

GENETIC INSIGHTS INTO GIANT CELL ARTERITIS: A CASE REPORT WITH NARRATIVE REVIEW

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ABSTRACT

Giant Cell Arteritis (GCA) is the most common primary vasculitis affecting medium- and large-sized arteries in individuals over 50 years of age. It is a medical emergency, as delayed diagnosis and treatment may result in irreversible complications, particularly permanent vision loss. Although the diagnosis of Giant Cell arteritis is primarily based on clinical evaluation supported by laboratory and imaging findings, recent advances have highlighted the contribution of genetic susceptibility to disease pathogenesis. Variants within the HLA region, particularly HLA-DRB1, together with several non-HLA genes involved in immune regulation and inflammatory pathways, have been associated with an increased risk of GCA and may influence disease severity and therapeutic response. We report the case of a 68-year-old male who presented with persistent bilateral temporal headache, intermittent fever, and markedly elevated inflammatory markers. Colour doppler ultrasonography and magnetic resonance vessel wall imaging demonstrated characteristic inflammatory changes involving the superficial temporal arteries confirming the diagnosis of Giant Cell Arteritis. The patient showed marked clinical improvement following prompt initiation of high-dose corticosteroid therapy. This case is presented alongside a narrative review of the current literature on the genetic basis of GCA, emphasizing established and emerging susceptibility loci, their role in disease pathogenesis, and their evolving clinical significance. While genetic testing is not yet routinely incorporated into clinical practice, ongoing advances in genomics have improved our understanding of disease mechanisms and may contribute to the future risk stratification, biomarker discovery and personalized therapeutic strategies. This article highlights the importance of maintaining a high index of suspicion for GCA in older adults presenting with persistent headache and systemic inflammatory changes while illustrating the growing role of genetics in understanding and managing this complex vasculitis.

KEYWORDS: Genetics, Giant Cell Arteritis, Vasculitis, HLA-DRB1, Case report, Narrative review

1. INTRODUCTION

Giant Cell Arteritis (GCA) is a chronic granulomatous vasculitis that involves blood vessels, predominantly in people over 50. This condition typically presents with headaches, claudication of the jaw, scalp tenderness, and visual disturbances(1). It is characterized by inflammation of the arteries, especially the temporal artery, which may lead to vision loss and is often associated with intracranial and extracranial aneurysms(2). In some cases, Giant Cell Arteritis may be difficult to recognize because the symptoms are non-specific, for instance, fatigue and fever, which is why it is especially critical to get treated in the elderly population timely(3). Scalp necrosis, although rare, is associated with Giant Cell Arteritis and is a rare occurrence and a medical emergency that requires urgent management(4).

The incidence of Giant Cell arteritis (GCA) increases with age and is rarely diagnosed in people under the age of 50. It is also more common in women than in men, although this trend is not consistent across all populations. Recent epidemiological studies indicate that women are affected approximately three times more than men(5)(6). Most epidemiological studies of Giant Cell Arteritis have been conducted in the United States and Europe, among Caucasian populations, with little information coming from outside Europe(7). Ethnic Variations have also been seen, with lower incidence rates being reported from Māori, Pacific Islander, and Asian groups in New Zealand (8)(9). Although GCA is largely confined to people of European and North American origin, recently it has been found to be more prevalent in African Americans and Hispanics than previously reported. It is uncommon in Asians and Middle Easterners(10).

The risk of blindness due to acute ischemic events that occur during a Giant Cell arteritis (GCA) has been its most feared complication since the mid-20th century. Fortunately, this devastating outcome is now less frequent since the introduction of corticoid treatment. Nevertheless, the incidence of GCA-related visual loss has remained steady for the past few decades. Ophthalmological manifestations can inaugurate the disease, making diagnosis challenging(11). The commonest ophthalmic presentation is anterior ischaemic optic neuropathy with optic disc pallor and swelling; also recognised are diplopia, central retinal artery occlusion, and amaurosis fugax(12).

Large-vessel involvement is now recognized as a major part of the GCA phenotype rather than a rare complication. Large-vessel vasculitis was common and thoracic aorta was the most frequently affected site(13). Its involvement

had not only an increased risk of late aortic aneurysm but also greater resistance to glucocorticoids, longer treatment courses and poorer cardiovascular outcomes(14).

