**RESEARCH PAPER**

# Giant Cell Arteritis: Rethinking an Old Disease Through Modern Era

Natsir R[1], Irawati N[1], Wibowo MD[1], Wiratama PA[2], Handarini TW[3], Rahmawati LD[4]

[1] *Head and Neck Surgery Department, Faculty of Medicine Airlangga University / Dr. Soetomo General Hospital, Surabaya, Indonesia*
[2]*Anatomical Pathology Department, Faculty of Medicine Airlangga University / Dr. Soetomo General Hospital, Surabaya, Indonesia*
[3]*Radiology Department, Faculty of Medicine Airlangga University / Dr. Soetomo General Hospital, Surabaya, Indonesia*
[4] *Division of Rheumatology, Internal Medicine Department, Faculty of Medicine Airlangga University / Dr. Soetomo General Hospital, Surabaya, Indonesia*

**ABSTRACT**
Giant cell arteritis (GCA) is a common disease of the geriatric age group in the western world, with a prevalence of 0.2% in the fifty plus age group. It is known to be an important cause of morbidity, with irreversible visual loss being the most ominous complication. This diagnosis should be considered in all cases of new onset headache in elderly patients. Not only there has not been any report of GCA from South East Asia Continent, we also present a GCA case with rare and unusual presentation. In this report, we describe the clinical details of an elderly patient with giant cell arteritis, came to a tertiary institute in East Java with tongue necrosis after reduction of dislocated temporomandibular joint (TMJ). She denied any polymyalgia rheumatica (PMR) and visual loss but had a severe headache and abnormalities on the superficial temporal artery (STA) area on examination. STA biopsy yielded histopathological confirmation for GCA. The case highlights the importance of assessing the possibility of GCA through appropriate clinical history and physical examination as well as the use of superficial temporal artery biopsy, to clinch the diagnosis..

**Keywords**: Giant cell arteritis, tongue necrotic, lip necrotic.
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## INTRODUCTION

**GCA is a chronic vasculitis targeting medium and large-sized arteries, especially branches of the external carotid artery but most notably the superficial temporal arteries. This complex disease predominantly affects individuals over 50. Histopathological examination typically shows transmural inflammation with necrosis area and multinucleated giant cells.[1] Incidence and prevalence of GCA differ greatly across geographic regions and ethnic groups. Women are more affected compared with men and disease risk rises steeply along with advancing age.[2]**

In GCA, activated vascular dendritic cells in large arteries play a crucial role in activating naïve CD4 T cells and producing chemokines to attract macrophages and lymphocytes. This activation transforms T cells into Th1 cells, which also in turn stimulate macrophages. The consequences of this cascade are the formation of giant cells and proliferation of vascular smooth cells. This process results in the thickening of the artery's intimal layer. In addition, pro-inflammatory cytokines such as IL-6 and IL-1β secreted from macrophages will stimulate further differentiation of naïve CD4+ T cells into Th17 effector cells, triggering a systemic inflammatory response responsible for symptoms of the disease.[3]

Main symptoms of GCA including the presence of severe temporal headaches, scalp tenderness or ulceration, jaw claudication, diplopia, amaurosis fugax, fever, and PMR. Rarely, this condition may result in bilateral tongue and lip necrosis.[4-6] If left untreated, GCA poses a significant risk of life-altering ischemic complications, including irreversible vision loss, myocardial infarction, and stroke, demanding the urgent need for timely diagnosis and intervention.[7,8]

While jaw and tongue claudication are relatively common in GCA, tongue necrosis in GCA is considered a rare symptom (less than 1%). It is postulated that severe ischemic condition, often associated with involvement of the branches of the external carotid artery (especially the lingual artery) is required because the tongue normally has robust collateral circulation. Necrosis may be preceded by milder tongue/oral ischemic symptoms (pain, pallor, intermittent claudication), but by the time necrosis develops, prognosis becomes more serious, and risk of permanent damage (even auto-amputation of necrotic tissue) increases. Because tongue necrosis is so rare, many clinicians may not consider GCA initially when a patient presents with oral pain/ulceration, leading to delays in diagnosis, and hence higher risk of irreversible ischemic damage.[6,9-11]

Case Report

A 64-year-old female patient presented with temporomandibular joint dislocation and cerebrovascular infarct. After completing reposition TMJ with manual reduction technique under sedation, she developed tongue and lip discoloration accompanied by swelling on left

**Author for Correspondence: Natsir R*

preauricular side (Fig 1). She was referred to our tertiary care institute.

