Annex 3.

VILNIUS UNIVERSITY

MEDICAL FACULTY

The Final thesis

Large Vessel Vasculitis

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Table of Contents

1. Summary

Atypical manifestation of Giant Cell Arteritis (GCA): a literature review was performed to summarize current knowledge on extracranial GCA and the arteries it involves. Extracranial GCA is becoming more frequently diagnosed due to the increasing recognition among doctors and the development of advanced technologies of various imaging techniques. GCA is a systemic large vessel vasculitis with unknown etiology, typically affecting the temporal artery and associated with common complaints such as jaw claudication, new onset of headache, and constitutional symptoms such as fever, malaise, and weight loss. In a fraction of cases, GCA may present with atypical manifestations which may be reflected with other involvement of the classic clinical features the literature describes. Due to the nonspecific clinical presentation and low sensitivity of temporal artery biopsies, extracranial GCA is usually diagnosed by imaging: Computed tomography (CT), Magnetic Resonance Imaging (MRI), CT angiography, fluorodeoxyglucose - positron emission tomography (F-FDG-PET), and Ultrasound (US). Furthermore, since other than cranial arteries such as the aorta and its branches are involved, it may cause complications such as an aortic aneurysm or dissection, aortic arch syndrome, arm claudication, and stroke. Treatment of extracranial GCA has been controversial in the recent literature, in general, the same strategy is applied as in patients with classic temporal arteritis, and surgical procedures may be indicated depending on the medical condition and the characteristics of the patient.

Key words: Giant cell arteritis, large vessel vasculitis, temporal artery, jaw claudication, extracranial.

2. List of Abbreviations

GCA – Giant Cell Arteritis

HLA- DR4- Human Leukocyte Antigen – DR isotype

PMR- polymyalgia rheumatica

ESR- erythrocyte sedimentation rate

TAB- temporal artery biopsy

CBC- complete blood count

US- ultrasound

CTA- computer tomographic angiography

MRA- magnetic resonance angiography

FDG-PET - fluorodeoxyglucose - positron emission tomography

LR- limb restricted

CRP- C reactive protein

3. Introduction

GCA is a large vessel vasculitis of unknown origin that causes chronic inflammation of large and medium-sized arteries, specifically the branches of the carotid artery (1). GCA is most common in women over the age of 50, with peak incidence occurring between the ages of 70-79 (2). Even though the etiology is unknown, there are some factors that contribute to genetic predisposition (HLA-DR4) (3) such as ethnicity, recent research has shown a much higher incidence of GCA among Scandinavian countries and those of Scandinavian descent. Studies showed an annual incidence of 15 per 100,000 persons over the age of 50, which is similar to that in Scandinavia (56). Moreover, up to 50% of patients with GCA also have PMR (4), which is a condition that causes stiffness of the shoulder, girdles, neck and torso. Patients usually present with constitutional symptoms such as fever, and weight loss. Most of the time, the fever is usually low grade, although, in about 15% of GCA patients, the fever surpasses 39 ºC, which causes to false diagnosis (57). In addition, the majority of patients (more than two-thirds) commonly experience headaches (58) during the course of the disease, classically, it can present as throbbing, dull, or pulse pain, and is usually located over the temples. Arterial inflammation involves specifically the extracranial branches of the common carotid, internal carotid, and external carotid arteries (the temporal artery is the most affected one).

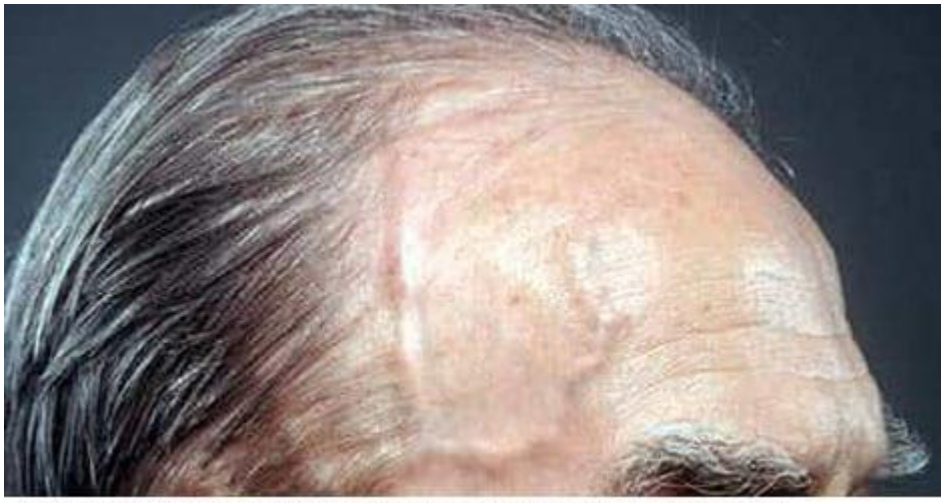


Figure 1

The majority of the patients experience jaw claudication which is a condition occurring in mastication that causes mandibular pain or fatigue that is relieved by stopping. Vision loss and diplopia can occur due to inflammation of the ophthalmic artery and ischemic processes of the blood flow towards the optic nerve.

Although the pathophysiology is not fully understood, it is believed to be due to an immune response to cell-mediated endothelial damage. GCA is becoming increasingly recognized as a result of awareness in the medical community and advancements in technology and imaging methods. GCA is detected using a combination of laboratory tests such as CRP and ESR, which are both inflammation-related markers. ESR usually is elevated in case of GCA to a level of 50 mm/h (5)(6). Moreover, the gold standard diagnostic test for GCA is a temporal artery biopsy (7). An additional test that is usually used to examine GCA is duplex ultrasound (10) (12) (13). Supportive findings (10) (12) are Edema and thickening of the vessel wall (halo sign), non-compressible artery (compression sign) – stenosis, and occlusion (15). Additional imaging studies (14) are indicated when high clinical suspicion for GCA in order to differentiate other types of vasculitis (17)(18). The initial approach towards newly diagnosed GCA or recurrent patients is high dose glucocorticoid therapy for 2-4 weeks (11) (17)(19), this is due to the complication which leads to permanent vision loss if the patient is left untreated (21). In some cases, extracranial vessels such as ascending aorta and its anastomoses, leading to claudication of the limbs with or without temporal involvement (22) could be called limb-restricted GCA or atypical manifestation of the disease.

The aim of the literature review is to describe all of the atypical manifestations of GCA throughout cases and provide more accurate clinical features and characteristics. Moreover, various imaging modalities for clinical assessment in order to provide a better diagnosis will be reviewed.

4. Epidemiology of extracranial involvement in GCA

Since patients with extracranial GCA were not systematically analyzed in early retrospective studies, extracranial involvement may have been underestimated (25). One study using very liberal diagnostic criteria have found, that 83% patients with GCA demonstrate extracranial arteries involvement using PET in large arteries (26). Through an overview of reported prevalence, most commonly, the aorta and its proximal limb branches are reported to be the most commonly affected, including the subclavian, axillary, and brachial arteries, in contrast, the lower limbs arteries were significantly less affected (27,28), as can be seen on the reported extracranial involvement in the table 1. Moreover, according to the epidemiological data that are obtained to use the following manifestations of extracranial GCA, it seems to be in higher predominance between females at age above 50 (2,37,31), and especially in elderly patients with a fever or elevated ESR of unknown origin (31,38,39), in addition to that, several studies have shown that female develop GCA 3 times more than men due to the fact females are more sensitive to autoimmune diseases due to an unclear mechanism. Some biological factors might be affecting the cause, especially hormones such as estrogen which is linked to the influence of immunity (42).

