with symptoms consistent with a stroke, such as left sided weakness, confusion, and facial asymmetry. Etiological investigation showed an occlusion of the vertebral artery due to inflammation consistent with Giant Cell Arteritis. Such a case serves as a reminder not to discount Giant Cell Arteritis as a possible cause of stroke.

Conclusion: The aforementioned cases should be of note to any clinician practicing in primary care or an emergency setting. Quick and accurate recognition and recalling of potential presentations of Giant Cell Arteritis may allow the prompt initiation of therapy and the avoidance of complications, be they morbidity or mortality.

Keywords: Giant Cell Arteritis; Clinical Presentation; Headache; Ischemic; Review

Resumo

Introdução: A Arterite de Células Gigantes (GCA) é uma vasculite que se pode apresentar numa grande variedade de sintomas e sinais. De forma a compreender como reconhecer e tratar rapidamente esta doença, que pode levar a complicações, apresentamos três casos com sintomas incomuns.

Casos: O primeiro caso trata-se de um homem de 81 anos com curta cefaleia noturna diária que o acordava entre as 3 e 5 da manhã, sem sintomas autonómicos. Um estudo doppler e uma biópsia da artéria temporal foi compatível com Arterite de Células Gigantes. Este aparenta ser primeiro caso reportado de Arterite de Células Gigantes manifestando-se como cefaleia hípnica. O segundo caso é de uma mulher de 63 anos que se apresenta com ptose direita e diplopia após o início de uma cefaleia intensa. Embora a cefaleia tenha desaparecido com o início de corticoterapia, a parésia incompleta do terceiro par craniano tornou-se permanente. Este caso ilustra a importância de se investigar a possibilidade de Arterite de Células Gigantes em sintomas oftálmicos, mesmo quando não se trata de diminuição da acuidade visual. O terceiro caso relata a apresentação de um homem de 77 anos com sintomas consistentes com Acidente Vascular Cerebral, tais como hemiparesia esquerda, confusão e assimetria facial. A investigação etiológica mostrou oclusão da artéria vertebral devido a Arterite de Células Gigantes. Tal caso deve servir como aviso para não descartar Arterite de Células Gigantes como potencial causa de Acidente Vascular Cerebral.

Conclusão: Os casos supracitados devem ser tidos em conta por qualquer clínico que exerça num contexto de cuidados primários ou emergência. O reconhecimento rápido e correto de possíveis apresentações de Arterite de Células Gigantes permitirá a iniciação rápida de terapia e evitará as suas complicações, sejam elas de morbilidade ou mortalidade.

Palavras-chave: Arterite de Células Gigantes; Apresentação clínica; Cefaleia; Isquémico; Revisão

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Introduction

Giant-Cell Arteritis, Temporal Arteritis or Horton's disease is a vasculitis, usually granulomatous, that affects large and medium-sized vessels. Such vessels are the aorta and its branches, especially branches of the carotid and vertebral arteries. The vessel most often involved is the temporal artery, from which the disease gets its name (Jennette, 2013).

It is rare under fifty years of age, with a peak incidence between seventy and eighty years of age, and is two to three times more frequent in females (Smith & Swanson, 2014). The pooled incidence is 10 cases per 100.000 people over 50 years of age (Li et al., 2021). The incidence of Giant Cell Arteritis is higher in northern European populations than their southern European counterparts. It also appears to be lower in non-Caucasian populations (Sharma et al., 2020).

Although its pathogenesis is unknown, the role of genetic predisposition has been suggested. The genetic predisposition of Giant Cell Arteritis is carried in MHC class II molecules, mainly HLA-DRB1*04 (although HLA-DRB1*01 appears to be protective) (Carmona et al., 2014)(Mackie et al., 2015).

It's clinical presentation and onset are varied. Giant Cell Arteritis may begin abruptly in close to 20% of cases, or insidiously with constitutional symptoms. A new onset unilateral (temporal) headache is the most reported symptom (Younger, 2019). Other common symptoms are discussed further in the discussion.

If Giant Cell Arteritis is suspected, inflammatory markers (especially erythrocyte sedimentation rate/ESR) are the initial laboratory test. (Thomas et al., 2022). The diagnosis of Giant Cell Arteritis is based on temporal artery biopsy with characteristic transmural inflammatory infiltrate or ultrasound with doppler of the temporal artery with characteristic "halo sign" (Ponte et al., 2022). Doppler ultrasound has become a method of choice in the diagnosis of this condition, as it is quick and non-invasive with good sensitivity and very high specificity (close to 95%) (Nakajima et al., 2023). Discussion of sensitivity and diagnostic difficulties such as "skip lesion" on biopsy are outside the scope of this work.

Nevertheless, diagnostics should not delay prompt treatment with high-dose glucocorticoids (Hellmich et al., 2020). Although prognosis is good if treatment is quickly initiated, untreated Giant Cell Arteritis carries with it a high risk of complications, as discussed later.

An association with polymyalgia rheumatica is well described, with approximately 50% of Giant Cell Arteritis patients presenting with the disease (Weyand & Goronzy, 2014).

Due to high morbidity in untreated Giant Cell Arteritis, it is important to recognize the varied clinical pictures it might present as. The most feared complication that may result from not treating Giant Cell Arteritis is loss of vision. Though patients typically present with loss of vision in one eye, and later the other eye may be affected, bilateral anterior or posterior ischemic optic neuropathy can be the initial symptom (Tian et al., 2018)(Albarrak et al., 2018). Although clinicians are well aware of this risk, other complications from non-treatment must be recognized and promptly addressed. Rare manifestations must be studied and reported.

