A giant deception: jaw pain and headache following routine dental extraction

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CLINICAL PRESENTATION

A 56-year-old Caucasian woman presented with a 4-week history of worsening left-side jaw pain and headache after a routine dental extraction in a general dental practice. The lower left first permanent molar had been extracted because of an unrestorable carious lesion. The extraction had been straightforward, without any immediate complication. Over the coming days, the patient developed gradual-onset left-side pain and headache, radiating from the angle of the left mandible upwards to her left temple. The pain was episodic and aching in nature, occasionally disappearing completely before returning again. The patient described exquisite tenderness of the left jaw and left scalp at the times of her headaches. She denied any history consistent with jaw claudication.

The patient's symptoms persisted and gradually got worse. She began to feel fatigued and described anorexia and vague abdominal discomfort. Strangely, she also reported that her arms became cold when her headaches occurred. She denied any visual symptoms at any stage. Eventually, she presented to the emergency department because of unresolving severe headache and subjective fevers at home.

The patient's past medical history was unremarkable. Her only medication was a selective serotonin reuptake inhibitor. She had undergone a diagnostic laparoscopy many years ago. She lived at home with her partner and 11-year-old daughter. She did not drink alcohol and smoked 10 cigarettes per day.

On arrival, her vital signs were normal. On physical examination, she was noted to be pale. There was no trismus, with normal 3-finger mouth opening, and no palpable submental, submandibular, or cervical chain lymphadenopathy. The extraction site of the lower left molar tooth appeared to be healing well, with no evidence of alveolar osteitis and no intraoral collection, draining sinus, or discharge. The left-side muscles of mastication, particularly the left masseter and left temporalis muscles, were exquisitely tender to palpation. There was left-side intra-articular disk displacement with reduction. The head and scalp appeared normal to visual inspection. Neurologic examination of the cranial nerves, peripheral nervous system, and cerebellar examination yielded normal results, and gait was normal. Cardiac auscultation revealed a soft systolic murmur, with radiation to the carotids. Abdominal examination elicited mild global tenderness despite a soft abdomen with no organomegaly, and bowel sounds were normal. The peripheries were unremarkable, with palpable distal pulses, and there was no finger clubbing or any immunologic or vascular phenomena. There was no upper limb blood pressure discrepancy.

Laboratory investigations showed new normocytic anemia (hemoglobin 9 g/dL); markedly elevated C-reactive protein (CRP) of 290 mg/L; erythrocyte sedimentation rate (ESR) of 123 mm/hr; and thrombocytosis of 760×10^9/L. Urine dipstick and microscopy results were normal. The chest radiograph was clear (Figure 1). Electrocardiography showed normal sinus rhythm.

The patient underwent computed tomography (CT) of the facial bones and brain (Figure 2). Both were normal, with no evidence of fascial space collection or abscess in the head and neck and no evidence of osteomyelitis of the mandible. The patient went on to have lumbar puncture. Cerebrospinal fluid (CSF) was normal. Transthoracic echocardiography showed trivial tricuspid regurgitation, but otherwise was normal. The patient was admitted to the ward for further investigation, and was started on broad-spectrum antibiotics after blood culture specimens were taken.

The following day, the patient became pyrexial, with a temperature of 38.3°C. Her hemoglobin level continued to drop to a nadir of 7.5 g/dL, and 1 unit of red blood cell concentrate was transfused. The patient had no history of melena, hematemesis, or bleeding per rectum or per vagina. The results of esophagogastroduodenoscopy and full colonoscopy were normal. The patient's platelet count continued to rise, and her CRP failed to improve despite 2 days of intravenous antibiotics.

Although the symptoms and history did not clearly indicate a diagnosis of cranial arteritis, the presence of scalp tenderness and high inflammatory markers was enough to prompt temporal artery biopsy. Bilateral temporal artery biopsy was performed, and both the right

