Review

Respiratory and otolaryngologic manifestations of giant cell arteritis

T.F. Imran[1], S. Helfgott[2]

[1]*Rutgers University, New Jersey Medical School, Newark, USA;*
[2]*Division of Rheumatology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA USA.*

Tasnim F. Imran, MD
Simon Helfgott, MD

Please address correspondence to:
Simon Helfgott, MD,
Division of Rheumatology,
Brigham and Women's Hospital,
45 Francis Street B-3,
Boston MA 02115, USA.
E-mail: shelfgott@partners.org

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ABSTRACT

Objective. *The classical presentation of giant cell arteritis (GCA) includes the new onset of headache, scalp tenderness, facial pain or jaw claudication in an older patient. Many patients with GCA have features consistent with the diagnosis of polymyalgia rheumatic (PMR) and nearly all have elevated markers of inflammation such as the erythrocyte sedimentation rate (ESR) or the serum C-reactive protein (CRP) Respiratory and ear-nose-throat (ENT) signs and symptoms such as cough, tongue infarction, trismus, hearing loss and facial swelling are less commonly described, yet they may be the initial presentation of GCA*

Our aim was to review the published literature on the topic of respiratory and otologic manifestations of GCA.

Methods. *A literature search was performed on PUBMED and MEDLINE using the following keywords: GCA, temporal arteritis, pulmonary, respiratory, ENT, cough, tongue necrosis.*

Results. *The upper and lower airways manifestations of GCA include a wide variety of conditions that could be caused by ischaemia due to the vasculitis.*

Conclusions. *It is important to recognise these atypical presentations because they may be the sole initial manifestation of the disease. Early suspicion and confirmation of the diagnosis of GCA can help to prevent more catastrophic consequences of unrecognised disease, including stroke and blindness.*

Introduction

Giant cell arteritis (GCA) is an ancient disease. One of the first descriptions of GCA can be found in Ali Ibn Isa's Tazkiratul-Kahhaleen, Notebook of the Oculist, published in the tenth century AD. Ibn Isa describes migraines, headaches in patients with chronic eye disease and "acute, sharp, catarrhal affections, including those showing heat in and inflammation of the temporal muscles" and that these conditions may lead to vision loss (1). In the English literature, one of the earliest descriptions of GCA is attributed to Sir Jonathan Hutchinson, who, in 1890, described a patient who had "red streaks on his head" which were painful and prevented him from wearing his hat. These red streaks were thought to be swollen temporal arteries (2). Horton *et al*. characterised GCA as being a systemic illness (3). They observed tenderness over the scalp, painful nodules along the temporal arteries, headaches, and weight loss and jaw stiffness in two patients. In 1938, the observation of an increased erythrocyte sedimentation rate was first noted (4) and a decade later striking improvement of symptoms after steroid treatment was first reported (5).

Headache is the most common symptom, occurring in about 70% of patients with GCA. The headache may be variable in location, intensity and quality. However, it is often of new onset. Jaw claudication occurs due to ischaemia of the masseter muscles, leading to pain when chewing tough foods. Visual symptoms such as vision loss and diplopia may develop in about a third of patients. The most concerning complication is blindness due to its irreversible nature. Other manifestations entail large vessel involvement including aortic aneurysm and dissection, aortic arch syndrome, and limb artery stenosis (6, 7).

Respiratory symptoms involving the upper and lower airways are occasionally observed. These include dry cough, throat and tongue pain and hoarseness. Patients may present with otolaryngologic symptoms such as

tongue necrosis, dysphagia, and submandibular swelling. The presence of these symptoms may be overlooked in some patients, further delaying the diagnosis. Given the risk for permanent visual loss and other major morbidities, identifying the link between the respiratory tract, otolaryngologic manifestations and other more classical features of GCA can help to expedite the diagnosis and initiate appropriate therapy. Glucocorticoids are a highly effective therapy for GCA and should be initiated early and utilised for the shortest period of time, to avoid long-term adverse effects (8). This review is intended to increase clinicians' awareness of the less commonly seen respiratory and otolaryngologic symptoms of GCA.