In order to better a clinician's understanding of rare, but nevertheless relevant, manifestations that may help to achieve a prompt diagnosis, we report on three cases with unusual or confounding presenting symptoms. The patients' clinical history is reported objectively while further ideas on the clinical case are considered in the discussion.

Patients and Methods

Cases were selected from patients admitted to the Neurology Department or observed in the outpatient headache clinic of Hospital de Santa Maria, a large tertiary University hospital in Lisbon, Portugal.

A literature search was the conducted to assess other rare or otherwise unusual inaugural manifestations of Giant Cell Arteritis.

Case reports

Case 1:

An 81-year-old man presented to the outpatient headache clinic due to a 2-month history of daily headache between 3 and 5 AM. The pain was described as 10/10 in intensity and localized to the left temporal region. These painful crises lasted for 30 min and were unresponsive to acetaminophen and coffee, but there was relief when the patient got out of bed. During the day the patient experienced no symptoms. The patient also complained of tiredness, anorexia, weight loss and jaw claudication when opening the mouth and chewing.

The patient had a personal history of essential hypertension and diabetes mellitus. Surgical, and familial history were unremarkable.

On physical examination there was no ptosis, miosis, or lacrimation. There was no hardness of the superficial temporal arteries or pulse abnormalities.

The remainder of the physical examination, including the neurological exam, was normal.

Laboratory workup with full blood count was unremarkable, to note a slightly increased Erythrocyte Sedimentation Rate (ERS) = 39 mm/h and a borderline normal C Reactive Protein (CRP) = 0.53 mg/dL.

A CT scan of the Head showed no abnormalities, and a Doppler Ultrasound (US) of the right temporal artery suggested GCA.

The diagnosis of GCA was assumed, and the patient was started on glucocorticoids (prednisolone) and the dosage was tapered.

The patient later returned to the outpatient clinic for revaluation. He mentioned that the daily waking between 3 and 5 AM persisted, but that there was no pain when he awoke.

A biopsy specimen of the right temporal artery was obtained that was compatible with the diagnostic assumption.

The patient’s symptoms remained controlled with a steroid based regimen, tapered to 5 mg prednisolone. The patient refused a steroid-sparing regimen with methotrexate.

Case 2:

A 63-year-old woman presented to the emergency department with a 3-week history of ptosis and diplopia. The condition began as a progressively increasing left occipital headache for 2 hours, before becoming a holocephalic headache. The patient denied feeling nauseous, vomiting, or losing consciousness. The following day the patient noticed right sided ptosis. The patient also denied changes in visual acuity and jaw claudication.

On admission, right sided ptosis was observed, and the patient complained of diplopia with levoversion of the eyes. The pupils were isochoric, and the pupillary light reflex exam showed no abnormalities. No exophthalmia was observed. No other abnormalities were observed.

The diagnosis of incomplete palsy of the right cranial nerve III was assumed.

The patient had a history of essential hypertension, dyslipidaemia, goiter with subclinical hypothyroidism, asthma, and cervical hernias. Current medications included: Rosuvastatin, Valsartan + Hydrochlorothiazide, Tiotropium Bromide and Fluticasone + Salmeterol.

The patient's laboratory workup with full blood count was normal with the sole exception of an elevated ESR of 49 mm/hr, and CRP was normal. An EKG was performed and was normal.

The patient was then admitted to the neurovascular unit of the hospital for a workup of potential causes. The same day the patient was submitted to a head MRI which showed "slight pattern of leukoencephalopathy preferably involving bifrontal white matter. No evidence of subarachnoid signal abnormalities. Empty sella turca. Hypoplasia of the P1 segment of the posterior cerebral artery."

Other diagnostic exams performed during this admission included lumbar puncture with cerebral spinal fluid analysis which showed no deviations from normal and a cerebral angiography which also showed no abnormalities. Duplex ultrasound of the temporal artery showed: "normal velocity of blood flux, no halo sign".

No other laboratory tests performed, including VDRL, APS antibodies, thyroid function, and ANA antibodies, were abnormal.

After 7 days in hospital, the patient was discharged being capable of self-care, with indication to continue the diagnostic workup in an outpatient setting. At time of discharge ESR was 62 mm/h, CRP was normal.

While an outpatient, a CT scan of the eyes and an Electromyography were normal.

For two years, the patients suffered from the aforementioned palsy of the cranial nerve III. Eventually, the patient also developed dysfunction of the Temporomandibular Joint and began complaining of pain when chewing and at palpation of the temporal arteries. The diagnosis of Giant Cell Arteritis was assumed, the patient started on prednisolone 5mg, and a biopsy of the temporal arteries was arranged. Although the biopsy was negative, the patient's pain improved considerably with the corticosteroids (on a higher 10mg dosage).

Three years later, the patient was once again submitted to a Doppler Ultrasound. On this occasion, a typical halo of the temporal artery was seen, and the diagnosis established.

A histopathological diagnosis has never been established.

The patient switched to a steroid sparing regimen (MTX + Folic acid) but later interrupted methotrexate due to pulmonary fibrosis. As the patient had a familial history of pulmonary fibrosis (the patient's mother) the causal relation was put into question. Azathioprine was started.

The patient continued to suffer from occasional crisis, in which the ptosis became more noticeable and distressing for the patient. On those occasions, the typical halo on temporal doppler ultrasound was no longer observed.