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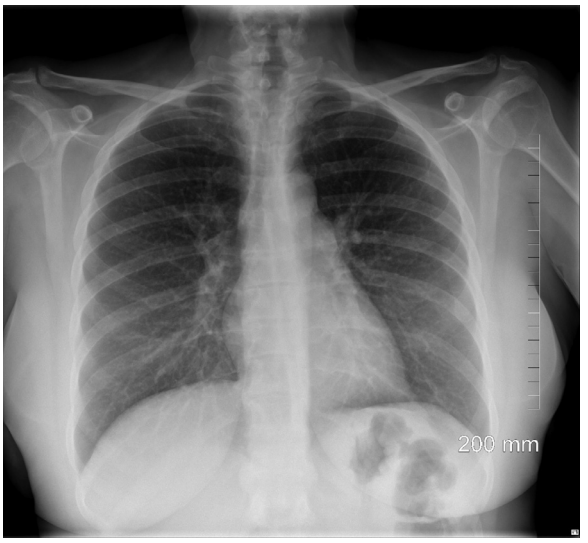

Fig. 1. postero-anterior chest radiograph showing normal appearances of the lung parenchyma, heart, mediastinum and bony structures.

and left temporal arteries were normal, with an intact internal elastic lamina bilaterally and no inflammation seen in either sample (Figures 3 and 4).

DIFFERENTIAL DIAGNOSIS

Based on the above history, presentation, and laboratory findings, the following differential diagnoses were considered: (1) fascial space infection and sepsis occurring after dental extraction; (2) infective endocarditis; (3) central nervous system (CNS) infection; (4) temporomandibular joint dysfunction occurring after dental extraction; (5) persistent idiopathic facial pain; (6) cranial arteritis/systemic vasculitis.

Initially, it was felt that this patient's clinical presentation represented infection occurring after dental extraction. She reported pain at the site of the dental extraction, and subjective fevers at home and documented fever of 38.3˚C in the hospital. The markedly elevated inflammatory markers were also reflective of robust systemic inflammation of whatever cause, possibly infection and sepsis. The relatively benign results on physical examination argued against a diagnosis of postoperative infection. Normal vital signs on presentation, lack of trismus, normal appearance of the healing socket, and absence of lymphadenopathy or other features of local or spreading fascial space infection all indicated that the problem lay elsewhere. Nonetheless, the patient was justifiably started on broad-spectrum