Table 1. Sites of vasculitis and the arterial segment involvement

- Aorta Thoracic	45-65% (29,30,31,32,33)
Ascending	12-45% (30,31,32)
Aortic arch	58% (30,31,32)
Descending	Unknown
Abdominal	27-54% (29,30,31,32,33)
-Cerebral Carotid	17-62% (29,30,31,32,33,34)
Vertebra- basilar	8-17% (33,34)
-Extremities Subclavian	26-100% (30,31,32,33,34,35)
Axillary	18-44% (30,31,32,33,34,35)
Iliac	15-62% (30,35,31,32)
Femoral	12-53% (30,31,32,34,35,36)
-Other Renal	8-25% (31, 33)
Coronary	Unknown
Mesenteric	18-23% (31, 33)

5. Diagnosis

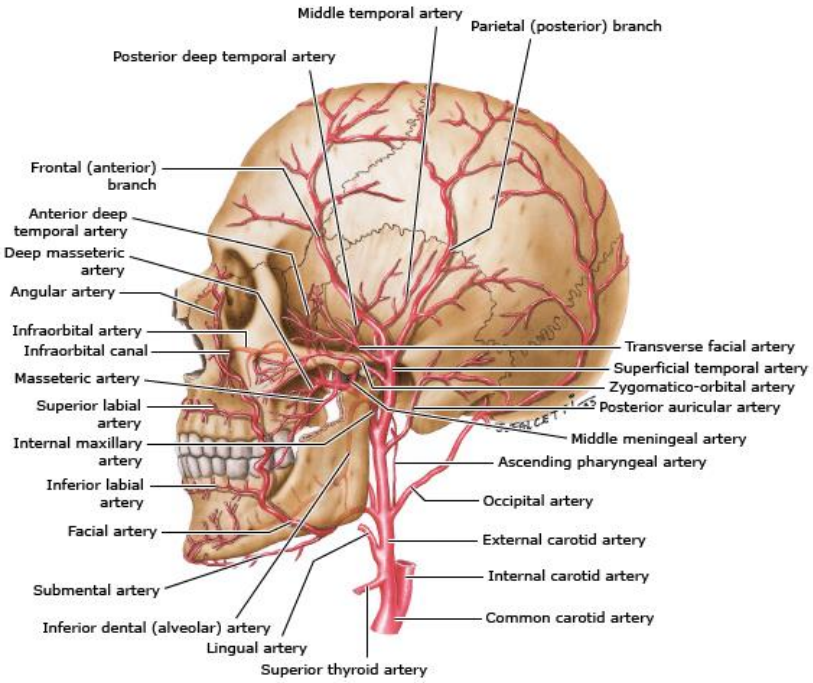
A non-specific set of symptoms and signs often makes extracranial GCA difficult to diagnose. It is also often difficult for biopsy to access affected arteries (35). Consequently, due to a lack of awareness of this disease, an extensive (average up to six months) diagnosis delay may occur, especially when it is an extracranial GCA, leading to significant morbidity and mortality (40, 41).

5.1.Clinical signs and features

Patients with extracranial GCA may experience general and cardiovascular symptoms. It is impossible to estimate the prevalence of the various signs and symptoms from the literature since it is largely made up of small, selected, or mixed series. In spite of this, there are a few conclusions that can be interpreted. In the course of physical examination, the patient can be asymptomatic regarding the setting of the disease, however, during the cardiovascular examination, nonspecific symptoms may appear, which are considered to be more prevalent in extracranial GCA (35). Vascular features include diminished limb blood pressure, which can appear as limb claudication, hence, on physical examination, it is important to palpate and measure the arteries blood flow: carotid, subclavian, axillary, brachial, and radial. As well as to compare the blood pressure in both arms. Furthermore, bruits and aortic murmurs should be inspected on auscultation in order to identify any sign of an aortic aneurysm (complication) (43). In addition, other less common manifestations of GCA to be considered to check are the central nervous system manifestations, Based on cohort GCA studies, 24.6% of patients (43 out of 175) had cranial ischemic complications (44,45). The majority of strokes occured in the vertebrobasilar system (44,45) and manifested with vertigo, ataxia, dysarthria, homonymous hemianopia, or bilateral cortical blindness (46), as well as other neurological dysfunction the peripheral nervous system, thus cranial examination should be performed, as well as neuroimaging in order to exclude other pathologies (47). In some cases, with long duration of the disease and lack of proper treatment, lingual infarctions are seen as a result of artery infarction and subacute strokes (48). One case describes an atypical presentation of GCA of a 77-year-old man, with a history of altered mental status that was unable to protrude his tongue and when examined closely the right side of the

tongue showed discoloration. A cerebral angiogram revealed narrowing of both external and internal carotid arteries which most likely led to the tongue discoloration and lack of mobility.

Figure 2. Arteries of the scalp (49)



Other atypical features that have been described in GCA include- dysarthria (50), and sensorineural hearing loss (51) due to audiovestibular damage, in a prospective study analyzing the frequency of an outcome of audiovestibular abnormality in GCA patients, it was found that almost 90% of patients featured 8th nerve dysfunction in some degree. Breast mass vasculitis (52) is an uncommon manifestation of GCA, it may present as a systemic disease or an isolated lesion in the breast and sometimes may imitate breast cancer. The vasculitis features are not expressed as well the histological characteristics are absent. Generally, these patients do not require systemic therapy and can be cured through resection alone. Pericarditis was another condition linked with GCA, these atypical findings were diagnosed in 71-year-old women with echocardiography and left temporal artery biopsy (53), and pericardial effusion was completely remitted after treatment with corticosteroids. In a literature review of published cases, a total of 79 patients were diagnosed with LR-GCA (limb restricted). all cases in which TAB were negative and patients above 50 years old were excluded, as well patients who didn't respond to steroids treatment.

The patients were evaluated by their symptoms of complaints such as a history of bilateral progressive numbness of the hands, positive PMR, and hypertension. All lab results included CBC and biochemistry panels such as cholesterol, triglyceride, and coagulation tests were in the normal range for ruling out atherosclerosis, as well as tubersclerosis and syphilis infections. All patients denied typical symptoms of GCA (headache, jaw claudication, and visual symptoms). Limb claudication was the main complaint. The diagnostic tools that were performed in order to identify the pathology were arterial color Doppler US of the upper extremities which showed bilateral occlusions, and CT to confirm the occlusions. FDG-PET was assessed in order to show claudication by FDG uptake in the brachial and axillary arteries. (Seen in figure 3).

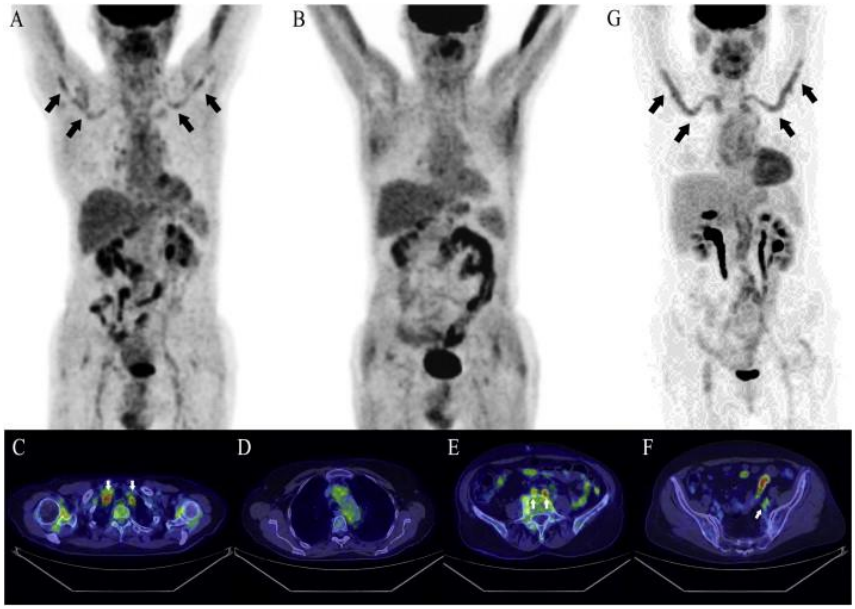


Figure 3 Giant cell arteritis restricted to the limb arteries: An overlooked clinical entity panel of A. coronal reconstructions of FDG-PET study of patient (24)

Regarding the treatment in the performed study, the patients were administered a tapering dose of oral prednisone starting at 1mg/kg daily and slowly decreasing the amount (in order not to cause any complications related to steroids) with a low dose of aspirin until the establishment of remission of clinical and laboratory symptoms to the normal state.

5.1. Laboratory

Extracranial GCA does not have a specific laboratory test since it is atypical. Usually patients with GCA present with elevated inflammatory markers of ESR which can exceed 100 mm/hour, (54),

and CRP. However, a retrospective study with biopsy-proven GCA found normal values of ESR and CRP in 4% out of 177 patients (55), hence none of the two ESR and CRP is specific for GCA, thus, the markers are not diagnostically reliable or in fact, are controversial.

5.2. Imaging

Since extracranial GCA often has atypical symptoms and nonspecific blood test results, in clinical practice, several imaging modalities are used to give the most accurate diagnosis. Each modality has its own advantages and limitations. As well, it is highly important to distinguish extracranial GCA from atherosclerosis which represents the main differential diagnosis (59). Duplex ultrasound is the first-line imaging technique used in GCA, the supportive finding may reveal thickening of the vessel and noncompressible arteries (60). Other arteries such as the aorta that may be involved in extracranial pathology are more challenging and less sensitive to investigate due to the deep anatomical location. For suspected extracranial involvement, more sensitive imaging modalities are required, therefore MRI or MRA are suitable for contrast enhancement of the vessel wall, in order to assess the mural inflammation and vessel wall thickening (28), which should be done up to the 4^{th} day of the steroid therapy induction, that is due to the rapid decline in MRI sensitivity from the steroids use which might lead to false negatives results (61). In addition, CTA and PET-FDG are other sensitive imaging modalities that are used when predominant extracranial involvement is suspected, also in order to assess the vessel wall inflammation.