Nevertheless, the patient remained stable with steroids and azathioprine.

Case 3:

A 77-year-old man presented to the emergency department with a 1-hour history of nausea, dizziness, vomiting, diplopia, difficulty moving his right eye and stuttering. The symptoms began when the patient was walking his dog. The patient did not complain of weakness, loss of sensation, fever, thoracic pain, shortness of breath, headache, or jaw claudication. There was no loss of consciousness and no history of anomalous movements.

On admission, facial asymmetry was observed, as well as horizontal nystagmus. The Romberg test was positive.

The patient's personal, familial, and surgical history were of no interest.

Laboratory workup was unremarkable, with the exception of a CRP level of 3,58 mg/dL. A head CT scan showed: Chronic Microvascular Leukoencephalopathy".

Due to the patient's symptoms improving, he was discharged with advisement that neurological evaluation in an outpatient setting should be sought.

Three weeks later, the patient again presented to the emergency department due to worsening of the neurological symptoms. The patient was suffering from confusion with spatial disorientation and visual hallucinations. That day, he had begun not recognizing his wife and son.

There was a left-sided weakness, inability to keep his balance and falling frequently. The patient was also unable to hold objects with his left hand. Neither the patient nor the family reported the patient suffered from fever, cough, shortness of breath, nausea, or gastrointestinal tract symptoms in the last few days.

On admission, exuberant behaviour consistent with the associated visual and auditory hallucinations was observed. The neurological exam was as follows:

- Easily distractible but sometimes focused.
- Oriented to person. Knows his name, doesn't know his age. Disoriented to space and time.
- Immediate recall is preserved (3/3). Delayed recall affected (0/3).

- Acalculia.
- Isochoric pupils. Pupillary light reflex exam showed no abnormalities. No visual field defects on confrontation. No ophthalmic palsy, nystagmus, or diplopia.
- No facial asymmetry, symmetrical tongue protrusion.
- Pronator drift test positive in the upper left limb. Grade 3 muscular strength on all extremities.
- Finger-to-nose test shows left sided dysmetria.
- Hyperreflexia in the upper and lower limbs. Babinski sign bilaterally positive. Left-sided Hoffman sign present.

A new head CT scan showed worsening of the leukoencephalopathy bilaterally in the temporal and occipital white matter. Laboratory workup was normal besides an elevated CRP of 2,25 mg/dL.

A lumbar puncture was performed, which was normal besides an increase in proteins in the cerebrospinal fluid (69,8 mg/dL).

The patient was admitted to the neurology department for monitoring and etiological workup.

Since the diagnosis was acute cerebrovascular event, a neurovascular study was carried out, including duplex ultrasound of the carotid, vertebral and temporal arteries and transcranial doppler ultrasound.

- Carotid arteries duplex ultrasound documented diffuse thickening of arterial walls.
- Vertebral arteries duplex ultrasound showed a circumferential halo suggestive of inflammatory process in the left and right vertebral artery and a high resistance velocimetric pattern, suggestive of occlusion in the right vertebral artery.
- Transcranial doppler showed an increase in flow velocity in the MCA, ACA, and distal basilar artery suggestive of severe stenosis possibly associated with inflammatory process.
- Superficial Temporal Arteries: Halo sign present bilaterally, suggestive of severe inflammatory progress.

- Conclusion: Apparent occlusion of the right vertebral artery, leading to large involvement of the anterior and posterior intracranial circulation. Suggestive of vasculitis.

Temporal artery biopsy was then performed, which confirmed the diagnosis of Giant Cell Arteritis. A methylprednisolone pulse was started for 3 days, and then switched to prednisolone 1 mg/kg/day.

The patient was considered for Tocilizumab therapy (anti-IL-6R) due to the severity of the presentation, but as the IGRA was indeterminate it was delayed.

A physiotherapy regimen was started, with marked improvement before being discharged.

Discussion

The reported cases show that Giant Cell Arteritis can have a non-typical presentation besides its usual cluster of signs and symptoms.

The usual clinical picture of Giant Cell Arteritis may consist of insidious symptoms such as headache (68%), low-grade fever (42%), weight loss (50%), malaise (40%), and jaw claudication (45%) (Calamia & Hunder, 1980). The classic symptom of the disease is a temporal headache, with tenderness and induration of the temporal artery. Acutely, Giant Cell Arteritis can present with vision loss, as will be discussed shortly (Thomas et al., 2022).

Besides these typical symptoms, that often lead to diagnosis, that we have described, we will now focus on presentations that, being rare or leading to complications, are of interest to the physician.

The first case presented is an example of the need for a careful history taking and for an extensive differential diagnosis for a patient presenting with nocturnal headache. At first glance, the symptoms of the patient might be taken to be a case of Cluster headaches.

Cluster headaches are a type of trigeminal autonomic cephalalgias. This entity is characterized by attacks of severe strictly unilateral pain (orbital, supraorbital or temporal) lasting from 15 to 180 minutes and associated with autonomic symptoms (e.g., lacrimation, nasal congestion, miosis, etc.) (Olesen, 2018). Peak incidence for this disease is also between 20 years and 30 years of age (May et al., 2018). A survey from the United States of America of 1134 individuals diagnosed with cluster headache found that only 3% of respondents were diagnosed after 51 years of age (Rozen & Fishman, 2012). Although there have been some cases of cluster headache onset in the age range of this patient reported in the literature, no marked difference in clinical presentation when referring to autonomic symptoms has been observed (Zidverc-Trajkovic et al., 2014)(Manzoni et al., 2012).