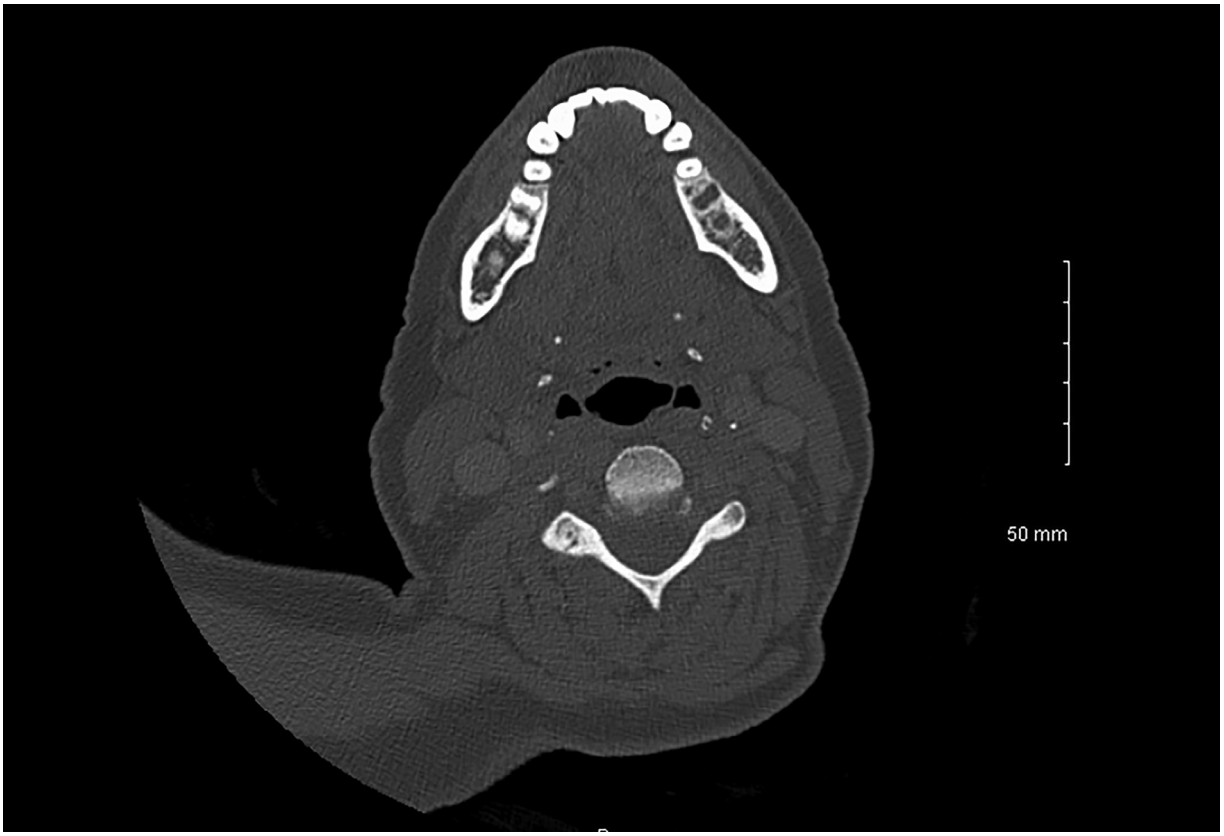

Fig. 2. Axial section of a CT of the mandible showing a normal healing socket and no evidence of fascial space infection or osteomyelitis.

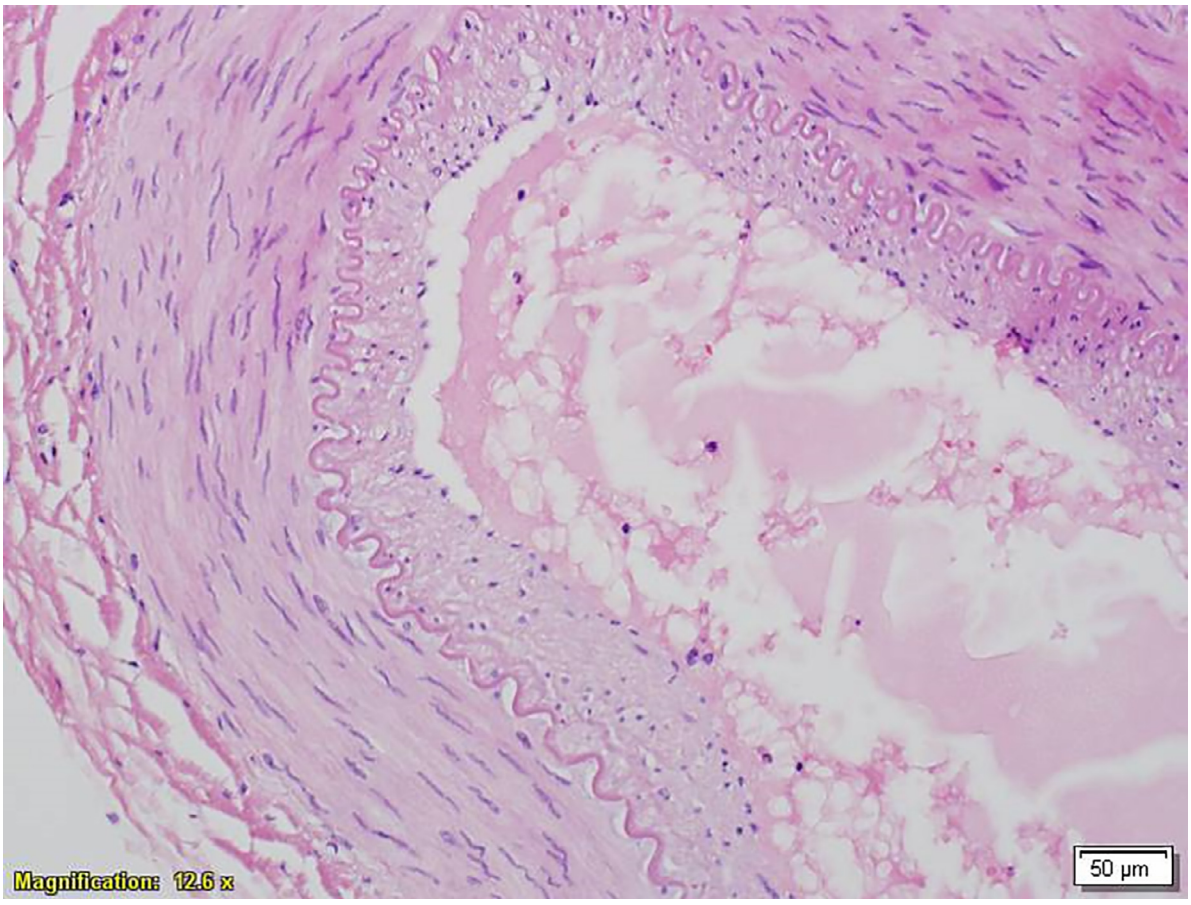

Fig. 3. Right temporal artery biopsy showing intact internal elastic lamina and no inflammation.

empiric antibiotics after peripheral blood culture specimens were taken.