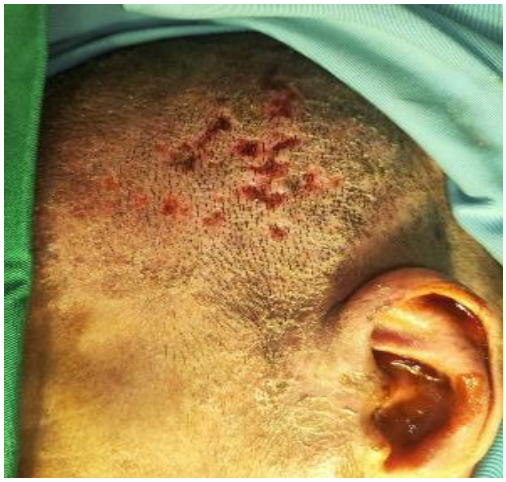
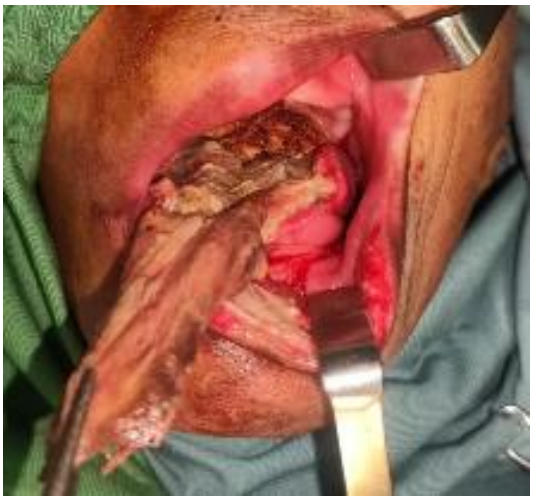


**Fig. 1. Ulcer on left temporal site**

Two weeks earlier she had moderate headache located in frontotemporal area, jaw claudication and skin ulceration on left temporal region. Her past medical history included hypertension which was controlled by anti-hypertension drug. She was treated previously with a course of antibiotics, antiplatelet and neurotropic medications. She denied any symptoms of fever, malaise, arthralgia, weigh or vision loss.

Vital signs were within normal limits with no evidence of cardiac or pulmonary abnormalities. Edema and discoloration involving the whole anterior tongue with limited movement were the main findings on physical examination (Fig 2). Left temporal artery tenderness was noted with mild abscess and pulseless (Fig 3).

**Fig. 2. Bilateral necrotic appearance of the** tongue



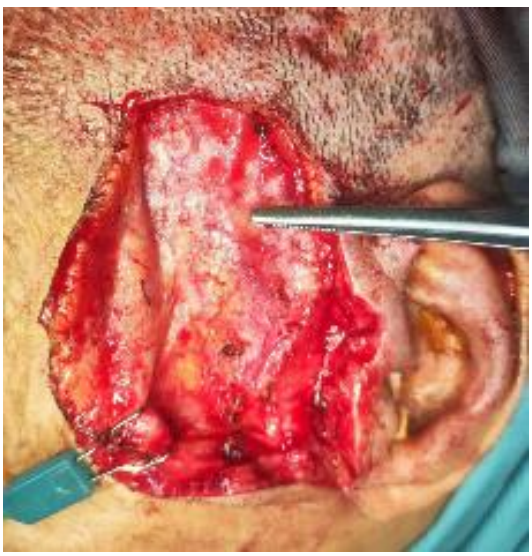


**Fig. 3. Thickened and pulseless left superficial** temporal artery

Hematologic testing revealed mild anemia. Elevation in both C-reactive protein (CRP) and erythrocyte sedimentation (ESR) (19.28 mg/dL and 140 mm/hr, respectively) was concordant with an acute inflammatory process. Antineutrophil cytoplasmic antibody was negative. The comprehensive metabolic panel was unremarkable.