However, since the patient never presented with autonomic symptoms and was much older than the age of peak incidence, alternative diagnosis must be considered. One such alternative is hypnic headaches.

Hypnic headaches, also known as alarm clock headaches, are frequently recurring headache attacks that happen only during sleep, causing wakening and not causing autonomic symptoms (Olesen, 2018). The typical attack averages 80 minutes and occurs on most, but not all, days of the month (Diener et al., 2012). Interestingly, during these attacks, patients may perform certain "purposeful" activities, such as reading or watching television. This differentiates these attacks from the marked agitation seen in cluster headache (Donnet & Lantéri-Minet, 2009). First described in 1988 in a group of 6 patients, mostly men in the seventh decade of life or beyond (Raskin, 1988). Through the decades, the original description was expanded to include unilateral forms (40% of such headaches) and longer duration (up to 3 hours). The male predominance initially suggested has not been confirmed, the majority of patients are female (de Simone et al., 2006)(Diener et al., 2012). More than a third of patients also described suffering at least once from migraine during their lives (Holle et al., 2013). The most commonly non-headache comorbidities are Hypertension and Obstructive Sleep Apnea, the latter being suggested as a potential mechanism for the disease. Nevertheless, polysomnography studies of hypnic headache patients have found no temporal link between drops in oxygen saturation and the attacks (Liang & Wang, 2014). Another proposed mechanism was due to the link between the onset of attacks and REM sleep (Lanteri-Minet, 2014), although newer evidence appears to suggest most attacks occur during NREM sleep (Holle et al., 2013).

This description could be compatible with the aforementioned patient. This appears to be the only Giant-Cell-Arteritis-associated headache presenting as a hypnic headache-like clinical course. So far, Migraines, Cluster Headaches, Hypnic headaches and paroxysmal hemicranias have also been described as related to sleep (Ferini-Strambi et al., 2019). In more broad terms, this appears to be the only headache in a Giant Cell Arteritis patient to be related to sleep. More research must be done into any potential

links between the inflammation seen in GCA and the pathophysiology of hypnic headaches.

The second patient allows us to have a discussion on its atypical presentation (right-sided ptosis/incomplete palsy of the third cranial nerve).

Palsy of the third cranial nerve must be thoroughly investigated. Life-threatening conditions associated with it, such as an enlarging aneurysm of the posterior communicating artery, cavernous sinus thrombosis or space occupying lesions must be excluded, as well as history taking to assess potential head trauma (Kung & van Stavern, 2015)(Ng et al., 2016). Although a rare presentation, an isolated third cranial nerve palsy has been previously documented in at least 7 cases in the last 10 years (Thurtell & Longmuir, 2014)(Hiraoka et al., 2021)(Martis et al., 2020)(Chan, 2021). Microvascular ischemia leading to demyelination of the oculomotor nerve has been proposed as the mechanism for this finding in GCA (Thurtell & Longmuir, 2014).

Other cranial nerve palsies have also been reported in GCA, such as the fourth cranial nerve (Tamhankar et al., 2013), the sixth cranial nerve (Margolin & Jeeva-Patel, 2021), including bilaterally (Jay & Nazarian, 1986), or even the facial nerve (Claeys et al., 2021). Eight nerve palsy has also been reported, presenting as sudden neurosensorial deafness (Kramer et al., 1988)(Jacob et al., 1990)(Wolfovitz et al., 1987).

Curiously, left recurrent laryngeal nerve palsy occurring due to compression (Ortner's syndrome) has also been reported in at least 2 cases (Daou et al., 2006)(Edrees, 2012). The mechanism of this presentation is the occurrence of aortic arch aneurysm, as will be discussed later.

An even rarer presentation of nerve palsies has also been reported with a single case report. A combined involvement of the abducens, right recurrent laryngeal and acoustic nerve was present in a patient (Fytili et al., 2015). It is worthy of note that this recurrent laryngeal nerve involvement was not due to aortic aneurysms (as that is only likely in the left recurrent laryngeal nerve due to its anatomic relation).

As previously discussed, one of the most feared complications of Giant Cell Arteritis is its effect on vision. Not the presence of diplopia or ptosis such as in this case, but the occurrence of sudden, complete, and irreversible blindness of (usually) one of the eyes. Sequential involvement of both eyes is rare (Kokloni et al., 2022). High dose oral or IV corticosteroids are the treatment regimens most commonly recommended to prevent the unaffected eye from suffering vision loss. Although effective, the clinician should be aware that the lack of progression is not a certainty, even weeks after the regimen is started (le Goueff et al., 2019).

Once vision loss has occurred, reversal or improvement of visual acuity is unlikely. Studies have suggested that the rate of visual recovery is 5%-34%, despite optimal high-dose IV corticosteroids (Danesh-Meyer et al., 2005). The cause of blindness in Giant Cell Arteritis is varied but understood. In a 60-year retrospective study, 8,2% of newly diagnosed cases of Giant Cell Arteritis had permanent vision loss, 85% of which were due to ischemic optic neuropathy. In the same cohort, 1,6% of patients had central retinal artery occlusion and 0,3% had cilioretinal artery occlusion. In a fifth of the patients, permanent vision loss occurred without constitutional symptoms (Chen et al., 2016). Another possible cause is involvement of the anterior segment of the eye, though it is rare (Shakir & Steuer, 2013)(Hayreh & Zimmerman, 2003).

The third case presented allows us to discuss another possible presentation of Giant Cell Arteritis, large vessel vascular involvement causing or mimicking a stroke.