Infective endocarditis was also considered, given the temporal relationship of the onset of symptoms after dental extraction, along with fevers and raised inflammatory markers. The soft systolic murmur heard on cardiac auscultation was, as yet, of uncertain significance. The fact that the patient had no predisposing risk factors (no history of intravenous drug use, cardiac surgery, or native valvular heart disease), negative results on blood culture, and no vegetation demonstrated on echocardiography all argued against this diagnosis. The urinalysis result was normal, and the patient's physical examination did not reveal any evidence of an immunologic or vascular phenomenon in keeping with infective endocarditis. On application of the modified Duke criteria, the patient was found to lack all of the major criteria and all but one of the minor criteria (fever of $> 38^{\circ}C$) for infective endocarditis. A diagnosis of infective endocarditis was, therefore, rejected.

The possibility of CNS infection was also considered. Although the patient's presentation was not typical of viral or bacterial meningitis (lack of meningism and photophobia on examination), the severity of her headache, along with high inflammatory markers and fever, was enough to prompt an investigation to rule this out. After CT of the brain, the patient underwent lumbar puncture for assessment of CSF. Normal white blood cell count and biochemistry of CSF effectively ruled out CNS infection. Subsequently, the CSF culture result was negative.

The marked tenderness of the left-side muscles of mastication and intra-articular disk displacement with reduction could have constituted a temporomandibular joint disorder (TMD) after dental extraction. Equally, persistent idiopathic facial pain, previously known as *atypical facial pain*, might also have formed a plausible part of the differential diagnosis, given that this condition can sometimes present after minor dental surgery and persist in the absence of any apparent local cause. However, neither of these conditions would have explained the markedly elevated inflammatory markers or the normocytic anemia.

Temporal arteritis was included in the differential diagnosis, given the patient's scalp tenderness and high inflammatory markers. Although this was initially considered in the differential diagnosis as a remote