The results of recent studies indicate that FDG-PET diagnostic accuracy increased significantly, particularly when performed on patients without immunosuppression or steroids uptake (62), nevertheless, due to its high cost, a higher amount of radiation, and inaccessibility of PET, CT is often the modality of choice.

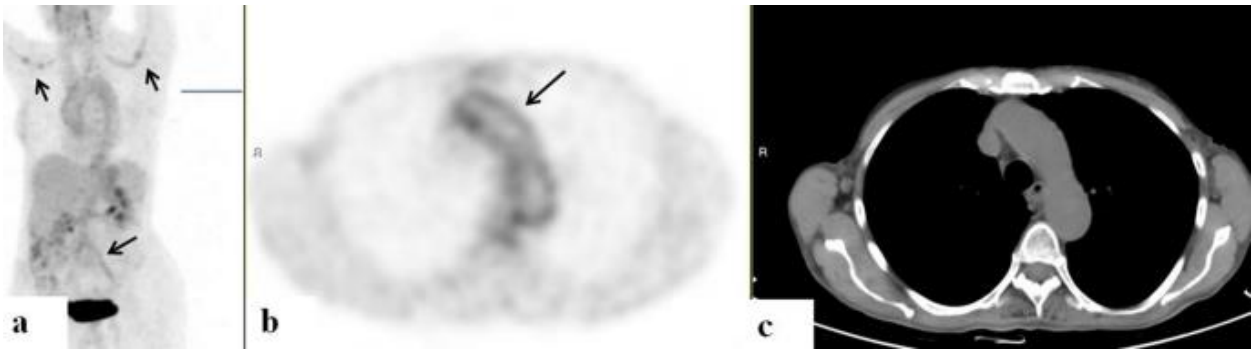


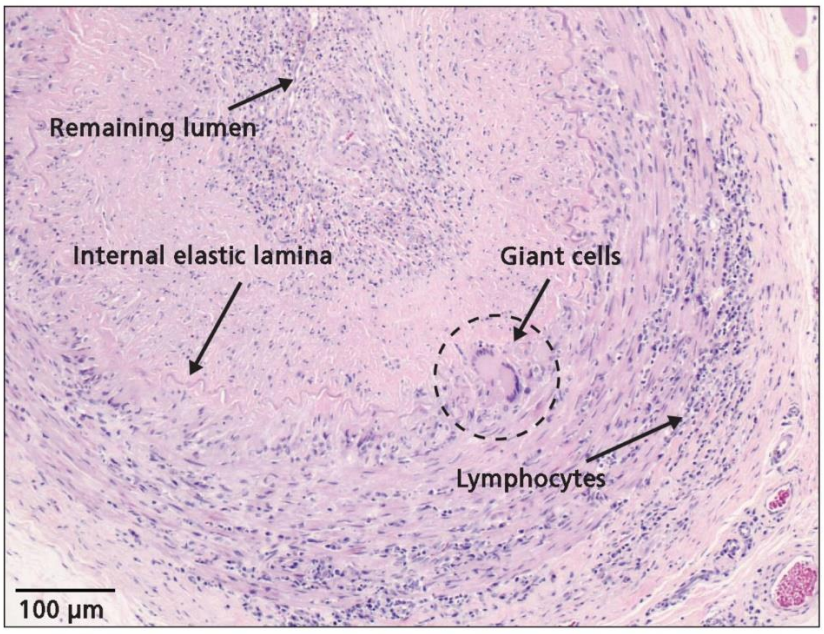
Figure 4. FDG-PET/CT: maximum intensity projection (MIP) (**a**) a representative PET (**b**) and CT (**c**) axial slices. A 75-year-old woman with giant cell arteritis. PET demonstrates increased uptake (arrows) along the vessel walls of the aorta, subclavian, and common iliac arteries (63).

5.3. Biopsy

The confirmation of extracranial GCA usually first emerges from imaging modalities performed for the assessment of any other etiologies such as malignancy or infection, and biopsies are generally out of reach, except if vascular surgery is necessary (64), for instance, during aneurysm repair or any other vascular surgery. On an elective clinical biopsy, temporal arteritis is uncommonly related in the extracranial GCA setting (64). In a retrospective trial, out of 57 patients with large vessel GCA in whom the patient eventually underwent a temporal artery biopsy, it was found out that 33 patients were detected with positive biopsy thus, the sensitivity of TAB in extracranial GCA is up to 58% (40)(65). The sensitivity most likely depends on the clinical features that indicate the presence of temporal arteritis (66). It is adviced to perform artery biopsy in patients with suspected extracranial GCA, even though false-negative results may occur, due to the fact that positive result is highly specific for GCA. Nevertheless, another claim suggests high imaging modalities are highly indicative of extracranial GCA, as negative biopsy does not exclude extracranial GCA.

It is important to know, that according to the results of different studies, the temporal artery biopsy after steroids were administered tend to show less specific pathological features. From the histopathology point of view, the changes in extracranial and temporal arteries are similar in case of GCA (67). The features include the proliferation of the intima and granulomatous inflammation, which cause the thickening of the intima (leading to artery stenosis). Lymphocytes and other cells fusion form the giant cells which may not be present in all cases but may be found in the media and in the intima, however, the sensitivity can be affected by the fragmentation of the internal elastic lamina and the disturbed media anatomy (68-69).

Figure 5. High-power hematoxylin & eosin stained section of the superficial temporal artery biopsy specimen revealing pan-arteritis with giant cells (70)



6. Differential Diagnosis

When inflammation of large arteries is suspected after various diagnostic modalities such as laboratory, imaging, and clinical symptoms, other types of vasculitis than GCA have to be differentiated especially with the absence of cranial GCA symptoms, however, several other distinguishing features can be found in other vasculitides.

One of the main diseases to be differentiated is another large artery vasculitis Takayasu arteritis. The histopathology and imaging findings of Takayasu and GCA are almost identical and are very hard to distinguish. Both are differentiated by age of the patient, as GCA never takes place in individuals younger than 50, while Takayasu arteritis usually tends to begin at the average age of 13-38 (71). In addition, the clinical expression is also different for instance, renovascular hypertension due to renal artery stenosis (72) does not occur in GCA, and other features that occur in the presence of GCA such as anterior ischemic optic neuropathy and PMR are not seen in Takayasu arteritis.

Secondary large vessel vasculitis is infrequent and could be caused by infection, such as tuberculosis, syphilis, HIV, or in other systemic inflammatory diseases, such as rheumatoid arthritis, systemic lupus erythematosus, sarcoidosis, or IgG4-related aortitis that can be associated with the underlying clinical features (constitutional symptoms), or trigger the disease (73), moreover, there are several other types of vasculitis, mainly small and medium vessel vasculitides which can present with similar symptoms, however, these diseases differ in the location of their vascular distributions, their histopathology, and the organs they affect (75).

Atherosclerosis is another of the main differential diagnostics that has to be ruled out, since it may build up atherosclerotic plaque leading to hardening and narrowing of the artery which manifests with limb claudication or stenosis, which can be seen with extracranial GCA clinical features, given the occurrence of dyslipidemia in older patients over 50 is highly associated (74). Nonarteritic anterior ischemic optic neuropathy (NAAION) can be mistaken for GCA complication mostly because of a presentation of sudden visual loss in the elderly.

Risk factors of NAAION include hypertension, diabetes mellitus, and the use of certain drugs that can manifest side effects similar to GCA. Laboratory tests could show normal levels of CRP and ESR, the main tool for diagnosing NAAION is an endoscopy performed to measure the crowded optic nerve head and small physiologic cup, revealing a small cup-to-disc ratio, which as well could be hard to differentiate, although the treatment remains the same with steroids (76).

7. Complications and Prognosis

Large vessel complication is frequently associated with GCA, predominantly in those with extracranial GCA, since the large vessels are already inflamed. The most common complications are permanent vision loss (77) if left untreated, cerebral ischemia (78), aortic aneurysm, and aortic dissection (79).