Giant Cell Arteritis presents as a stroke in under 10% of cases, nearly all of them in the vertebrobasilar system (such as in this case) when compared to the carotid system (Gonzalez-Gay et al., 2009). Such involvement was the case in the described patient. Bilateral involvement of the vertebral arteries has also been described, with a very high mortality rate (Rüegg et al., 2003).

Perhaps expectedly, the presence of ophthalmic ischemic symptoms appears to be the greatest predictor of developing a stroke (De Boysson et al., 2017).

Patients may present with a large variety of symptoms, including lateral medullary syndrome (Wilkinson & Russell, 1972).

Conversely, Giant Cell Arteritis appears to cause less than 1% of all strokes (Wiszniewska et al., 2007). Patients that present with elevated inflammatory markers, anaemia, and multiple stenosis/occlusions of the vertebrobasilar system should be assessed for Giant Cell Arteritis with ultrasound of the temporal artery (Elhfnawy et al., 2020).

The mechanism of the stroke is usually attributed to high grade stenosis or occlusions of the aforementioned arteries (Zarar et al., 2014). It has also been suggested that some cases derive from embolization of thrombosed vessels damaged by the inflammatory process (Salvarani et al., 2006).

The mortality of Giant Cell Arteritis patients that develop strokes is high, particularly if intracranial arteries are affected. Such a presentation is rare, under 1% of patients develop these symptoms (Salvarani et al., 2006)(Sanchez-Alvarez et al., 2020). Although as previously discussed, affection of the vertebrobasilar system is more common, carotid artery affection appears to be more correlated with intracranial involvement (Oerding et al., 2021). A review of 47 cases of Giant Cell Arteritis with intracranial involvement reported the mortality as 53%, with 24% of the surviving patients having residual neurological deficits (Alsolaimani et al., 2016). It has been suggested that involvement of the intracranial arteries may represent a subset of Giant Cell Arteritis, characterized by worse clinical outcomes and failure to respond to monotherapy with corticosteroids (Salvarani et al., 2006)(Alsolaimani et al., 2016).

However, it's important to be aware that some cases described as "Giant Cell Arteritis with intracranial involvement" could, in actuality, be cases of Primary Central Nervous System Vasculitis (also known as Primary Angiitis of the Central Nervous System), a much rarer and seldom recognized disorder. This disease presents with symptoms similar to Giant Cell Arteritis with intracranial involvement such as headache and stroke, but has no extracranial inflammatory process (Godasi et al., 2022). The diagnostic criteria are, thus, the presence of unexplained neurological deficits, documentation of arteritic process in the CNS by angiography or biopsy, and no evidence of systemic vasculitis (Calabrese & Mallek, 1988). Pathologically, the diseases are also very similar, with multiple granulomas and inflammatory infiltrate in the affected arteries (Calabrese et al., 1997).

Another example of a Giant Cell Arteritis presenting as neurological symptoms besides headaches or stroke comes from a case of a 73-year-old man with cardiovascular risk factors presenting with unsteadiness and malaise, which was initially assumed to be benign paroxysmal positional vertigo. Further workup revealed bilateral vertebral artery narrowing, leading to encephalopathy. Temporal artery biopsy confirmed the diagnosis (Pauls et al., 2021).

Some cases have also been described of sensorineural hearing loss in patients with Giant Cell Arteritis (Shi & Malik, 2022). Although the pathogenesis in not completely understood, it is suggested that the cause is inflammatory involvement of the posterior circulation or terminal cochleovestibular vasculature (Junejo et al., 2017). More recently, it has been suggested that some amount of hearing loss is common in Giant Cell Arteritis (53% of patients) and that it has a good response to steroids (56% of patients with hearing loss improve) (Saravanan et al., 2019).

Concluding the discussion brought about by the clinical cases, what follows is a review of other rare or otherwise remarkable presentations of Giant Cell Arteritis.

The effect of Giant Cell arteritis on the cardiovascular system isn't limited to large and medium-sized vessels. Cardiac manifestations such as myocarditis have also been reported (Kushnir et al., 2016), sometimes as the inaugural symptom (Margolin & Jeeva-Patel, 2021). Involvement of the pericardium (pericarditis) is also a documented manifestation (Gomes de Pinho et al., 2022)(Fayyaz & Rehman, 2021). Likewise, Giant Cell Arteritis may also mimic an Acute Coronary Syndrome. The clinician should be mindful of the possibility of Giant Cell Arteritis as the cause of such a syndrome, especially in older patients who present with recurrent symptoms (Nair et al., 2012).

Giant Cell Arteritis is also the leading cause of inflammatory aortitis (Booth et al., 2013). A long-term follow-up of 48 Giant Cell Arteritis patients with aortic involvement found that only in one patient did aortic involvement precede the diagnosis of Giant Cell Arteritis. Most often, the involvement of the aorta was asymptomatic (Marie et al., 2009). However, initial presentation can also be dire. Such as when a 30-year-old woman with no diagnosis of Giant Cell Arteritis presented to the emergency department with

cardiogenic shock secondary to tamponade (Booth et al., 2013). This aortitis usually culminates in the formation of aneurysms (Crain et al., 2021).

In another study of 41 cases of Giant Cell Arteritis patients presenting with thoracic aorta aneurysm, 3 of the patients (approximately 7%) developed the aneurysm before Giant Cell Arteritis diagnosis and 16 of them eventually suffered from an aneurysm rupture (Evans et al., 1994).