Methods

A literature review using the PUBMED and MEDLINE databases was performed with the following keywords: giant cell arteritis, temporal arteritis, pulmonary, respiratory, ear-nose-throat, cough, and tongue necrosis. Case reports, controlled studies, retrospective studies and review articles were included. Studies published in languages other than English were excluded. Table I lists these sources.

Clinical manifestations

Orofacial manifestations

Since GCA has a predilection for involvement of cranial arteries, it should not be surprising to observe orofacial signs and symptoms in some patients. These can be divided into two distinct groups: those that are associated with ischaemia and those that demonstrate features of localised inflammation. In the former category, one can observe temporal and scalp pain, jaw pain and complaints of claudication. Jaw claudication is elicited in about half of patients. Tongue or scalp necrosis has been rarely observed, yet GCA is the most common cause of tongue necrosis (9). It is often localised to small areas of the tongue mucosa due to an extensive collateral blood supply network in the tongue (10).

Some patients complain of dysphagia, which is due to involvement of the pharyngeal vessels (11). In the second category, one may observe non-specific facial swelling (9, 12). In one prospective study of 345 patients with GCA, the frequency of facial oedema was 12% (13). Similarly, a chart and literature review of 260 patients with GCA found 37 cases (14%) of head and neck swelling that lasted at least one day (13). Head and neck swelling appeared to be a transient but heralding feature, preceding the development of GCA. The swelling mainly involved the orbital region, the lower part of the cheeks and maxillae. Periorbital pain has also been described as a presenting feature of GCA (14). Less commonly, oedema was noted in the lateral and anterior aspects of the neck, the tongue and the supraclavicular space. The swelling typically resolves following with therapy and in some patients it may spontaneously remit over time (13). Tongue pain may be tested by assessing for repetitive rapid protrusion of the tongue, which may produce pain, burning or fatigue (10). The tongue has a rich blood supply; thus necrosis is rare and indicates extensive vascular involvement. The presence of tongue necrosis portends a worse prognosis as these patients tend to be older and also have a higher incidence of vision loss. However, the non-specific swelling may be mistaken for other diagnoses including sinusitis and angioedema.

As noted earlier, jaw claudication, is the most specific non-neurological sign of GCA and may be misdiagnosed as a temporomandibular joint disorder (15).However, trismus or reduction in jaw opening, is much less recognised. One retrospective analysis of 88 patients, noted six to have reduction in jaw opening. These patients had a more acute presentation with shorter time to diagnosis (average of four weeks versus twelve weeks), and there was a high correlation with eye involvement in about half of the patients (16).

Submandibular swelling has also been noted to be an initial manifestation of giant cell arteritis (14, 17, 18). Ruiz-Masera *et al*. reported a case of a 75 year-old woman who presented with a submandibular mass, ultimately requiring resection of the gland. The diagnosis of GCA was made following a review of the histopathology of the mass (17). Other less commonly reported symptoms include necrosis at the tip of the nose, lip necrosis, paresthesias felt over the chin, glossitis, and dental pain (19).

Audiovestibular manifestations

One of the earliest links of deafness with GCA was provided by Cook *et al*., who described seven patients who developed unilateral, and subsequently bilateral deafness which improved spontaneously (20). A later study found that 5 out of 68 patients with GCA had bilateral sensorineural deafness, which did not improve after steroid therapy (21). Progressive hearing loss as an initial manifestation of GCA has also been reported in a handful of cases, with improvement of hearing loss noted in some patients (21). Whether or not the hearing loss is reversible and to what extent, may depend on how early the corticosteroid treatment is initiated. Audiovestibular manifestations may occur prior to other symptoms of GCA (22). Thus, early recognition of these signs is important since the treatment of this condition with corticosteroids may be quite different than the more watchful approach that is often used in the management of patients with these issues. In addition, missing the diagnosis of GCA and the opportunity to initiate appropriate therapy may lead to even more dire consequences.Thus, in a patient with PMR and new audiovestibular symptoms, the clinical suspicion of underlying GCA should be considered and higher doses of corticosteroids may need to be instituted (4).