Irreversible vision loss is the most feared complication of GCA, which can be unilateral or bilateral, painless and sudden. Permanent vision loss due to GCA occurs from retinal artery occlusion (anterior ischemic optic neuropathy- AION) as a consequence of ischemia of the ciliary artery (a branch of the ophthalmic artery supplied by the internal carotid artery) which is one of the main sources of blood supply to the optic nerve. According to a cohort study, approximately 85% of vision loss caused by GCA is caused by AION (80). In GCA, strokes are uncommon and quite rare, in descriptive cohorts, it was found that the frequency of strokes in GCA patients is low, with rates of approximately 1.5-7% in the 1-4 weeks of diagnosis of GCA (44, 81). In GCA strokes, both the vertebrobasilar and internal carotid arteries can be involved, but the vertebrobasilar system is most commonly affected (82).

The vertebrobasilar system accounts for more than half of all strokes caused by GCA (78). In the case of GCA affecting the vertebral arteries, this can cause neurological symptoms such as vertigo, ataxia, and bilateral cortical blindness (83). Bilateral involvement of the vertebral arteries can cause rapidly progressive neurological deficits in the brainstem and/or cerebellum with a high mortality rate and is highly suggestive of GCA (84). Additionally, it is found that GCA patients are at greater risk of experiencing cerebrovascular and cardiovascular events compared to those without GCA (85). The clinical identification of aortic aneurysm has been reported in 10-20% of cases (86). The thoracic aorta, specifically the ascending aorta, is more commonly affected than the abdominal aorta. Despite this, clinically or laboratory evidence of systemic GCA activity is usually minimal or nonexistent.

Individuals with GCA are at an elevated risk for aortic aneurysms as compared to those without GCA. According to a cohort study of 96 patients with biopsy-proven GCA, these patients are 17

times more likely to develop thoracic aortic aneurysms and 2.4 times more likely to develop isolated abdominal aortic aneurysms than individuals of the same age and gender (87). Aortic aneurysm detection time is dependent on whether systematic imaging is performed between diagnosis of GCA and detection of aneurysm.

However, in most cases, clinical identification of an aortic aneurysm is delayed. A descriptive research of 41 patients with GCA found that 3 of them developed aneurysms before the GCA was diagnosed, 5 were diagnosed with GCA and aneurysm at the same time, and for the remaining 33 patients, the detection of aneurysms took place at a median of 7 years after GCA diagnosis was established (88). In addition, risk factors include being male, polymyalgia, hypertension and for those who are at a younger age (88, 23).

The biopsy examination obtained during the surgery or autopsy may show a wide range of results, including fibrosis and different levels of active aortitis, which may show giant cells. Moreover, it is difficult to determine the predictive roles of risk factors like age, sex, smoking, hypertension, hyperlipidemia, and other background diseases. Furthermore, patients with large vessel GCA are more likely to develop distal aortic events, such as abdominal aortic aneurysms, at a higher frequency (90).

Although subclinical or clinical aortitis is prevalent in GCA, significant complications associated with aortic dissection and rupture are uncommon. There were only 1 to 6% of GCA patients who experienced aortic dissection or rupture, according to two large-scale referral center retrospective studies (86). The aortic wall becomes more prone to dissection due to inflammation, which weakens the elastic lamina (91). Hypertension and delayed diagnosis further increase the likelihood of dissection (86) and it is typical for dissections to occur around 2.5 years after a diagnosis of GCA (25).

7.1. Mortality

Patients with GCA who show acute aortic pathology as their first clinical manifestation are at higher risk of mortality, which varies between 44-80%. Whether or not they have had extracranial involvement (92-95). Studies have shown that the mortality rate is particularly increased in GCA patients with thoracic aortic dissections and aneurysms, however, there is no established increase in mortality for patients with other large-artery complications (93, 96).

A retrospective study has also indicated that patients with extracranial GCA, specifically aortitis, have a higher incidence of vascular events, including stroke, and a higher mortality rate from vascular causes compared to those without aortic involvement (97). Furthermore, GCA patients have a significantly higher risk of mortality due to ischemic heart disease, compared to patients with ischemic heart disease without GCA (98).

8. Treatment

The extent and intensity of treatment required for extracranial GCA are unclear. Due to the lack of randomized clinical trials, immunosuppressive therapy is not supported by evidence, however, patients with proven or suspected extracranial GCA are treated similarly to those with typical GCA. A study included 36 patients with extracranial GCA, a total of 11 patients who received steroids did not develop any new aneurysms, while six of the 25 patients who were not treated did (99). Symptoms such as fever, myalgia, malaise, and anemia often improve quickly in patients with extracranial GCA following steroid treatment. Additionally, a recent prospective study found that following one year of treatment with glucocorticoids, CTA symptoms of vasculitis improved (100).

Moreover, antiplatelet treatment (low aspirin dose-81 mg per oral) should be added to all patients affected with GCA or extracranial GCA, because as established by meta-analysis, it protects against the development of new severe ischemic complications, without increasing bleeding risks (101-102). When treatment is prescribed, it is initially common to start with a high dose of glucocorticoids in order to prevent any complications of ischemic events (vision loss or stroke). The possibilities vary, depending on the state of the patient whether the complications are absent or present.

In an uncomplicated disease, glucocorticoids are administered orally. Usually prednisolone 40–60 mg once daily in the morning is given. In ischemic organ damage (vision impairment) initial pulse therapy with IV glucocorticoids is given before oral glucocorticoids (103). Maintenance therapy is needed, usually, after the acute symptoms have resolved or in case of asymptomatic features according to imaging modalities (decrease of inflammation features). Gradually tapering of glucocorticoids to the lowest dose is needed to control symptoms, the dosage is typically low for most of this time. The aim is that in a few months, the dose should be reduced to 15–20 mg of oral prednisolone, followed by 5 mg after 1 year, at which point the dose can be further tapered and stopped (103).

Duration of the treatment varies since it is possible for patients to experience a chronic and recurrent course of the disease (104). Furthermore, it is important to take into consideration to

administer prophylactic measures in order to prevent complications of glucocorticoid therapy (osteoporosis, peptic ulcers and etc.). Adjunctive therapy with glucocorticoid sparing agents, such as Tocilizumab (IL-6 antagonist) has been studied in individuals with cranial GCA and could be inspected for extracranial GCA use, it is considered in patients who are at high risk to develop complications from long term glucocorticoids use or who are in relapse, as well the treatment could use to lower the dose of glucocorticoids (105). However, there are limited evidence about long-term effects of tocilizumab treatment on disease progression due to its effect on IL-6 (106).

8.1. Surgery

In active inflammatory process surgical procedures are usually not preformed, since inflammation interfere with healing process and increases the risk of complication. Furthermore, vessel inflammation makes it more difficult for the surgeon to evaluate the damage. However, patients who are treated with steroids, usually respond well. At the point the inflammation is stabilized, reconstructive surgery in the setting of GCA related aortic aneurysm is suitable. Following a surgical repair, patients should undergo lifelong screening evaluations of the remaining aorta. This is needed because a significant percentage of patients with GCA-related aortic aneurysms will require intervention for more distal disease. This involves regularly monitoring the aorta with imaging tests such as CT scans or MRIs to detect any new aneurysms or growth of existing one (90).

9. Conclusion

Due to the lack of clinical trials, it is difficult to diagnose extracranial GCA, since it appears with various clinical features that might suggest otherwise, however, in a clinical setting of different laboratory results suggest high levels of inflammation in patients above the age of 50 with a suspicious arterial disease, imaging modalities such as CTA, MRI or PET scan should be used, because the evidence of the inflammation of blood vessel walls can help to identify areas of active inflammation and differentiate GCA from other pathologies that can show similar features.

In addition, in order to be more precise with the diagnosis, these advances in imaging modalities can also help to track the progression of the disease and the response to treatment. For instance, to evaluate the effectiveness of treatment, as well, repeat imaging studies can be used to guide therapy adjustments. Generally, developing more sensitive and specific imaging methods for diagnosing and treating GCA could improve patient outcomes. These highly advanced modalities can help patients avoid serious complications such as vision loss, aneurysms or strokes by allowing earlier detection and more accurate diagnosis.

The treatment of extracranial GCA remains debatable. There is no consensus regarding the treatment of all cases, or whether the same treatment protocol should be used for all cases as for cranial GCA.