The prevalence of aortic involvement in Giant Cell Arteritis is high but uncertain. The prevalence has been reported to range from 22% to 45%, but outliers exist (García-Martínez et al., 2008) (Nuenninghoff et al., 2003)(Kebed et al., 2018). Specifically looking at thoracic aorta aneurysms, the relative risk appears to be double in Giant Cell Arteritis patients when compared to the general population (Robson et al., 2015).

Interestingly, although this association exists, aortic involvement appears to be greater in patients following clinical remission and with lesser inflammation (lower acute phase reactants) (García-Martínez et al., 2008)(Nayar et al., 2013).

Besides aortic involvement, cervical and subclavian arterial involvement has also been reported, with prevalence inferior to 10%. Iliac artery involvement appears to be even rarer (<1%) (Nuenninghoff et al., 2003).

Such a broad potential of arterial involvement can confound diagnosis. That was the case of a 67-year-old woman who presented to her primary care physician with leg pain. As the symptoms were consistent with vascular claudication due to peripheral arterial disease (of which the most common cause is atherosclerosis). As such, that diagnosis was accepted until symptoms progressed in an unusual fashion, and the correct diagnosis was established, and treatment started (Kelly et al., 2017).

Cases of initial presentation as critical arm ischemia have also been reported (Ratschiller et al., 2018). The physician should not minimize the probability of dire acute presentations of Giant Cell Arteritis, especially in older patients. Accurate diagnosis and prompt treatment are a necessity.

Although these examples eventually progressed to more “classical” presentations, Giant Cell Arteritis can also be restricted to limb arteries. A review of 79 patients with elevated

ESR, negative temporal biopsy and affection of limb arteries found that in none of the patients were constitutional symptoms reported. Almost all of the patients had only involvement of upper limb arteries (85%) (Berti et al., 2015). Another review of 6212 patients with Giant Cell Arteritis found that only 19 had lower extremity vasculitis, most presenting with rapidly progressing limb claudication. Of the 19 patients, 5 ended up requiring revascularization therapy. Close to half never had cranial symptoms (Kermani et al., 2009).

The outcome of the cardiovascular manifestations of Giant Cell Arteritis should not be understated. Aortic aneurysms and acute myocardial infarctions have long been described as important causes of mortality in these patients (Säve-Söderbergh et al., 1986). Recent large-scale retrospective studies have analysed the mortality of Giant Cell Arteritis patients and found little effect (or even a small increase) on mean age of death. The presence of this condition appears, nevertheless, to affect the most likely cause of death. These patients appear to have an increased risk of dying of large-vessel and cardiovascular disease than the general population (Aouba et al., 2018) (Brekke et al., 2019). These findings underscore the importance of not discounting cardiovascular symptoms in older patients at risk of (or diagnosed with) Giant Cell Arteritis.

The capacity of Giant Cell Arteritis to affect varied arteries carries with it a boundless clinical picture of ischemic complications, be they presenting complications or otherwise. One such complication is tongue necrosis.

Giant cell arteritis may cause stenosis of the lingual artery, a branch of the external carotid artery. Patients may present with pain, edema, and erythema of the tongue, possibly developing into ischemia and necrosis of the tongue (Lobato-Berezo et al., 2014). Although tongue necrosis is a rare complication, with only a few dozen cases reported (De Siqueira Sobrinho et al., 2017), most present as unilateral ischemia. Owing to the great arterial supply of the tongue, bilateral infarctions are rare, but nevertheless exist. Such cases appear to number in the single digits (Zaragoza et al., 2015)(Zadik et al., 2011). Autopsy studies appear to show that a large percentage of patients have some lingual artery involvement, although not sufficient to clinically manifest (Goicochea et

al., 2007). An association with the use of ergotamine derivatives has been proposed as a potential cause of tongue necrosis in Giant Cell Arteritis (Pendás et al., 1994)(Bondenson et al., 1992). This hypothesis remains unconfirmed.

Scalp necrosis also is a rare but important complication of Giant Cell Arteritis, sometimes simultaneously with tongue necrosis (Jalaledin et al., 2022). The occurrence of scalp necrosis appears to be correlated with an increased risk of vision loss (Tsianakas et al., 2009).

Besides cranial or thoracic arteries, Giant Cell arteritis has also been described as affecting abdominal arteries. These cases are exceedingly rare. One such example is three cases describing Giant Cell Arteritis presenting as hepatitis, with markedly increased Liver Damage Tests (one patient had an ALP level of 3091 UI/L) (Riordan & Riordan, 2021). Cases have also been published describing involvement of arteries in the female reproductive system (mainly uterine arteries) (Butendieck et al., 2018) and the male reproductive system (presenting as orchitis)(Patil et al., 2017)(Osuorji et al., 2021). Another consideration when discussing the female reproductive system must be made for breast disease. Giant Cell Arteritis may also manifest itself primarily in the female breast (no cases of male breast affection appear to be described in the literature). No specific involvement has been described, so patients are usually misdiagnosed until biopsy of the lesion establishes the causative process as a vasculitis (Kadotani et al., 2010).

The association of Giant Cell Arteritis with Polymyalgia rheumatica is well established and outside the scope of this work.

Association with other autoimmune diseases has been suggested. One such example is Ulcerative Colitis (Sy et al., 2016). At least 6 patients have so far been as presenting with this association, the suggested link hinging on increased IL-12 production as the cause of both diseases (Sanges et al., 2016). Association of Giant Cell Arteritis with Crohn's

disease appears to be even rarer, with no statistically significant association so far reported (Bekele et al., 2021). However, one must not lose sight of the possibility of a spurious association, given the small number of case reports in relation to the large population of both diseases.