Spontaneous ear pain has been described as an initial manifestation of GCA (23). In addition, a recent prospective study with 44 patients with GCA showed that audiovestibular dysfunction was significantly more common in patients with GCA than among age-matched controls (4). A patient was defined as having abnormal vestibular tests if any of these three findings were noted: spontaneous nystagmus, head-shaking nystagmus, or an abnormal caloric test. Using these criteria, audiovestibular manifestations such as hearing loss, tinnitus, vertigo, and diz-

Table I. Patient characteristics, initial presentation and diagnosis.

Author (Year)	Study type	Study title	Patient characteristics	Initial presentation	Diagnostic methods / Outcome
Huston *et al*. (1978)	Retrospective	Temporal arteritis: a 25 year epidemiologic, clinical and pathologic study	-Mayo Clinic patients Olmsted county, MN 1950-1974	-Headache: 90% -Tender temporal artery: 69% -Jaw claudication: 67% -Tongue claudication: 7% -Absent temporal artery pulse: 40% -Weight loss: 55% -PMR: 48%	Either positive temporal artery biopsy or -Classic manifestations of temporal arteritis including ESR, and at least 4 of: tender, swollen temporal artery, jaw claudication, blindness, PMR and response to corticosteroids
Browne (1982)	Case series	Oral necrosis Accompanying giant cell arteritis	-Patient 1: 69-year-old man; -Patient 2: 89-year-old woman	Patient 1: hypothermia, lip necrosis, tongue necrosis, difficulty swallowing Patient 2: grossly enlarged and painful right arm and breast with ecchymosis; aneurismal dilatation of the aorta, painful and swollen tongue one month later	Patient 1: Temoral artery biopsy: non-specific, Buccal biopsy showed granulation tissue, elevated ESR Patient 2: Clinical findings, elevated ESR
Cohen *et al*. (1982)	Case report	Facial swelling and giant cell arteritis	-62-year-old white woman	Severe facial swelling, glossitis, odynophagia	Temporal artery biopsy positive
Francis *et al*. (1982)	Case report	Acute hearing loss in GCA	-59-year-old man	-Acute hearing loss: 48 hour history of ear discomfort with increasing deafness -4 weeks of temporal-occipital headache - ESR: 102	-Biopsy negative -Symptoms reversed with corticosteroid therapy
Pedersen *et al*. (1983)	Case report	Lingual infarction in giant cell arteritis	-77-year-old woman	-3 weeks of left tongue & jaw pain; unable to speak or swallow -6 months prior: muscular pains and fatigue	-Left temporal artery biopsy showed GCA -Tongue biopsy showed ischaemic infarction
Bradley *et al*. (1984)	Case report	Giant cell arteritis with pulmonary nodules	-59-year-old woman	-Left arm, bilateral foot and ankle pain for 6 months -Hip stiffness worse in morning; PMR symptoms; ESR >100	-Lung nodule biopsy showed giant cells in granulomas -Temporal artery biopsy positive -Lung biopsy: diffuse granulomatous inflammation and necrosis -After a decrease in prednisone dose, the patient developed lung lesions, chronic productive cough
Coppeto (1984)	Case report	Spontaneous ear pain as the initial presenting manifestation of giant cell arteritis	-82-year-old woman	-Left periauricular pain, lightheadedness; episodes were associated with chewing or talking -Left ear-ache -Weight loss over the past month attributed to pain with swallowing	Temporal artery biopsy positive
Larson *et al*. (1984)	Case series	Respiratory tract symptoms as a clue giant cell arteritis to	16 patient cases	-Cough, sore throat, hoarseness -Diffuse tenderness of the anterior neck -4 to 9% of patients with GCA had respiratory manifestations as initial presentation -Cough: most common, non-productive, frequent, dry, sometimes preceded other symptoms, sensation of choking	Temporal artery biopsy positive
Acritidis *et al*. (1988)	Case-control	Pulmonary function of non-smoking patients with giant cell arteritis and/or PMR; a controlled study	26 non-smoking patients with GCA and 28 control patients	-Normal lung function: GCA patients 31%, controls: 50% -Isolated small airway disease: GCA patients 46.2%, Controls: 50% - Obstructive lung disease: 1 GCA patient -Restrictive: 1 GCA patient -Diffuse interstitial lung disease: 1 patient, controls: none	-Diffuse interstitial lung disease and restrictive lung disease were seen only in patients with biopsy proven GCA: may be related to underlying process
Machado *et al*. (1988)	Retrospective	Trends in incidence and clinical presentation of Temporal Arteritis in Olmsted County, MN 1950-1985	Population of Olmsted County, MN	Respiratory symptoms occurred in: -31% 1950-69 -16% 1970-79 -26% 1980-85 Facial pain occurred in: -19% 1950-69 -11% 1970-79 -13% 1980-85	Temporal artery biopsy positive or classic manifestation of GCA, including elevated ESR and 4 of: tender, swollen temporal artery or jaw claudication or blindness or PMR or favorable response to corticosteroids
Sonnenblick *et al*. (1989)	Review	Non-classical organ involvement in temporal arteritis	-Patients with respiratory symptoms	-Respiratory tract symptoms: dry cough -Direct lung involvement: diffuse reticular pattern, visceral disseminated form -Involvement of large pulmonary arteries -Auditory system: sensorineural hearing loss	Lung biopsies confirmed diagnosis