10. SOURCES:

1. Crowson, C. S., Matteson, E. L., Myasoedova, E., Michet, C. J., Ernste, F. C., Warrington, K. J., Davis, J. M., 3rd, Hunder, G. G., Therneau, T. M., & Gabriel, S. E. (2011). The lifetime risk of adult-onset rheumatoid arthritis and other inflammatory autoimmune rheumatic diseases. *Arthritis and rheumatism*, *63*(3), 633–639. https://doi.org/10.1002/art.30155

2. Gonzalez-Gay, M. A., Miranda-Filloy, J. A., Lopez-Diaz, M. J., Perez-Alvarez, R., Gonzalez-Juanatey, C., Sanchez-Andrade, A., Martin, J., & Llorca, J. (2007). Giant cell arteritis in northwestern Spain: a 25-year epidemiologic study. *Medicine*, *86*(2), 61–68. https://doi.org/10.1097/md.0b013e31803d1764

3. Richardson, J. E., Gladman, D. D., Fam, A., & Keystone, E. C. (1987). HLA-DR4 in giant cell arteritis: association with polymyalgia rheumatica syndrome. *Arthritis and rheumatism*, *30*(11), 1293–1297. https://doi.org/10.1002/art.1780301113

4. Gonzalez-Gay, M. A., Barros, S., Lopez-Diaz, M. J., Garcia-Porrua, C., Sanchez-Andrade, A., & Llorca, J. (2005). Giant cell arteritis: disease patterns of clinical presentation in a series of 240 patients. *Medicine*, *84*(5), 269–276. https://doi.org/10.1097/01.md.0000180042.42156.d1

5. Wallach JB. *Interpretation of Diagnostic Tests*. Philadelphia, PA: Lippincott Williams & Wilkins; 2007

6. Ness, T., Bley, T. A., Schmidt, W. A., & Lamprecht, P. (2013). The diagnosis and treatment of giant cell arteritis. *Deutsches Arzteblatt international*, *110*(21), 376–386. https://doi.org/10.3238/arztebl.2013.0376

7. Brkic A, Terslev L, Møller Døhn U, Torp-Pedersen S, Schmidt WA, Diamantopoulos AP. Clinical Applicability of Ultrasound in Systemic Large Vessel Vasculitides. *Arthritis & Rheumatology*. 2019; 71(11): p.1780-1787. doi: 10.1002/art.41039.| Open in Read by QxMD

8. Oh, L. J., Wong, E., Gill, A. J., McCluskey, P., & Smith, J. E. H. (2018). Value of temporal artery biopsy length in diagnosing giant cell arteritis. *ANZ journal of surgery*, *88*(3), 191–195. https://doi.org/10.1111/ans.13822

9. Poller, D. N., van Wyk, Q., & Jeffrey, M. J. (2000). The importance of skip lesions in temporal arteritis. *Journal of clinical pathology*, *53*(2), 137–139. https://doi.org/10.1136/jcp.53.2.137

10. Schmidt W. A. (2018). Ultrasound in the diagnosis and management of giant cell arteritis. *Rheumatology (Oxford, England)*, *57*(suppl_2), ii22–ii31. https://doi.org/10.1093/rheumatology/kex461

11. Ponte, C., Rodrigues, A. F., O'Neill, L., & Luqmani, R. A. (2015). Giant cell arteritis: Current treatment and management. *World journal of clinical cases*, *3*(6), 484–494. https://doi.org/10.12998/wjcc.v3.i6.484

12. Wallach, J.B. (2007) Interpretation of Diagnostic Tests. 8th Edition, Lippincott Williams & Wilkins, Philadelphia.

13. Bardi, M., & Diamantopoulos, A. P. (2019). EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice summary. *La Radiologia medica*, *124*(10), 965–972. https://doi.org/10.1007/s11547-019-01058-0

14. Bley, T. A., Wieben, O., Uhl, M., Thiel, J., Schmidt, D., & Langer, M. (2005). High-resolution MRI in giant cell arteritis: imaging of the wall of the superficial temporal artery. *AJR. American journal of roentgenology*, *184*(1), 283–287. https://doi.org/10.2214/ajr.184.1.01840283

15. AbuRahma, A., & Bergan, J. (Eds.). (2010). *Noninvasive peripheral arterial diagnosis*. Springer Science & Business Media.

16. Schmidt W. A. (2018). Ultrasound in the diagnosis and management of giant cell arteritis. *Rheumatology (Oxford, England)*, *57*(suppl_2), ii22–ii31. https://doi.org/10.1093/rheumatology/kex461

17. Lyons, H. S., Quick, V., Sinclair, A. J., Nagaraju, S., & Mollan, S. P. (2020). A new era for giant cell arteritis. *Eye (London, England)*, *34*(6), 1013–1026. https://doi.org/10.1038/s41433-019-0608-7

18. Hunder, G. G., Bloch, D. A., Michel, B. A., Stevens, M. B., Arend, W. P., Calabrese, L. H., Edworthy, S. M., Fauci, A. S., Leavitt, R. Y., & Lie, J. T. (1990). The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis and rheumatism*, *33*(8), 1122–1128. https://doi.org/10.1002/art.1780330810

19. Hellmich, B., Agueda, A., Monti, S., Buttgereit, F., de Boysson, H., Brouwer, E., Cassie, R., Cid, M. C., Dasgupta, B., Dejaco, C., Hatemi, G., Hollinger, N., Mahr, A., Mollan, S. P., Mukhtyar, C., Ponte, C., Salvarani, C., Sivakumar, R., Tian, X., Tomasson, G., … Luqmani, R. A. (2020). 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. *Annals of the rheumatic diseases*, *79*(1), 19–30. https://doi.org/10.1136/annrheumdis-2019-215672

20. Buttgereit, F., Matteson, E. L., & Dejaco, C. (2020). Polymyalgia Rheumatica and Giant Cell Arteritis. *JAMA*, *324*(10), 993–994. https://doi.org/10.1001/jama.2020.10155

21. Aiello, P. D., Trautmann, J. C., McPhee, T. J., Kunselman, A. R., & Hunder, G. G. (1993). Visual prognosis in giant cell arteritis. *Ophthalmology*, *100*(4), 550–555. https://doi.org/10.1016/s0161-6420(93)31608-8

22. Brack, A., Martinez-Taboada, V., Stanson, A., Goronzy, J. J., & Weyand, C. M. (1999). Disease pattern in cranial and large-vessel giant cell arteritis. *Arthritis and rheumatism*, *42*(2), 311–317. https://doi.org/10.1002/1529-0131(199902)42:2<311::AID-ANR14>3.0.CO;2-F

23. García-Martínez, A., Hernández-Rodríguez, J., Arguis, P., Paredes, P., Segarra, M., Lozano, E., Nicolau, C., Ramírez, J., Lomeña, F., Josa, M., Pons, F., & Cid, M. C. (2008). Development of aortic aneurysm/dilatation during the followup of patients with giant cell arteritis: a cross-sectional screening of fifty-four prospectively followed patients. *Arthritis and rheumatism*, *59*(3), 422–430. https://doi.org/10.1002/art.23315

24. Berti, A., Campochiaro, C., Cavalli, G., Pepe, G., Praderio, L., Sabbadini, M. G., & Dagna, L. (2015). Giant cell arteritis restricted to the limb arteries: An overlooked clinical entity. *Autoimmunity reviews*, *14*(4), 352–357. https://doi.org/10.1016/j.autrev.2014.12.005

25. Evans, J. M., Bowles, C. A., Bjornsson, J., Mullany, C. J., & Hunder, G. G. (1994). Thoracic aortic aneurysm and rupture in giant cell arteritis. A descriptive study of 41 cases. *Arthritis and rheumatism*, *37*(10), 1539–1547. https://doi.org/10.1002/art.1780371020

26. Blockmans, D., de Ceuninck, L., Vanderschueren, S., Knockaert, D., Mortelmans, L., & Bobbaers, H. (2006). Repetitive 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a prospective study of 35 patients. *Arthritis and rheumatism*, *55*(1), 131–137. https://doi.org/10.1002/art.21699

27. Assie, C., Janvresse, A., Plissonnier, D., Levesque, H., & Marie, I. (2011). Long-term follow-up of upper and lower extremity vasculitis related to giant cell arteritis: a series of 36 patients. *Medicine*, *90*(1), 40–51. https://doi.org/10.1097/MD.0b013e318206af16

28. Kermani, T. A., Matteson, E. L., Hunder, G. G., & Warrington, K. J. (2009). Symptomatic lower extremity vasculitis in giant cell arteritis: a case series. *The Journal of rheumatology*, *36*(10), 2277–2283. https://doi.org/10.3899/jrheum.090269

29. Agard, C., Barrier, J. H., Dupas, B., Ponge, T., Mahr, A., Fradet, G., Chevalet, P., Masseau, A., Batard, E., Pottier, P., Planchon, B., Brisseau, J. M., & Hamidou, M. A. (2008). Aortic involvement in recent-onset giant cell (temporal) arteritis: a case-control prospective study using helical aortic computed tomodensitometric scan. *Arthritis and rheumatism*, *59*(5), 670–676. https://doi.org/10.1002/art.23577 .