The inclusion of Giant Cell Arteritis as a large vessel vasculitis also raises a particular issue that should not be ignored. Although useful as a classification, the clinician should be aware that the distinction in the clinical diagnostic criteria between Giant Cell Arteritis and Takayasu arteritis (the other classically defined large vessel vasculitis) is more useful when comparing classical and common manifestations of both diseases (Grayson et al., 2022). A case that illustrates this point relates to a 56-year-old woman with limb claudication and reduced upper extremity pulse that presented to the emergency department (Zampeli et al., 2021). This patient scores 5 points in the 2022 ACR/EULAR Takayasu classification criteria, which places them in the classification that claims 99,2% specificity. Nevertheless, this patient was diagnosed with Giant Cell Arteritis when taking into account a positive temporal artery biopsy. That is not to say that this particular misdiagnosis is dire, as the recommended treatment regimen is similar (the mainstay is, as previously discussed, high dose glucocorticoids) (Hellmich et al., 2020).

Besides the presumptive vascular involvement described above, Giant Cell Arteritis can also manifest itself only with non-characteristic symptoms, such as fever of unknown origin (Calamia & Hunder, 1981) (Olopade et al., 1997), or chronic cough (Prabhavalkar et al., 2012).

To conclude, a brief discussion on laboratory evaluation of Giant Cell Arteritis. Although the limitations of definitive diagnosis have not been discussed (temporal artery halo sign on ultrasound or positive temporal artery biopsy)(Ponte et al., 2022), laboratory testing, especially Erythrocyte Sedimentation Rate and C Reactive Protein, is usually the first diagnostic test performed and evaluated by a physician. Both inflammatory markers are usually elevated. Although Erythrocyte Sedimentation Rate is more classically associated

with Giant Cell Arteritis, C Reactive Protein appears to be more sensitive (Kermani et al., 2012). In spite of its usefulness, consideration, or lack thereof, of Giant Cell Arteritis as a possible diagnosis due to laboratory values is not good practice. A considerable percentage of patients may present with normal Erythrocyte Sedimentation Rate (22,5% in one particular study) (Ellis & Ralston, 1983). Visual manifestations (including loss of vision) also appear to be more prevalent in patients with normal inflammatory markers (Martins et al., 2020), underlining the need for prompt diagnosis even with a normal laboratory evaluation.

Conclusion

We hope that these cases will contribute to the scientific literature on Giant Cell Arteritis, and that they will be useful to physicians while assessing patients.

Quick and accurate recognition and recalling of potential presentations of Giant Cell Arteritis may allow the prompt initiation of therapy and the avoidance of complications, be they morbidity or mortality.

Resumo em Português

Introdução: A Arterite de Células Gigantes (GCA) é uma vasculite que afeta vasos de grande ou médio calibre, podendo apresentar-se numa grande variedade de sintomas e sinais. É rara em doentes com menos de 50 anos de idade. A sua apresentação clínica é variada, podendo começar abruptamente ou de forma insidiosa. O sintoma mais comumente reportado é uma cefaleia unilateral temporal. O diagnóstico tem por base a clínica, avaliação laboratorial e imagiologia (Doppler) ou biópsia da artéria temporal. No entanto, o exames complementares de diagnóstico não devem atrasar o tratamento, dado que o protelar do mesmo se associa a complicações potencialmente desastrosas. A complicação mais característica da arterite de células gigantes é a perda permanente de visão súbita unilateral.

De forma a compreender como reconhecer e tratar rapidamente esta doença, que pode levar a complicações, apresentamos três casos com sintomas incomuns.

Métodos: Os casos clínicos foram selecionados de doentes tratados em internamento no serviço de Neurologia ou observados em consulta de cefaleia no Hospital de Santa Maria em Lisboa, Portugal. Foi realizada uma pesquisa bibliográfica de forma a encontrar manifestações raras inaugurais da Arterite de Células Gigantes.

Casos e Discussão: O primeiro caso trata-se de um homem de 81 anos com curta cefaleia noturna diária que o acordava entre as 3 e 5 da manhã, sem sintomas autonómicos. A dor era descrita como 10/10 de intensidade e localizada à região temporal esquerda. Estas crises duravam 30 minutos e não cediam a paracetamol. Durante o dia o doente não tinha sintomas. Outras queixas incluíam cansaço, anorexia, perda ponderal e claudicação mandibular. A história familiar não era relevante. Ao exame objetivo não existia ptose, miose, lacrimejo nem endurecimento ou alterações do pulso da artéria temporal superficial. O doente iniciou terapêutica com corticoides e um estudo doppler e biópsia da artéria temporal foram compatíveis com Arterite de Células Gigantes.

Inicialmente, este doente poderá ser erradamente considerado um doente com cefaleias em salvas. A presença de dor unilateral severa que dura entre 15 e 180 minutos seria consistente com essa hipótese diagnóstica. No entanto, a ausência de sintomas

autonómicos diminui a probabilidade da mesma, para além de ser um início tardio da doença, se se tratasse de cefaleias em salvas.

O caso descrito parece ter mais em comum com a apresentação de uma cefaleia hípnica. Ou seja, uma cefaleia recorrente que acontece apenas durante o sono, acordando o doente sem causar sintomas autonómicos. Curiosamente, durante estes ataques, os doentes tendem a realizar tarefas como ler ou ver televisão, ao invés do que acontece nos doentes com cefaleias em salvas, marcadamente agitados.