If left untreated, patients may experience stroke that could occur as a complication of the disease. Other possible consequences of the GCA include aortic aneurysm, dissection, and rupture. Delay in diagnosis can also occur if patients are not aware of the significance of GCA symptoms, such as jaw claudication and temporal artery abnormality, and therefore do not seek healthcare promptly(15).

The disease is clinically important due to the high risks of developing severe complications, such as loss of vision and heart diseases. Being the most frequent vasculitis to occur in people aged over 50, it is essential to recognize its symptoms early and start the treatment promptly to prevent serious consequences(16)(17). Early diagnosis and treatment may prevent irreparable damage and enhance positive patient outcomes(18).

1.1 GENETICS IN GIANT CELL ARTERITIS

Genetics plays a significant role in GCA aetiology. However, the contribution of genetic risk factors is limited since these factors mainly act as susceptibility markers. According to the largest genome-wide association studies conducted in 2015 and 2017, the most important genetic risk factor for giant cell arteritis is the HLA region, whereas other regions contribute only modest amounts to the overall genetic risk (19)(20). GCA is genetically correlated with biological aging processes, including telomere length and epigenetic age acceleration. A 2025 study identified associations with known GCA genes including PTPN22 and PLG as well as novel candidate loci(21). It has also been found that common CRP variants can also affect who gets GCA as well as how the disease behaves once it appears(22).

Genetics can also help to identify novel risk loci, to construct a polygenic risk score, and to demonstrate the potential of genetics to identify patients at risk of developing GCA before severe complications occur(23). It could also play a role in defining the inflammatory status at diagnosis as carriage of specific alleles was linked to distinct baseline C-reactive protein (CRP). In particular, the association of rs1205 polymorphism with the number of patients presenting with an eosinophil-rich temporal artery infiltrate was also described. The presence of rs1205 T allele was additionally related to a shorter glucocorticoid treatment period, a lower cumulative dose of prednisone, and a higher likelihood of achieving remission, which altogether suggest a less severe clinical course and more favorable treatment response. By contrast, an equivalent effect was not observed for rs3093068, which appeared unrelated to outcome measures at follow-up(22).

This article presents a case of Giant Cell arteritis and reviews the current evidence regarding its genetic basis and clinical implications.

CASE REPORT

A 68-year-old male with no known comorbidities presented with a one-month history of throbbing headache predominantly involving the bilateral temporal regions, accompanied by intermittent fever. There was no significant past medical history, and his family history was non-contributory. General physical examination was unremarkable, with stable vital signs (Blood pressure 120/80mmHg and pulse rate 95 beats per minute.). Neurological examination revealed an alert, oriented and cooperative patient with no known focal neurologic deficits.

Laboratory investigations demonstrated markedly elevated inflammatory markers, with an erythrocyte sedimentation rate (ESR) of 120 mm/hour and C-reactive protein of 175.7 mg/L. Haematological evaluation revealed normocytic anaemia (haemoglobin 8.6g/dL), Leucocytosis ($19 \times 10^3/\mu\text{L}$), and thrombocytosis ($679 \times 10^3/\mu\text{L}$). Renal and Liver function tests were within normal limits.

In view of fever, headache, and elevated inflammatory markers, lumbar puncture was done which was negative. MRI brain plain contrast was done which was non conclusive. Since the patient reported of persistent headache despite antibiotics and with raised inflammatory markers, a diagnosis of Giant Cell Arteritis was considered.

Colour Doppler ultrasonography of bilateral superficial temporal arteries was also performed. The examination revealed hypoechoic intima-media thickening involving the bilateral superficial temporal arteries and the branches, resulting in luminal narrowing with increased flow velocity. MRI Vessel wall imaging was done, which revealed diffuse mural enhancement and wall thickening of superficial temporal arteries and its branches on both sides with edema in adjacent soft tissue plane and temporalis muscle. Strong mural enhancement and wall thickening was also visible in the external carotid artery branches, features which were consistent with a diagnosis of Giant Cell Arteritis. Histopathological confirmation by temporal artery biopsy was recommended, however, the patient declined to undergo the procedure.

A diagnosis of Giant Cell arteritis was established based on characteristic clinical presentation elevated inflammatory markers and characteristic imaging findings, and the patient received intravenous methylprednisolone pulse therapy for 5 days, followed by oral corticosteroids. Supportive treatment, including antiplatelet therapy, calcium supplementation, and proton inhibitor prophylaxis, was initiated. The patient demonstrated marked clinical improvement, with resolution of symptoms and a significant reduction in inflammatory markers and was discharged in stable condition with regular Outpatient follow up.