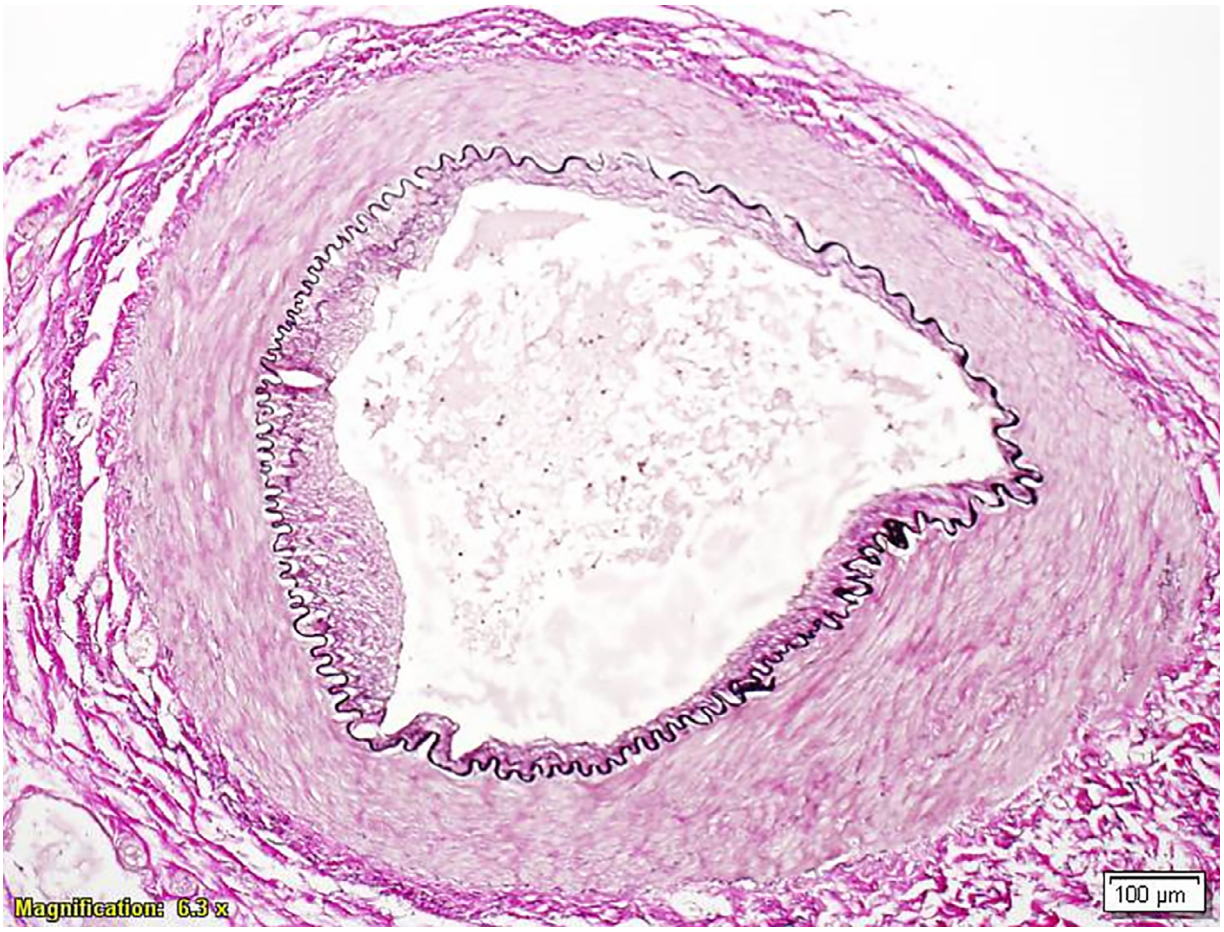

Fig. 4. Left temporal artery biopsy showing an intact internal elastic lamina (stained with van Gieson stain).

possibility, some of the patient's symptoms raised concerns, pointing to this possibility. Even though the patient's history was negative for symptoms of jaw claudication or transient monocular blindness, suspicion was high enough to prompt temporal artery biopsy, which ultimately yielded normal results on histology.

DIAGNOSIS

In the search for a diagnosis, CT of the thorax/abdomen/pelvis was carried out (Figure 5). Subtle thickening of the wall of the thoracic aorta was seen, suggestive of vasculitis of a large vessel.

The patient went on to undergo positron emission tomography/computed tomography (PET/CT), which showed diffuse ^{18}F-fluorodeoxyglucose (FDG) uptake in the thoracic aorta, subclavian arteries, and carotid arteries bilaterally (Figures 6 and 7).

After bilateral temporal artery biopsy, despite the negative histopathologic results, a clinical and radiologic diagnosis of large vessel giant cell arteritis (LV-GCA) was made.

In hindsight, the history of dental extraction immediately preceding the onset of this patient's symptoms proved to be an enormous red herring. Many of the patient's symptoms were entirely consistent with vasculitis of a large vessel. Her history of scalp tenderness was significant. Her complaint of cold upper limbs may have reflected an ischemic phenomenon, given the involvement of both subclavian arteries on PET/CT. All of the laboratory findings (anemia, thrombocytosis, and high inflammatory markers) were consistent with the diagnosis. The patient fulfilled the typical patient demographic for this condition, being a female of European descent in her 50s. The "systolic murmur radiating to the carotids" heard on cardiac examination probably reflected bilateral carotid artery bruits, given the carotid artery involvement on imaging.

MANAGEMENT

The patient was started on oral prednisolone 60 mg once daily. She improved clinically, anemia and thrombocytosis began to resolve, and CRP and ESR fell. Methotrexate was commenced as a steroid-sparing agent.