Table I continues

Author (Year)	Study type	Study title	Patient characteristics	Initial presentation	Diagnostic methods / Outcome
Ginzburg *et al*. (1992)	Case report	Lingual infarction: a review of the literature	-79-year-old woman	-Tongue necrosis -3 month history of right facial and jaw pain -Acute right ocular blindness -1 month prior: fatigue, lethargy, tongue swelling with inability to eat	-Patient refused biopsy -Clinical diagnosis -Improvement with glucocorticoid therapy
Mangenelli *et al*. (1992)	Case report	Trismus and facial swelling in a case of temporal arteritis	-71-year-old woman with euthyroid goiter	-Left temporal headache, fever, malaise, anorexia -3 weeks later: masseter spasm, painful chewing -Lower facial swelling -One episode of amaurosis fugax	Biopsy of left temporal artery -Oedema improved with 4-6 weeks of steroid therapy
Romero *et al*. (1992)	Case series	Pleural Effusion as manifestation of temporal arteritis	-67-year-old woman -71-year-old woman	Patient 1: -3 month history of malaise, weight loss, shoulder pain, frontoparietal headache, jaw claudication, cough, scanty sputum, and left pleuritic chest pain -Pleural effusion: exudates with high protein Patient 2: -1 month history of temporal headache, fatigue and jaw claudication -Right pleuritic chest pain, productive cough -Pleural effusion: exudate	-Temporal artery biopsy positive -1 patient had pleural biopsy: atypical mesothelial hyperplasia with inflammatory cells
Zenone *et al*. (1994)	Case report	Unusual manifestations of GCA: pulmonary nodules, cough, conjunctivitis & otitis with deafness	Fever, dry cough, dyspnea and chest pain	-Bilateral conjunctivitis, otitis with hearing loss, weight loss, rhinitis -ESR: 58 -Headaches, muscle pain	Temporal artery biopsy positive
Ruiz-Masera *et al*. (1995)	Case report	Submandibular swelling as the first manifestation of giant cell arteritis	-75-year-old woman	-Right submandibular pain and difficulty swallowing for several months	Submandibular mass histopathology confirmed the diagnosis of GCA
Ghanchi *et al*. (1996)	Case report	Facial swelling in giant cell (temporal) arteritis	79-year-old Caucasian woman with hypertension	-Sudden, painless blurring of vision -Shoulder pain, malaise, fatigue -"Heavy" feeling on the affected side of the face -A month prior: swelling of face on left and around left eye, pain with chewing	Confirmed later with left temporal artery biopsy
Hellmann *et al*. (2002)	Case report	Temporal Arteritis: a cough, toothache and tongue infarction	-79-year-old woman	-Blindness in right eye -1 month prior: fatigue, dry cough, then toothache, burning sensation on left side of tongue, weight loss; ESR: 115	Temporal artery biopsy positive
Amor-Dorado *et al*. (2003)	Prospective	Audiovestibular manifestations in GCA	-44 patients with GCA -10 patients with biopsy negative, isolated PMR	-90% of GCA patients had abnormal vestibular tests compared to patients with isolated PMR	Hearing loss, vestibular function improved after 3 months of therapy in some cases, and in almost all cases with 6 months of therapy
Forderreuther *et al*. (2003)	Case report	Giant cell arteritis presenting as a periorbital pain syndrome and a submandibular mass	-72-year-old woman	-Intense, gnawing, constant pain around left eye, mild lacrimation -Two years later, the patient developed a submandibular mass	Submandibular mass histopathology -confimed GCA with transmural inflammation
Gonzalez-Gay *et al*. (2005)	Retrospective	GCA: Disease patterns of clinical presentation in a series of 240 patients	-Single hospital population of Lugo, Spain, between January 1, 1981, and June 15, 2004	-Headache: 86.4% -Severe ischaemic manifestations: 54.6% - Abnormal temporal artery on exam and anaemia may predict the risk of severe ischaemic complications related to GCA	Temporal artery biopsy positive
Shmerling *et al*. (2006)	Case report	An 81 year-old woman with temporal arteritis	-81-year-old woman	-Difficulty opening mouth -Retro-orbital pain -Lumps on head -Upper URI symptoms before onset of headache -No fevers, chills -ESR: 46 -Atypical headache	Temporal artery biopsy positive