30. Jain, D., Dietz, H. C., Oswald, G. L., Maleszewski, J. J., & Halushka, M. K. (2011). Causes and histopathology of ascending aortic disease in children and young adults. *Cardiovascular pathology : the official journal of the Society for Cardiovascular Pathology*, *20*(1), 15–25. https://doi.org/10.1016/j.carpath.2009.09.008

31. Le Hello, C., Lévesque, H., Jeanton, M., Cailleux, N., Galateau, F., Peillon, C., Veyssier, P., Watelet, J., Letellier, P., Courtois, H., & Maïza, D. (2001). Lower limb giant cell arteritis and temporal arteritis: followup of 8 cases. *The Journal of rheumatology*, *28*(6), 1407–1412

32. Walter, M. A., Melzer, R. A., Schindler, C., Müller-Brand, J., Tyndall, A., & Nitzsche, E. U. (2005). The value of [18F]FDG-PET in the diagnosis of large-vessel vasculitis and the assessment of activity and extent of disease. *European journal of nuclear medicine and molecular imaging*, *32*(6), 674–681. https://doi.org/10.1007/s00259-004-1757-9

33. Grayson, P. C., Maksimowicz-McKinnon, K., Clark, T. M., Tomasson, G., Cuthbertson, D., Carette, S., Khalidi, N. A., Langford, C. A., Monach, P. A., Seo, P., Warrington, K. J., Ytterberg, S. R., Hoffman, G. S., Merkel, P. A., & Vasculitis Clinical Research Consortium (2012). Distribution of arterial lesions in Takayasu's arteritis and giant cell arteritis. *Annals of the rheumatic diseases*, *71*(8), 1329–1334. https://doi.org/10.1136/annrheumdis-2011-200795

34. Aschwanden, M., Kesten, F., Stern, M., Thalhammer, C., Walker, U. A., Tyndall, A., Jaeger, K. A., Hess, C., & Daikeler, T. (2010). Vascular involvement in patients with giant cell arteritis determined by duplex sonography of 2x11 arterial regions. *Annals of the rheumatic diseases*, *69*(7), 1356–1359. https://doi.org/10.1136/ard.2009.122135

35. Schmidt, W. A., Seifert, A., Gromnica-Ihle, E., Krause, A., & Natusch, A. (2008). Ultrasound of proximal upper extremity arteries to increase the diagnostic yield in large-vessel giant cell arteritis. *Rheumatology (Oxford, England)*, *47*(1), 96–101. https://doi.org/10.1093/rheumatology/kem322

36. Czihal, M., Zanker, S., Rademacher, A., Tatò, F., Kuhlencordt, P. J., Schulze-Koops, H., & Hoffmann, U. (2012). Sonographic and clinical pattern of extracranial and cranial giant cell arteritis. *Scandinavian journal of rheumatology*, *41*(3), 231–236. https://doi.org/10.3109/03009742.2011.641581

37. Ninet, J. P., Bachet, P., Dumontet, C. M., Du Colombier, P. B., Stewart, M. D., & Pasquier, J. H. (1990). Subclavian and axillary involvement in temporal arteritis and polymyalgia rheumatica. *The American journal of medicine*, *88*(1), 13–20. https://doi.org/10.1016/0002-9343(90)90121-s

38. Meller, J., Sahlmann, C. O., Gürocak, O., Liersch, T., & Meller, B. (2009). FDG-PET in patients with fever of unknown origin: the importance of diagnosing large vessel vasculitis. *The quarterly journal of nuclear medicine and molecular imaging : official publication of the Italian Association of Nuclear Medicine (AIMN) [and] the International Association of Radiopharmacology (IAR), [and] Section of the Society of...*, *53*(1), 51–63.

39. Lensen, K. J., Voskuyl, A. E., van der Laken, C. J., Comans, E. F., van Schaardenburg, D., Arntzenius, A. B., Zwijnenburg, T., Stam, F., Gompelman, M., Zant, F. M., van Paassen, A. Q.,

Voerman, B. J., Smit, F., Anten, S., Siegert, C. E., Binnerts, A., & Smulders, Y. M. (2013). 18F-fluorodeoxyglucose positron emission tomography in elderly patients with an elevated erythrocyte sedimentation rate of unknown origin. *PloS one*, *8*(3), e58917. https://doi.org/10.1371/journal.pone.0058917

40. Brack, A., Martinez-Taboada, V., Stanson, A., Goronzy, J. J., & Weyand, C. M. (1999). Disease pattern in cranial and large-vessel giant cell arteritis. *Arthritis and rheumatism*, *42*(2), 311–317. https://doi.org/10.1002/1529-0131 (199902)42:2<311::AID-ANR14>3.0.CO;2-F

41. Calvo-Romero J. M. (2003). Giant cell arteritis. *Postgraduate medical journal*, *79*(935), 511–515. https://doi.org/10.1136/pmj.79.935.511

42. Hayreh, S. S., Podhajsky, P. A., & Zimmerman, B. (1998). Ocular manifestations of giant cell arteritis. *American journal of ophthalmology*, *125*(4), 509–520. https://doi.org/10.1016/s0002-9394(99)80192-5

43. Spence, R. K., Estella, F., Gisser, S., Schiffman, R., & Camishion, R. C. (1985). Thoracic aortic aneurysm secondary to giant cell arteritis: a reappraisal of etiology, treatment and possible prevention. *The Journal of cardiovascular surgery*, *26*(5), 492–495.

44. Nesher, G., Berkun, Y., Mates, M., Baras, M., Nesher, R., Rubinow, A., & Sonnenblick, M. (2004). Risk factors for cranial ischemic complications in giant cell arteritis. *Medicine*, *83*(2), 114–122. https://doi.org/10.1097/01.md.0000119761.27564.c9

45. Gonzalez-Gay, M. A., Vazquez-Rodriguez, T. R., Gomez-Acebo, I., Pego-Reigosa, R., Lopez-Diaz, M. J., Vazquez-Triñanes, M. C., Miranda-Filloy, J. A., Blanco, R., Dierssen, T., Gonzalez-Juanatey, C., & Llorca, J. (2009). Strokes at time of disease diagnosis in a series of 287 patients with biopsy-proven giant cell arteritis. *Medicine*, *88*(4), 227–235. https://doi.org/10.1097/MD.0b013e3181af4518

46. Wilkinson, I. M., & Russell, R. W. (1972). Arteries of the head and neck in giant cell arteritis. A pathological study to show the pattern of arterial involvement. *Archives of neurology*, *27*(5), 378–391. https://doi.org/10.1001/archneur.1972.00490170010003

47. Caselli, R. J., & Hunder, G. G. (1993). Neurologic aspects of giant cell (temporal) arteritis. *Rheumatic diseases clinics of North America*, *19*(4), 941–953.

48. De León-Benedetti, A., Torres, L. F., Mannava, S., Gultekin, S. H., & Margolesky, J. (2021). Giant Cell Arteritis Presenting With Lingual Artery Infarction. *The Neurohospitalist*, *11*(3), 275–276. https://doi.org/10.1177/1941874420984863 ;

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50. Lee, C. C., Su, W. W., & Hunder, G. G. (1999). Dysarthria associated with giant cell arteritis. *The Journal of rheumatology*, *26*(4), 931–932.

51. Amor-Dorado, J. C., Llorca, J., Garcia-Porrua, C., Costa, C., Perez-Fernandez, N., & Gonzalez-Gay, M. A. (2003). Audiovestibular manifestations in giant cell arteritis: a prospective study. *Medicine, 82*(1), 13–26. https://doi.org/10.1097/00005792-200301000-00002

52. Hernández-Rodríguez, J., Tan, C. D., Molloy, E. S., Khasnis, A., Rodríguez, E. R., & Hoffman, G. S. (2008). Vasculitis involving the breast: a clinical and histopathologic analysis of 34 patients. *Medicine*, *87*(2), 61–69. https://doi.org/10.1097/MD.0b013e31816a8d1f

53. Bablekos, G. D., Michaelides, S. A., Karachalios, G. N., Nicolaou, I. N., Batistatou, A. K., & Charalabopoulos, K. A. (2006). Pericardial involvement as an atypical manifestation of giant cell arteritis: report of a clinical case and literature review. *The American journal of the medical sciences*, *332*(4), 198–204. https://doi.org/10.1097/00000441-200610000-00007

54. Smetana, G. W., & Shmerling, R. H. (2002). Does this patient have temporal arteritis?. *JAMA*, *287*(1), 92–101. https://doi.org/10.1001/jama.287.1.92

55. Kermani, T. A., Schmidt, J., Crowson, C. S., Ytterberg, S. R., Hunder, G. G., Matteson, E. L., & Warrington, K. J. (2012). Utility of erythrocyte sedimentation rate and C-reactive protein for the diagnosis of giant cell arteritis. *Seminars in arthritis and rheumatism*, *41*(6), 866–871. https://doi.org/10.1016/j.semarthrit.2011.10.005