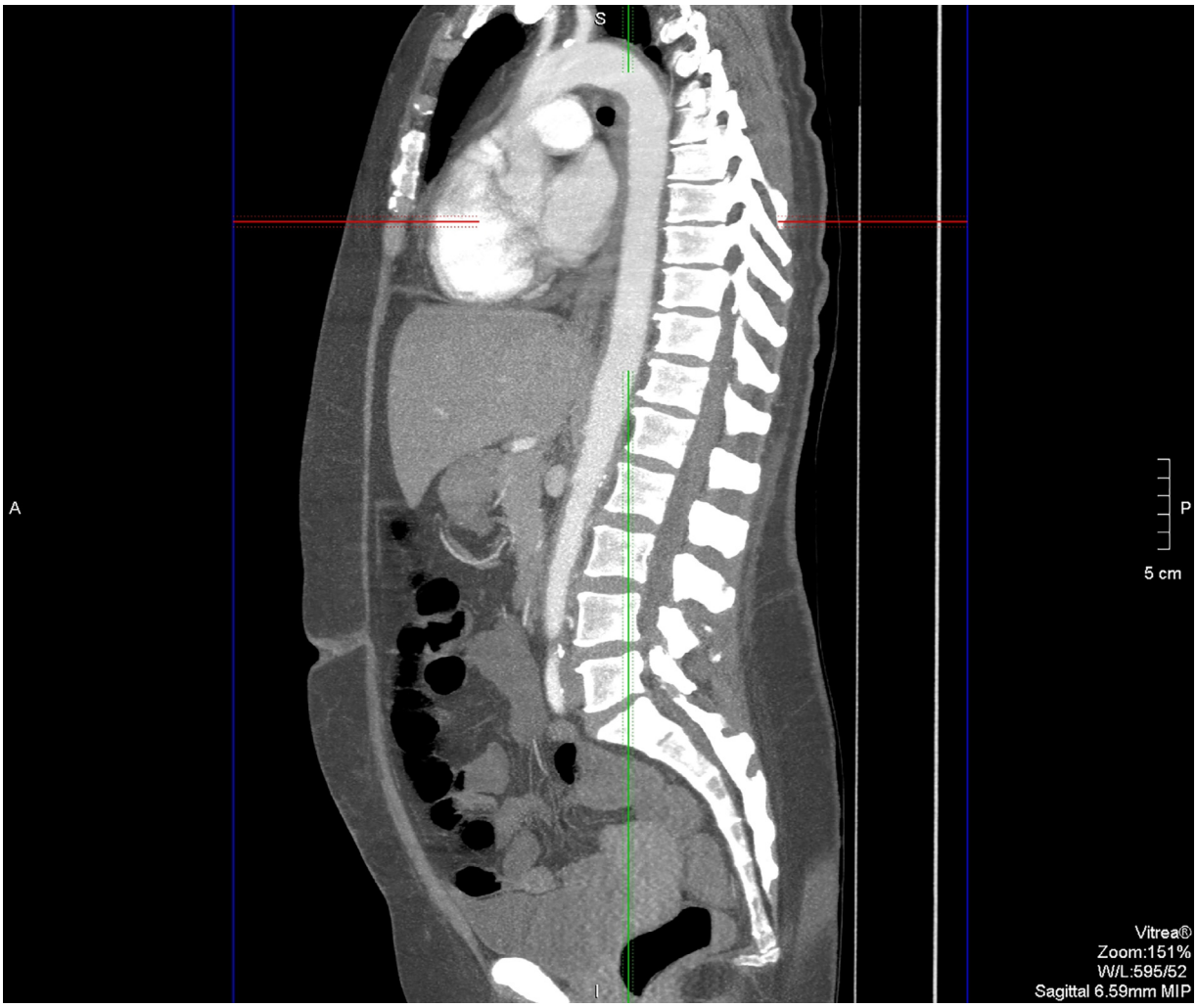

Fig. 5. Sagittal section of a CT of the aorta with intravenous contrast, showing subtle thickening of the wall of the aorta throughout.

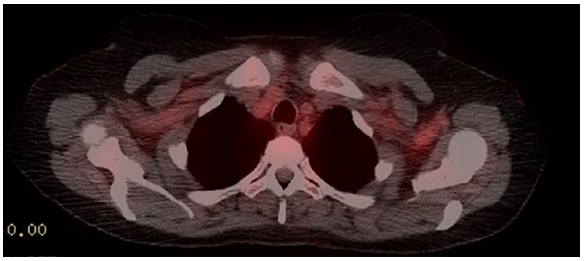

Fig. 6. Axial section of a PET CT demonstrating FDG-avidity in the right and left subclavian arteries and carotid arteries bilaterally.