Table I continues

Author (Year)	Study type	Study title	Patient characteristics	Initial presentation	Diagnostic methods / Outcome
Manganelli *et al*. (2006)	Review	Respiratory system involvement in systemic vasculitides	-Large-vessel, medium-vessel, and small vessel vasculitides are discussed	Respiratory symptoms in GCA: -Non-productive cough -Sore throat -Hoarseness -Choking sensation -Thoracic pain Less common symptoms: -Pleural effusion, interstitial lung disease -Basal interstitial fibrosis in 16% of 217 patients -Intra-alveolar hemorrhage	
Zimmermann *et al*. (2007)	Case report	Tongue infarction in GCA	-81-year old woman	-Tongue infarction, prodrome of headache and PMR symptoms -24 hour history of painful swollen tongue and dysarthria -Months of mild limb-girdle symptoms -ESR: 69, CRP: 61	Bilateral blind temporal artery biopsy (10 mm & 25 mm): negative
Zadik *et al*. (2011)	Case report	A 78-year-old woman with bilateral tongue necrosis	-78-year-old woman	-Tongue pain -Pain of right side of head, neck, face and shoulder worse while eating -Fatigue, visual blurring over 2 months, weight loss -ESR: 69, CRP: 6.1	Duplex sonography: occlusion of left artery, compatible with GCA

ziness were present in about two thirds of patients with GCA. Hearing loss was noted in 27% of patients. About 30% of patients had persistent head-shaking nystagmus that did not resolve after three months of corticosteroid treatment (4). However, vestibular symptoms generally improved after three months of treatment with steroids and some patients may actually compensate over time without any treatment.

Respiratory manifestations

Respiratory symptoms have been reported in up to one third of GCA patients seen at the Mayo Clinic (24). Rarely, the respiratory symptoms may be the initial form of presentation (25).

• *Chronic cough or sore throat*

A dry non-productive, persistent cough is the most common respiratory manifestation in GCA. It usually improves with steroid treatment (26). It may be associated with fever, and in rare cases may be the initial manifestation of the disease (27, 28). Some patients may have concomitant symptoms such as headache and PMR but may not voluntarily report these symptoms (19). Thus, it is vital to obtain a thorough review of systems to determine the likelihood of GCA as a cause.

• *Imaging of pulmonary involvement*

The mechanisms of pulmonary involvement in GCA have not been clearly elucidated, and may be related to a primary vasculitis of small and medium-sized vessels (26). Pulmonary symptoms may precede other manifestations of GCA, and thus an evaluation for underlying GCA should be done in an elderly patient who may not have the typical features of GCA and PMR.