3. REVIEW OF LITERATURE

3.1 OVERVIEW

Giant cell arteritis (GCA), also called Temporal arteritis or Horton's arteritis, is a chronic granulomatous vasculitis that involves medium and large arteries, especially thoracic aorta and its branches and the extracranial

branches of the carotid arteries. It has two recognized forms: a cranial form involving the temporal artery (temporal arteritis), and an extracranial form involving the aorta and its branches (large-vessel GCA or LV-GCA)(24).

GCA is the most common idiopathic systemic vasculitis in adults. It almost exclusively occurs in people over 50 years old, with the highest prevalence between the seventh and the eighth decades of life. It is also more common in women than in men. The disease is most prevalent in Scandinavia and northern Europe, with a gradient decreasing towards the south(24).

Pathogenesis is still not fully settled, but the core model is fairly consistent, consisting of genetic constituency, aging-related immune changes, and environmental triggers(21)(25). The initiation of the process occurs through an initial insult (such as mechanical injury, infection, reaction to medications, or autoimmunity) of the arterial adventitia, which provokes the local dendritic cells to produce chemokines that attract CD4⁺ helper T cells and macrophages into the vessel wall. The recruited T cells differentiate into cytokine-producing effector cells, mainly through Th1-mediated responses, characterized by high production of IFN-gamma, and Th17 responses. The T-cell activation by dendritic cells leads to the production of IFN-gamma and other cytokines and results in the enhanced inflammatory response. This process was initiated by the production of IL-6 by dendritic cells followed by the secretion of IL-18 by these cells which led to the T-cell activation and IFN-gamma production. Macrophages respond by producing matrix metalloproteinases (MMPs) and reactive oxygen species, resulting in further endothelial injury and disruption of the internal elastic lamina. In addition, macrophages produce nitric oxide and multinucleated giant cells, a key pathological feature of this condition(25). The chronic inflammatory process leads to concentric intimal thickening, loss of vascular smooth muscle cells, and vascular occlusion, resulting in stenosis and ischemia (26). The senescence-associated secretory phenotype (SASP) of aged cells which involves IL-6 and MMP-9 secretion could contribute to vascular inflammation and remodelling(21)

The 2022 ACR/EULAR criteria should be regarded as classification criteria for research purposes only, and they should not be used as an independent diagnostic tool. According to the criteria, age should be equal to or more than fifty, while a positive temporal artery biopsy or ultrasound halo sign, inflammatory markers, and ischemic cranial symptoms, such as monocular visual loss, are considered major criteria(27).

For diagnosis in everyday practice, the preferred imaging technique seems to be ultrasound of the scalp and axillary arteries, with FDG-PET or MRI as alternative tests for assessing cranial or extracranial vessels. Temporal artery biopsy is still considered an essential procedure for confirming the diagnosis when the clinical suspicion is high(28).

Treatment includes urgent high-dose glucocorticoid therapy; intra venous administration of steroids should be considered for the treatment of ischemic complications threatening vision. The best steroid-sparing agent is tocilizumab, especially in patients with relapsing disease or those at risk from glucocorticoid toxicity; methotrexate has a more limited role and is used sparingly and less consistently(29)(30).

3.2 PATHOGENESIS

In Giant Cell arteritis, it is the dendritic cells in the arterial adventitia that are likely to be the rheumatologic initiator. These dendritic cells may become activated, most probably through TLR engagement and then prime CD4⁺ T cells that traffic into the vessel wall.(31). A 2025 study suggests that some mature CD209⁺CD83⁺CCR7⁺ dendritic cells may even arise from monocytes under GM-CSF and IFN- γ (32).

Activated CD4⁺T cells are driven to differentiate into Th1 and Th17 lineages, which produce IFN- γ and IL-17 and contribute to macrophage and giant-cell activation. The subsequent cytokine cascade, which includes IL-1, IL-6, and TNF- α , results in vessel-wall inflammation that leads to intimal hyperplasia, vascular stenosis, and ischemia in GCA(33). Collectively, these immune mechanisms result in chronic vascular inflammation, progressive luminal narrowing and ischemic complications characteristic of Giant Cell Arteritis.