56. De Smit, E., Palmer, A. J., & Hewitt, A. W. (2015). Projected worldwide disease burden from giant cell arteritis by 2050. *The Journal of rheumatology*, *42*(1), 119–125. https://doi.org/10.3899/jrheum.140318

57. Calamia, K. T., & Hunder, G. G. (1981). Giant cell arteritis (temporal arteritis) presenting as fever of undetermined origin. *Arthritis and rheumatism*, *24*(11), 1414–1418. https://doi.org/10.1002/art.1780241113

58. Gonzalez-Gay, M. A., Barros, S., Lopez-Diaz, M. J., Garcia-Porrua, C., Sanchez-Andrade, A., & Llorca, J. (2005). Giant cell arteritis: disease patterns of clinical presentation in a series of 240 patients. *Medicine, 84*(5), 269–276. https://doi.org/10.1097/01.md.0000180042.42156.d1

59. Ninet, J. P., Bachet, P., Dumontet, C. M., Du Colombier, P. B., Stewart, M. D., & Pasquier, J. H. (1990). Subclavian and axillary involvement in temporal arteritis and polymyalgia rheumatica. *The American journal of medicine*, *88*(1), 13–20. https://doi.org/10.1016/0002-9343(90)90121-s

60. AbuRahma, A & Bergan, J. *Noninvasive Cerebrovascular Diagnosis*. Springer Science & Business Media; 2010

61. Hauenstein, C., Reinhard, M., Geiger, J., Markl, M., Hetzel, A., Treszl, A., Vaith, P., & Bley, T. A. (2012). Effects of early corticosteroid treatment on magnetic resonance imaging and ultrasonography findings in giant cell arteritis. *Rheumatology (Oxford, England)*, *51*(11), 1999–2003. https://doi.org/10.1093/rheumatology/kes153

62. Fuchs, M., Briel, M., Daikeler, T., Walker, U. A., Rasch, H., Berg, S., Ng, Q. K., Raatz, H., Jayne, D., Kötter, I., Blockmans, D., Cid, M. C., Prieto-González, S., Lamprecht, P., Salvarani, C., Karageorgaki, Z., Watts, R., Luqmani, R., Müller-Brand, J., Tyndall, A., … Walter, M. A. (2012). The impact of 18F-FDG PET on the management of patients with suspected large vessel vasculitis. *European journal of nuclear medicine and molecular imaging*, *39*(2), 344–353. https://doi.org/10.1007/s00259-011-1967-x

63. Ben Shimol, J., Amital, H., Lidar, M. *et al.* The utility of PET/CT in large vessel vasculitis. *Sci Rep* 10, 17709 (2020). https://doi.org/10.1038/s41598-020-73818-2

64. Janssen, S. P., Comans, E. H., Voskuyl, A. E., Wisselink, W., & Smulders, Y. M. (2008). Giant cell arteritis: heterogeneity in clinical presentation and imaging results. *Journal of vascular surgery*, *48*(4), 1025–1031. https://doi.org/10.1016/j.jvs.2008.04.054

65. Muratore, F., Kermani, T. A., Crowson, C. S., Green, A. B., Salvarani, C., Matteson, E. L., & Warrington, K. J. (2015). Large-vessel giant cell arteritis: a cohort study. *Rheumatology (Oxford, England)*, *54*(3), 463–470. https://doi.org/10.1093/rheumatology/keu329

66. Younge, B. R., Cook, B. E., Jr, Bartley, G. B., Hodge, D. O., & Hunder, G. G. (2004). Initiation of glucocorticoid therapy: before or after temporal artery biopsy?. *Mayo Clinic proceedings*, *79*(4), 483–491. https://doi.org/10.4065/79.4.483

67. Nesi, G., Anichini, C., Tozzini, S., Boddi, V., Calamai, G., & Gori, F. (2009). Pathology of the thoracic aorta: a morphologic review of 338 surgical specimens over a 7-year period. *Cardiovascular pathology : the official journal of the Society for Cardiovascular Pathology*, *18*(3), 134–139. https://doi.org/10.1016/j.carpath.2008.04.001

68. Hayreh S. S. (2021). Giant cell arteritis: Its ophthalmic manifestations. *Indian journal of ophthalmology*, *69*(2), 227–235. https://doi.org/10.4103/ijo.IJO_1681_20

69. Lie J. T. (1995). Aortic and extracranial large vessel giant cell arteritis: a review of 72 cases with histopathologic documentation. *Seminars in arthritis and rheumatism*, *24*(6), 422–431. https://doi.org/10.1016/s0049-0172(95)80010-7

70. Lunagariya, A., Rupareliya, C., Bollu, P. C., & Mahuwala, Z. (2018). Temporal Arteritis Presenting as an Isolated Bilateral Abducens Nerve Palsy: A Rare Case of a 65-year-old Male. *Cureus*, *10*(5), e2667. https://doi.org/10.7759/cureus.2667

71. Alnabwani, D., Patel, P., Kata, P., Patel, V., Okere, A., & Cheriyath, P. (2021). The Epidemiology and Clinical Manifestations of Takayasu Arteritis: A Descriptive Study of Case Reports. *Cureus*, *13*(9), e17998. https://doi.org/10.7759/cureus.17998

72. Kerr G. S. (1995). Takayasu's arteritis. *Rheumatic diseases clinics of North America*, *21*(4), 1041–1058.

73. Russo, M. G., Waxman, J., Abdoh, A. A., & Serebro, L. H. (1995). Correlation between infection and the onset of the giant cell (temporal) arteritis syndrome. A trigger mechanism?. *Arthritis and rheumatism*, *38*(3), 374–380. https://doi.org/10.1002/art.1780380312

74. Cho, S.M.J., Lee, H.J., Shim, J.S. *et al.* Associations between age and dyslipidemia are differed by education level: The Cardiovascular and Metabolic Diseases Etiology Research Center (CMERC) cohort. *Lipids Health Dis* **19**, 12 (2020). https://doi.org/10.1186/s12944-020-1189-

75. Merkel P. A. (2009). Noninfectious ascending aortitis: staying ahead of the curve. *The Journal of rheumatology*, *36*(10), 2137–2140. https://doi.org/10.3899/jrheum.090920

76. Biousse, V., & Newman, N. J. (2015). Ischemic Optic Neuropathies. *The New England journal of medicine*, *372*(25), 2428–2436. https://doi.org/10.1056/NEJMra1413352

77. Aiello, P. D., Trautmann, J. C., McPhee, T. J., Kunselman, A. R., & Hunder, G. G. (1993). Visual prognosis in giant cell arteritis. *Ophthalmology*, *100*(4), 550–555. https://doi.org/10.1016/s0161-6420(93)31608-8

78. Gonzalez-Gay, M. A., Vazquez-Rodriguez, T. R., Gomez-Acebo, I., Pego-Reigosa, R., Lopez-Diaz, M. J., Vazquez-Triñanes, M. C., Miranda-Filloy, J. A., Blanco, R., Dierssen, T., Gonzalez-Juanatey, C., & Llorca, J. (2009). Strokes at time of disease diagnosis in a series of 287 patients with biopsy-proven giant cell arteritis. *Medicine*, *88*(4), 227–235. https://doi.org/10.1097/MD.0b013e3181af4518

79. Spence, R. K., Estella, F., Gisser, S., Schiffman, R., & Camishion, R. C. (1985). Thoracic aortic aneurysm secondary to giant cell arteritis: a reappraisal of etiology, treatment and possible prevention. *The Journal of cardiovascular surgery*, *26*(5), 492–495.

80. Chen, J. J., Leavitt, J. A., Fang, C., Crowson, C. S., Matteson, E. L., & Warrington, K. J. (2016). Evaluating the Incidence of Arteritic Ischemic Optic Neuropathy and Other Causes of Vision Loss from Giant Cell Arteritis. *Ophthalmology*, *123*(9), 1999–2003. https://doi.org/10.1016/j.ophtha.2016.05.008

81. Wiszniewska, M., Devuyst, G., & Bogousslavsky, J. (2007). Giant cell arteritis as a cause of first-ever stroke. *Cerebrovascular diseases (Basel, Switzerland)*, *24*(2-3), 226–230. https://doi.org/10.1159/000104482

82. Soriano, A., Muratore, F., Pipitone, N., Boiardi, L., Cimino, L., & Salvarani, C. (2017). Visual loss and other cranial ischaemic complications in giant cell arteritis. *Nature reviews. Rheumatology*, *13*(8), 476–484. https://doi.org/10.1038/nrrheum.2017.98

83. Turney, T. M., Garraway, W. M., & Whisnant, J. P. (1984). The natural history of hemispheric and brainstem infarction in Rochester, Minnesota. *Stroke*, *15*(5), 790–794. https://doi.org/10.1161/01.str.15.5.790

84. Rüegg, S., Engelter, S., Jeanneret, C., Hetzel, A., Probst, A., Steck, A. J., & Lyrer, P. (2003).

Bilateral vertebral artery occlusion resulting from giant cell arteritis: report of 3 cases and review of the literature. *Medicine*, *82*(1), 1–12. https://doi.org/10.1097/00005792-200301000-00001 .