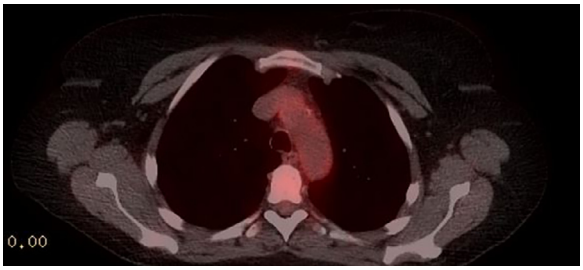

Fig. 7. Axial section of a PET CT demonstrating FDG-uptake consistent with aortitis.

DISCUSSION

Vasculitides comprise a heterogeneous group of disorders that are defined by the presence of inflammatory leukocytes in vessel walls, with damage to the mural structures. Large, medium, and small vessels can be affected, resulting in overlapping clinical and pathologic features in many instances. Vasculitis can occur as a primary process or secondary to systemic disease. Large vessel vasculitis is the most common primary vasculitis, comprising giant cell arteritis (GCA) and Takayasu

arteritis,[1,2] of which GCA is the most common in Western countries.[3]

GCA is a vasculitis of large- and medium-sized vessels, affecting the aorta and its major branches. The lifetime risk of developing GCA is 1% in females and 0.5% in males older than 50 years of age.[4,5] The condition rarely occurs in younger individuals, and peaks in incidence between ages 70 and 79 years.[6] It is most common among people of Northern European descent.[6]

Clinically, GCA is not a single entity, and the disease is considered to have predominantly cranial or large vessel phenotypes (cranial GCA and LV-GCA, respectively).

In cranial GCA (also referred to as *temporal arteritis*), branches of the external carotid artery are prominently implicated. Headache is common and is frequently centered at the temples but can be generalized, frontal, or occipital. Abnormal temporal arteries (pulseless, tender, and/or thickened) may be present, but scalp tenderness may be the only sign. Nearly one-half of patients experience jaw claudication, characterized by rapid onset of fatigue and pain affecting the muscles of mastication shortly after commencing chewing. This results from arteritic involvement of the vessels that supply the muscles of mastication (masseter, temporalis, medial, and lateral pterygoid muscles). Any branch of the external carotid artery may be affected, resulting in symptoms, including throat pain (ascending pharyngeal artery), tongue pain and/or tongue claudication (lingual artery), facial pain (facial artery), dental pain (maxillary artery, inferior alveolar artery), scalp pain, and scalp tenderness (posterior auricular artery, superficial temporal artery).

Rarely, lingual infarction[7] and scalp necrosis[8] can occur if the disease is a longstanding one and remains untreated. Macroglossia has also been reported.[9]

Transient monocular (or rarely binocular) visual disturbance may be a presenting complaint and is a worrying harbinger of permanent visual loss without prompt treatment. At least 80% of cases of visual loss in GCA result from anterior ischemic optic neuropathy as a result of ischemia and occlusion of the posterior ciliary artery, a branch of the ophthalmic artery from the internal carotid artery, the main arterial supply to the optic nerve.[10]

LV-CGA differs from cranial GCA in that it predominantly affects the aorta and its major branches. It tends to occur in slightly younger patients (average age 66 vs 72 years), with a lesser likelihood of presenting with headache and a greater likelihood of presenting with arm claudication.[11] Constitutional symptoms, such as fever, weight loss, anorexia, and polymyalgic symptoms, are also common and may be the *only* symptoms, especially in older adults. Aortitis can be complicated by aortic aneurysm or dissection.

There is a strong association between GCA and polymyalgia rheumatica, a condition characterized by morning stiffness affecting the shoulder and hip girdles, neck, and torso, and occurs in 40% to 50% of patients with GCA.[12]

Laboratory investigations usually reveal a robust inflammatory response, with elevated ESR and CRP. Normocytic anemia and reactive thrombocytosis are common.