3.3 GENETICS IN GIANT CELL ARTERITIS

Genetic susceptibility means inherited DNA differences that make someone more likely to get Giant Cell arteritis, not cause the disease by themselves. GCA is considered a polygenic and multifactorial disease determined by genetic factors along with aging and environmental influences(20)(21). The strongest and most consistent inherited risk lies in the HLA region, especially HLA class II and particularly HLA-DRB1 04 alleles. It has also been found that many variants each add modest risk rather than one mutation determining disease(20)(34).

Some individuals may be more predisposed to developing GCA since a combination of HLA and non-HLA genetic variants contributes to the risk of developing the disease. Those variations impact the activity of immune cells, inflammatory cascades, angiogenesis, and vessel-wall remodelling. In addition, genome-wide analyses identified several PTPN22, PLG, P4HA2, MFGE8, VTN, CCDC25, IL12B, IL17A, and other genes involved in GCA pathogenesis, including T-cell receptor signalling, neutrophil extracellular traps production, and angiogenesis(20)(19)(23). PTPN22 R620W is one of the clearest non-HLA inherited risk variants for GCA (20). The most consistent genetic signal in GCA is the HLA class II region(19,20). HLA-DRB1 04 is the classical allele most repeatedly linked to GCA susceptibility(20)(35). The largest recent GWAS added MFGE8 and VTN, also linked to angiogenesis, and CCDC25, linked to neutrophil extracellular traps(23)(36).

Additional or emerging genes include LRRC32 and REL from large-scale genetic analysis, though these signals are less established than PTPN22 or the HLA loci (20). Newer cross-trait and multi-omics studies also prioritized

genes such as SERPING1, SAR1B, SESN1, SMC4, and VLDLR, but these are better viewed as emerging candidates than core established loci(21)(37).

Overall, current evidence indicates that the HLA class II region remains the strongest genetic determinant of GCA susceptibility, while several non-HLA genes, including PTPN22, PLG, IL12B, IL17A, MFGE8, and VTN, appear to contribute more modestly to disease risk. Additional loci identified through multi omics studies remain promising but require further validation.

4. GENETICS AND CLINICAL PRACTICE

4.1 RISK PREDICTION

GCA risk prediction is not absolute since the association is probabilistic rather than deterministic. However, the strongest genetic associations are observed for HLA class II antigens, in particular, DRB104 alleles, although there are also non-HLA loci that appear to contribute to GCA susceptibility, which suggests that it is a multifactorial disorder, possibly involving multiple genes(38)(39)(40). Familial clustering and population difference could account for vulnerability. However, familial disease is uncommon, and the genetic predisposition may not be inevitable(41)(40). Current predictive models utilizing clinical scores or machine learning are not yet established for routine use(42).

4.2 BIOMARKERS

The biomarkers of GCA are valuable to help assess inflammation. However, they are insufficient for predicting the outcome of the disease or monitoring adequately. The levels of ESR and CRP are the commonly used laboratory tests for GCA, but they may be normal during relapse and therefore less helpful when the IL-6 receptor is blocked (43)(44). IL-6 is one of the most researched cytokines; however, its diagnosis performance is limited, and there is no single blood biomarker with sufficient accuracy to evaluate disease activity or monitor treatment in patients with GCA (43)(41). Vascular inflammation biomarkers include S100 family proteins, pentraxin-3, osteopontin, matrix metalloproteinases (MMP) 2/9, vascular endothelial growth factor (VEGF), YKL-40, and angiopoietins, of which some are independent of IL-6.

In addition, certain biomarkers can help risk-stratify GCA patients for developing specific complications such as pentraxin-3 for recent optic nerve ischemia and endothelin-1 for ischemic events(43). Furthermore, imaging is considered a functional biomarker, and vascular inflammation detected on follow-up scans during remission is associated with an increased risk of relapse (41)(44).

4.3 PERSONALIZED TREATMENT

Personalized treatment in GCA is increasingly based on clinical phenotype, pattern of imaging findings, and relapsing risk rather than genetics. Although glucocorticoids (GCs) remain the first-line therapy, their use is limited by a lack of curative properties and considerable morbidity associated with prolonged treatment and steroid-sparing agents are being increasingly utilized(38)(42)(10). Tocilizumab has demonstrated the most consistent glucocorticoid-sparing efficacy and is now considered an established therapeutic option for both treatment-naïve and relapsing patients with GCA (41)(45).