85. Tomasson, G., Peloquin, C., Mohammad, A., Love, T. J., Zhang, Y., Choi, H. K., & Merkel, P. A. (2014). Risk for cardiovascular disease early and late after a diagnosis of giant-cell arteritis: a cohort study. *Annals of internal medicine*, *160*(2), 73–80. https://doi.org/10.7326/M12-3046

86. Nuenninghoff, D. M., Hunder, G. G., Christianson, T. J., McClelland, R. L., & Matteson, E. L. (2003). Incidence and predictors of large-artery complication (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis: a population-based study over 50 years. *Arthritis and rheumatism*, *48*(12), 3522–3531. https://doi.org/10.1002/art.11353

87. Evans, J. M., O'Fallon, W. M., & Hunder, G. G. (1995). Increased incidence of aortic aneurysm and dissection in giant cell (temporal) arteritis. A population-based study. *Annals of internal medicine*, *122*(7), 502–507. https://doi.org/10.7326/0003-4819-122-7-199504010-00004

88. Evans, J. M., Bowles, C. A., Bjornsson, J., Mullany, C. J., & Hunder, G. G. (1994). Thoracic aortic aneurysm and rupture in giant cell arteritis. A descriptive study of 41 cases. *Arthritis and rheumatism*, *37*(10), 1539–1547. https://doi.org/10.1002/art.1780371020

89. Perruquet, J. L., Davis, D. E., & Harrington, T. M. (1986). Aortic arch arteritis in the elderly. An important manifestation of giant cell arteritis. *Archives of internal medicine*, *146*(2), 289–291.

90. Wang, H., Smith, R. N., Spooner, A. E., Isselbacher, E. M., Cambria, R. P., MacGillivray, T. E., Stone, J. H., & Stone, J. R. (2012). Giant cell aortitis of the ascending aorta without signs or symptoms of systemic vasculitis is associated with elevated risk of distal aortic events. *Arthritis and rheumatism*, *64*(1), 317–319. https://doi.org/10.1002/art.33343

91. Zehr, K. J., Mathur, A., Orszulak, T. A., Mullany, C. J., & Schaff, H. V. (2005). Surgical treatment of ascending aortic aneurysms in patients with giant cell aortitis. *The Annals of thoracic surgery*, *79*(5), 1512–1517. https://doi.org/10.1016/j.athoracsur.2004.10.039

92. Liu, G., Shupak, R., & Chiu, B. K. (1995). Aortic dissection in giant-cell arteritis. *Seminars in arthritis and rheumatism*, *25*(3), 160–171. https://doi.org/10.1016/s0049-0172(95)80028-x

93. Kermani, T. A., Warrington, K. J., Crowson, C. S., Ytterberg, S. R., Hunder, G. G., Gabriel, S. E., & Matteson, E. L. (2013). Large-vessel involvement in giant cell arteritis: a population-based cohort study of the incidence-trends and prognosis. *Annals of the rheumatic diseases*, *72*(12), 1989–1994. https://doi.org/10.1136/annrheumdis-2012-202408

94. Evans, J. M., O'Fallon, W. M., & Hunder, G. G. (1995). Increased incidence of aortic aneurysm and dissection in giant cell (temporal) arteritis. A population-based study. *Annals of internal medicine*, *122*(7), 502–507. https://doi.org/10.7326/0003-4819-122-7-199504010-00004

95. Gelsomino, S., Romagnoli, S., Gori, F., Nesi, G., Anichini, C., Sorbara, C., Stefàno, P., & Gensini, G. F. (2005). Annuloaortic ectasia and giant cell arteritis. *The Annals of thoracic surgery*, *80*(1), 101–105. https://doi.org/10.1016/j.athoracsur.2005.01.063

96. Nuenninghoff, D. M., Hunder, G. G., Christianson, T. J., McClelland, R. L., & Matteson, E. L. (2003). Mortality of large-artery complication (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis: a population-based study over 50 years. *Arthritis and rheumatism*, *48*(12), 3532–3537. https://doi.org/10.1002/art.11480

97. Espitia, O., Néel, A., Leux, C., Connault, J., Espitia-Thibault, A., Ponge, T., Dupas, B., Barrier, J. H., Hamidou, M. A., & Agard, C. (2012). Giant cell arteritis with or without aortitis at diagnosis. A retrospective study of 22 patients with longterm followup. *The Journal of rheumatology*, *39*(11), 2157–2162. https://doi.org/10.3899/jrheum.120511

98. Gonzalez-Gay, M. A., Rubiera, G., Piñeiro, A., Garcia-Porrua, C., Pego-Reigosa, R., Gonzalez-Juanatey, C., Sanchez-Andrade, A., & Llorca, J. (2005). Ischemic heart disease in patients from Northwest Spain with biopsy proven giant cell arteritis. A population based study. *The Journal of rheumatology*, *32*(3), 502–506.

99. Rojo-Leyva, F., Ratliff, N. B., Cosgrove, D. M., 3rd, & Hoffman, G. S. (2000). Study of 52 patients with idiopathic aortitis from a cohort of 1,204 surgical cases. *Arthritis and rheumatism*, *43*(4), 901–907. https://doi.org/10.1002/1529-0131(200004)43:4<901::AID-ANR23>3.0.CO;2-U

100. Prieto-González, S., García-Martínez, A., Tavera-Bahillo, I., Hernández-Rodríguez, J., Gutiérrez-Chacoff, J., Alba, M. A., Murgia, G., Espígol-Frigolé, G., Sánchez, M., Arguis, P., & Cid, M. C. (2015). Effect of glucocorticoid treatment on computed tomography angiography detected large-vessel inflammation in giant-cell arteritis. A prospective, longitudinal study. *Medicine*, *94*(5), e486. https://doi.org/10.1097/MD.0000000000000486

101. Martínez-Taboada, V. M., López-Hoyos, M., Narvaez, J., & Muñoz-Cacho, P. (2014). Effect of antiplatelet/anticoagulant therapy on severe ischemic complications in patients with giant cell arteritis: a cumulative meta-analysis. *Autoimmunity reviews*, *13*(8), 788–794. https://doi.org/10.1016/j.autrev.2014.02.006

102. Nesher, G., Berkun, Y., Mates, M., Baras, M., Rubinow, A., & Sonnenblick, M. (2004). Low-dose aspirin and prevention of cranial ischemic complications in giant cell arteritis. *Arthritis and rheumatism*, *50*(4), 1332–1337. https://doi.org/10.1002/art.20171

103. Hellmich, B., Agueda, A., Monti, S., Buttgereit, F., de Boysson, H., Brouwer, E., Cassie, R., Cid, M. C., Dasgupta, B., Dejaco, C., Hatemi, G., Hollinger, N., Mahr, A., Mollan, S. P., Mukhtyar, C., Ponte, C., Salvarani, C., Sivakumar, R., Tian, X., Tomasson, G., … Luqmani, R. A. (2020). 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. *Annals of the rheumatic diseases*, *79*(1), 19–30. https://doi.org/10.1136/annrheumdis-2019-215672

104. Borg, F. A., & Dasgupta, B. (2009). Treatment and outcomes of large vessel arteritis. *Best practice & research. Clinical rheumatology*, *23*(3), 325–337. https://doi.org/10.1016/j.berh.2009.04.001

105. Evans, J., Steel, L., Borg, F., & Dasgupta, B. (2016). Long-term efficacy and safety of tocilizumab in giant cell arteritis and large vessel vasculitis. *RMD open*, *2*(1), e000137. https://doi.org/10.1136/rmdopen-2015-000137

106. Unizony, S., Arias-Urdaneta, L., Miloslavsky, E., Arvikar, S., Khosroshahi, A., Keroack, B., Stone, J. R., & Stone, J. H. (2012). Tocilizumab for the treatment of large-vessel vasculitis (giant cell arteritis, Takayasu arteritis) and polymyalgia rheumatica. *Arthritis care & research*, *64*(11), 1720–1729. https://doi.org/10.1002/acr.21750