Direct involvement of the lung has been reported in a few cases of GCA. Chest radiographs may demonstrate either a diffuse reticular pattern or multiple nodules (29). Patients promptly improve with corticosteroid treatment, but in one study, the pulmonary abnormalities relapsed when corticosteroids were tapered (30). Intra-alveolar haemorrhage that was responsive to treatment was reported in one case of GCA (31).

Later reports have observed basal interstitial fibrosis, pleural effusion, interstitial infiltrates and nodules. For example, a case series detected interstitial fibrosis on chest radiographs in one sixth of 217 patients (26). The lung histopathology has shown a vasculitis of pulmonary arteries with giant cells along with interstitial, bronchial and sometimes peri-bronchial granulomas. Bronchoalveolar lavage in three GCA patients with respiratory symptoms revealed a T-lymphocyte alveolitis with a $CD4^+$ predominance (26). Romero described two patients diagnosed with GCA who presented with exudative pleural effusions with a high protein content and a predominance of polymorphonuclear cells. However, the pleural biopsy and the cytology studies of the effusion yielded non-specific findings (32).

Discussion

GCA is an inflammatory disease affecting large and medium-sized vessels that is characterised by medial and adventitial inflammation with giant cells, leading to the destruction of the elastic laminae (33). Although the precise etiology is not known, it has been proposed that GCA is T cell dependent and an antigen driven process (26). Though most of the literature on GCA has focused on the visual complications, GCA encompasses a wider spectrum of clinical features, including respiratory and otolaryngologic manifestations, which are less commonly reported but may be equally serious. Table I summarises the features of the otolaryngologic, audiovestibular and pulmonary involvement noted in prospective and retrospective studies, case series and case reports. When patients present with involvement of one of these organs, a high index of suspicion for GCA is required, since any delay can result in detrimental outcomes.

The head and neck swelling presentation, and jaw claudication symptoms may all be explained by involvement

of the external carotid artery system. In contrast, since the tongue has a rich blood supply and collateral circulation with the lingual, facial, pharyngeal, and palatine arteries, tongue necrosis may be localised to small areas of the tongue mucosa (10). In addition some patients with GCA may also have show features of a peripheral facial paresis, audiovestibular symptoms and dysphagia (4).

The exact mechanism(s) of audiovestibular dysfunction in GCA remain to be elucidated. However, it is likely that ischaemic complications of the vasculitis, and inflammatory involvement of the vertebrobasilar arteries or the terminal branches of the cochleovestibular vasculature are responsible (34).Auditory and vestibular functional areas are supplied primarily by the labyrinthine artery, which branches off of the anterior inferior cerebellar artery (34).

The most common respiratory manifestation of GCA is cough. Its precise etiology is not known. It is thought that cough receptors that are distributed throughout the airways, diaphragm and esophagus may play a role in this manifestation as they become irritated by inflammation of blood vessels. In addition, cough receptors that lie outside the respiratory tract may also be stimulated by the external auditory canals, eardrums, nose, and sinuses (26). In some patients, the disease itself may incite hyper-reactivity of the airways, leading to cough. As an example, arteritis of the bronchial mucosa has also been demonstrated (29). The hoarseness, sore throat, choking sensation, and tenderness of the cervical structures that may occur concurrently with cough may be due to ischaemia or inflammation in the arteries supplying the laryngeal and pharyngeal structures (26). Moreover, GCA can involve the main pulmonary arteries in addition to large and medium pulmonary elastic arteries. In some cases, there may be an overlap in symptoms of GCA with granulamatosis with polyangiitis (GPA) or other ANCA positive vasculitidies.

Conclusion

Though uncommon, patients with GCA may present with respiratory, audiovestibular, or otolaryngologic symptoms, which may or may not accompany other characteristic symptoms of GCA. Patients are often misdiagnosed with other conditions. The astute clinician should be keenly aware of these features, as timing is critical in establishing the diagnosis of GCA to prevent serious complications such as blindness and stroke. A better understanding of the respiratory and otolaryngologic features of GCA may provide clinicians with a better understanding of the myriad presentations of GCA.

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