Este aparenta ser primeiro caso reportado de cefaleia associada a Arterite de Células Gigantes manifestando-se como cefaleia hípnica. É necessária mais investigação sobre potenciais mecanismos que clarifiquem a ligação entre a inflamação observável na Arterite de Células Gigantes e a fisiopatologia da cefaleia hípnica.

O segundo caso é de uma mulher de 63 anos que se apresenta com ptose direita e diplopia após o início de uma cefaleia intensa, negando, no entanto, alterações da acuidade visual. A investigação da causa da parésia do terceiro par não permitiu um diagnóstico no internamento nem em ambulatório. Apenas cincos anos após a doente ter alta do internamento, um estudo doppler da artéria temporal permitiu a visualização do "halo" típico de Arterite de células gigantes. Após iniciar corticoterapia, a cefaleia desapareceu. No entanto, a parésia incompleta do terceiro par craniano tornou-se permanente.

Embora seja uma apresentação rara, a parésia do terceiro par craniano já foi descrita em pelo menos 7 publicações nos últimos 10 anos. O mecanismo proposto na literatura para esta manifestação na Arterite de Células Gigantes é isquémia microvascular, resultando na desmielinização do nervo oculomotor. Outras parésias já descritas na Arterite de Células Gigantes incluem parésia do quarto par craniano, do sexto par e, para além dos nervos cranianos oculares, do nervo facial e vestibulococlear.

Embora este caso se trate de uma apresentação com sintomas oftálmicos, não se trata de um caso que relata uma das mais importantes complicações da Arterite de Células Gigantes. A referida complicação é a ocorrência de cegueira súbita, completa e irreversível, normalmente unilateralmente. A instituição rápida de corticoterapia visa em parte evitar esta complicação. No entanto deve ser compreendido que a doença

pode progredir mesmo sob corticoterapia, inclusive semanas após o início da terapêutica.

Assim que a perda de visão se instalou, a mesma é normalmente irreversível. A taxa de recuperação da acuidade visual está estimada entre 5% e 34%, sob corticoterapia em altas doses. A maioria da perda de visão ocorre devido a neuropatia isquémica ótica, sendo uma percentagem reduzida dos casos atribuível a oclusão da artéria central da retina ou oclusão de outros vasos.

Este caso ilustra a importância de se investigar a possibilidade de Arterite de Células Gigantes em sintomas oftálmicos, mesmo quando não se trata de diminuição da acuidade visual.

O terceiro caso relata a apresentação de um homem de 77 anos com náuseas, tonturas, diplopia e gaguez. A TC crânio-encefálica não mostrou alterações para além de leucoencefalopatia microvascular crónica. O doente teve alta para o domicílio, devido a melhoria sintomática, regressando três semanas depois. Na segunda ocasião que recorreu ao serviço de urgência, o doente apresentava também hemiparesia esquerda, assimetria facial e alucinações visuais para além dos sintomas da primeira apresentação. A investigação etiológica inicial (TC crânio encefálica, avaliação laboratorial e punção lombar) não permitiu a obtenção de um diagnóstico. O doente ficou internado, realizando um estudo neurovascular. O estudo doppler dos vasos do pescoço mostrou oclusão da artéria vertebral direita com "halo" característico de Arterite de Células Gigantes. O mesmo sinal ecográfico foi observado bilateralmente nas artérias temporais superficiais. A sintomatologia do doente diminui após se instituir corticoterapia.

A Arterite de células gigantes apresenta-se como Acidente Vascular Cerebral em menos de 10% dos casos, quase todos envolvendo o sistema vertebrobasilar (tal como descrito neste doente). Não obstante, menos de 1% dos casos de AVC aparentam ser causados por Arterite de Células Gigantes. É recomendado que doentes que se apresentem com AVC e parâmetros inflamatórios elevados, anemia e múltiplas oclusões do sistema vertebrobasilar devem ser avaliadas com vista à possibilidade de serem diagnosticadas com Arterite de Células Gigantes.

A mortalidade destes doentes é elevada, dessa forma, este caso deve servir como aviso para não descartar Arterite de Células Gigantes como potencial causa de Acidente Vascular Cerebral.

É também digno de nota a grande variedade de manifestações da Arterite de Células Gigantes que se estendem para lá da cabeça e pescoço.

Uma dessas manifestações é a afeção do sistema cardiovascular, quer seja sob a forma de miocardite, pericardite, síndrome coronária aguda, aortite ou doença arterial periférica. Esta variedade pode ser, inclusive, responsável pela dificuldade na distinção entre Arterite de Células Gigantes e Arterite de Takayasu. Pois a Arterite de Células Gigantes pode manifestar-se exclusivamente com claudicação vascular e redução de pulsos nas extremidades superiores. Nestas circunstâncias, o recurso a meios de diagnostico como a ecografia doppler ou a biópsia tornam-se imprescindíveis.

Podem ainda ocorrer manifestações tais como necrose da língua, do couro cabeludo ou até do sistema reprodutivo masculino e feminino.

Conclusão: Os casos supracitados devem ser tidos em conta por qualquer clínico que exerça num contexto de cuidados primários ou emergência. O reconhecimento rápido e correto de possíveis apresentações de Arterite de Células Gigantes permitirá a iniciação rápida de terapia e evitará as suas complicações, sejam elas de morbilidade ou mortalidade.

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