Ultrasonography should be the primary modality used in the assessment of patients presenting with symptoms consistent with cranial GCA.[13] The noncompressible "halo" sign, a homogeneous, hypoechoic wall thickening that is well delineated toward the luminal side of the vessel, is the finding on ultrasonography most suggestive of GCA, with sensitivity of 77% and specificity of 96%.[14] CT and ^{18}F-fluorodeoxyglucose PET are not recommended for investigation of cranial arteritis.[13]

The best imaging modality for patients with suspected LV-GCA is unclear, but contrast-enhanced CT, MRI, and PET/CT have been employed to demonstrate arterial wall inflammation.

Temporal artery biopsy has traditionally been considered the gold standard for the diagnosis of GCA. Using 1-cm or greater segment for temporal artery biopsy is recommended because disease is often patchy and findings in the temporal arteries are distributed unevenly.[15] The mean sensitivity of unilateral temporal artery biopsy in a review of 2986 cases was 86.9%.[16] Bilateral temporal artery biopsy can increase diagnostic sensitivity by up to 12.7% compared with unilateral biopsy.[17] Of all the symptoms of GCA, it is a history of jaw claudication that most strongly predicts a positive result on temporal artery biopsy.[18] Glucocorticoid therapy can reduce the yield of temporal artery biopsy, with 78% being positive with less than 2 weeks of treatment, 65% after 2 to 4 weeks of treatment, and 40% after greater than 4 weeks of treatment.[19]

Histologically, GCA is characterized by panarteritis, which is most pronounced in the media and is composed of CD4+ lymphocytes and macrophages. These cells frequently undergo organization with formation of giant cells, but the absence of giant cells does not preclude the diagnosis. Inflammation leads to remodeling, hyperplasia, and disruption of the internal elastic lamina, resulting in partial or complete luminal occlusion and, thus, the corresponding clinical manifestations of ischemia.

Cases in which histopathology results are negative can be challenging. However, although temporal artery biopsy was deemed to be a mandatory step in the diagnosis of GCA in previous international guidelines, such as the European League Against Rheumatism (EULAR) guidelines from 2009,[20] the revised EULAR

guidelines now suggest that in patients with high clinical suspicion of GCA and a positive imaging test result, the diagnosis of GCA may be made without need for an additional test (e.g., biopsy or further imaging).[13,21] Ultrasonography, PET, MRI, and/or CT may be used for the detection of mural inflammation and/or luminal changes in the extracranial arteries to support the diagnosis of LV-GCA. In this regard, the role of temporal artery biopsy is becoming less clear in an era of advanced diagnostic imaging. Imaging results may, indeed, be considered confirmatory and helps avoid the need for biopsy and, thus, subjecting the patient to an invasive procedure.

Treatment has traditionally involved the expedient initiation of high-dose glucocorticoid therapy. Imaging and confirmation through biopsy should not delay treatment. To aid in the decision to commence high-dose oral steroids or pulsed intravenous steroids, the British Society for Rheumatology and the British Health Professionals in Rheumatology guidelines for the management of giant cell arteritis have subcategorized GCA into uncomplicated GCA (no history of jaw claudication or visual disturbance) and complicated GCA (jaw claudication, evolving visual loss or history of transient monocular blindness).[22] Uncomplicated GCA might be suitable for prednisolone 40 to 60 mg (and not < 0.75 mg/kg) daily until resolution of symptoms and laboratory abnormalities. Complicated GCA is more appropriately treated with intravenous methylprednisolone 500 to 1000 mg daily for 3 days before oral prednisolone. Bone protection and gastric protection should be commenced concomitantly.

Tocilizumab, an interleukin-6 receptor alpha inhibitor, is a new agent available for the treatment of GCA. When administered weekly or every other week in combination with a 26-week prednisolone tapering, tocilizumab was found to be superior to either 26-week or 52-week prednisolone tapering plus placebo with regard to sustained glucocorticoid-free remission.[23] Methotrexate can be used as an alternative.[21]

It is clinically important to know that interleukin-6 is the major regulator of acute protein synthesis, including CRP, in the hepatocyte.[24] Tocilizumab, therefore, flattens CRP levels to within normal limits, even in the context of intense inflammation or infection, and also reduces the ESR. Monitoring clinical response to treatment, therefore, cannot rely solely on the measurement of inflammatory markers, and remission or relapse must be determined by other means when patients are taking this agent.

CONCLUSIONS

This new case of GCA was a deceptive one in that it presented insidiously. Because GCA is the most common primary vasculitis, clinicians should remain alert to its possibility.

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