The concept of tailoring the duration of therapy based on clinical phenotype is gaining ground, with cranial-type presentation potentially requiring a shorter course whereas patients with large vessel involvement may need extended treatment and imaging monitoring(41). Genes involved in the modulation of GC response (NR3C1, HSD11B1, ABCB1) and the IL-6 pathway (IL6, IL6R, GP130) appear to be promising candidates for developing pharmacogenetic tests to guide therapeutic decision-making; however, these are still in discovery phase (41)(46). Apart from tocilizumab, other treatment options under investigation include abatacept, ustekinumab, Janus-kinase inhibitors, and upadacitinib, although most of these require further study to establish their role in the management of GCA (38,41).

4.4 FUTURE DIRECTIONS

Future studies should focus on composite biomarkers and standardized imaging follow-up rather than isolated factors. Reviews have emphasized the need for biomarkers, relapse definitions, and randomized trials that stratify based on predicted risk and balance therapeutic intensity (41,45). Mechanistically, recent studies have implicated PD-1/PD-L1, NOTCH, JAK/STAT, GM-CSF, tissue-resident immune cell trafficking, and vascular remodelling as likely sources of novel biomarkers and therapies (40)(47). Multi-omics approaches to risk prediction may yield improvements beyond those seen with individual polymorphisms, and clinical and genetic variables may interact across different populations(48). Similarly, improved preclinical models of large-vessel Giant Cell Arteritis (GCA) and treatment response are critically needed(49).

5. DISCUSSION

Giant Cell arteritis is the most common primary vasculitis affecting medium and large sized arteries in adults over 50 years of age. Early diagnosis is essential because delayed treatment may result in irreversible complications, particularly permanent vision loss. The present case demonstrates a classical clinical presentation of GCA, with persistent temporal headache, fever, elevated inflammatory markers, temporal artery tenderness, and characteristic doppler ultrasonography and Magnetic resonance findings. Prompt initiation of Corticosteroid therapy resulted in rapid clinical improvement, highlighting the importance of early recognition and treatment.

The laboratory findings observed in this patient, including markedly elevated ESR and CRP, thrombocytosis and leucocytosis and anaemia of inflammation, are well recognized features of active GCA. Although these findings are not disease specific, they support the presence of a significant systemic inflammatory response and when interpreted alongside clinical findings, they increase the suspicion of GCA. Diagnosis was established based on these findings as the patient did not consent for Temporal Artery Biopsy.

Recent advances have demonstrated that genetic susceptibility contributes to the development of GCA. Variants within the HLA region, particularly HLA-DR1, together with polymorphisms affecting cytokine and immune regulatory pathways such as IL-6 and IL-17 are believed to influence disease susceptibility and the intensity of vascular inflammation. These genetic factors do not independently establish the diagnosis but provide insight into the underlying dysregulation responsible for granulomatous inflammation and vascular injury.

Although genetic analysis was not performed in the patient, the clinical features closely reflect the inflammatory mechanisms described in the current literature. This illustrates that genetic susceptibility is likely one component of a multifactorial disease process in which ageing of the immune system and immune related vascular inflammation interact to produce the characteristic manifestations of GCA.

The characteristic Doppler ultrasound findings in this case emphasize the growing role of non-invasive vascular imaging in the diagnosis of GCA. Imaging techniques, when combined with careful clinical assessment and laboratory investigations, can facilitate early diagnosis and reduce dependence on temporal artery biopsy in appropriately selected patients.

Continued research into the genetic basis of Giant Cell Arteritis may improve future risk stratification, facilitate the identification of novel biomarkers and support the development of new personalized therapeutic strategies. While routine genetic testing has not yet become a part of clinical practice, advances in molecular medicine may eventually contribute to earlier diagnosis and more targeted treatment approaches.

This case reinforces the importance of maintaining a high index of suspicion for GCA in older patients presenting with persistent headache and elevated inflammatory markers. Integrating clinical findings with imaging and current knowledge of disease pathogenesis, provides a comprehensive understanding of this complex vasculitis and may ultimately improve patient outcomes.

6. CONCLUSION

Giant Cell arteritis is a medical emergency that requires early recognition and prompt treatment to prevent irreversible complications such as vision loss. This case demonstrates the characteristic clinical presentation and successful management of Giant Cell Arteritis through early diagnosis and corticosteroid therapy. Integrating current evidence on the genetic basis of Giant Cell Arteritis enhances our understanding of disease pathogenesis and while highlighting the growing contribution of genetic research to understand disease mechanisms, Identifying potential biomarkers and guiding future targeted therapies.

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8. CONFLICT OF INTEREST

The authors wish to declare no conflict of interest regarding the publication of this manuscript.

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