A tongue biopsy was performed and showed coagulative necrosis, and no malignant cells or amyloid deposits were identified. Chest radiograph showed aortosclerosis and CT angiography noted minimal abscess formation on left preauricular with no pathologic vascularization changes. Ultrasound of left temporal site did not show any abnormality on temporalis artery.

GCA was confirmed with biopsy result of the left temporal arteries (TAB), which showed mixed inflammatory infiltrate composed of lymphocyte, histiocyte, and multinucleated giant cells with focal destruction of internal elastic lamina and marked intimal thickening significantly decreasing the lumen of both arteries, consistent with GCA vasculitis (Fig 4).

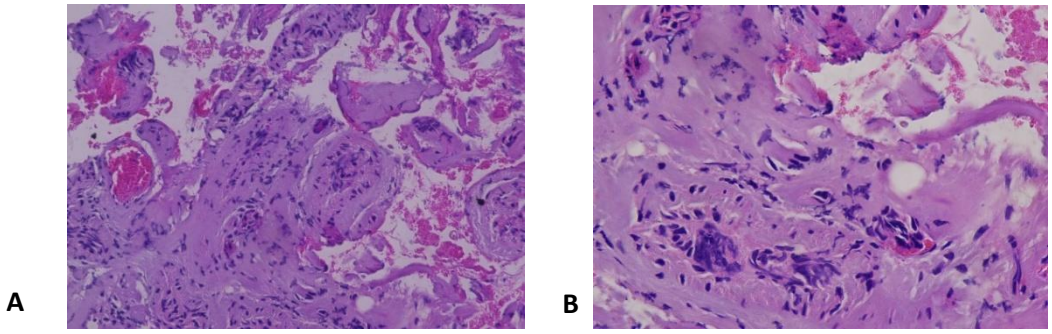



**Fig. 4. Histology feature from the patient's temporal artery biopsy. Panel A shows an inflammatory cell infiltrate with a cuff of lymphocytes and monocytes within the adventitia, inflammation across the media with involvement of an oedematous intima (*), and panel B shows presence of occasional multinucleated giant cells**

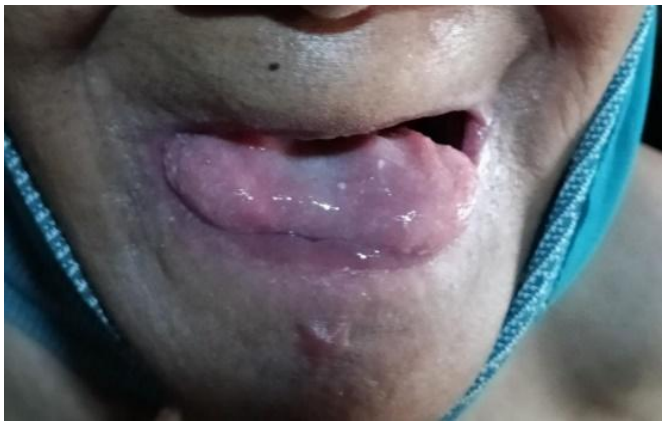


**Fig 5. Clinical appearance of the healed**

Treatment with high dose corticosteroids was initiated at 1 mg/kg. Full epithelization was evident a month later (Fig. 5). A tapering of oral steroid therapy was conducted with discontinuation of topical antifungal therapy. After a year of follow up, patient was in good health and gained in weight. Her tongue morphology was normal with minimal limitations during function.

tongue

## DISCUSSION

Vasculitis is classified by the size of the involved vessel as well as the presence or absence of anti-neutrophil cytoplasmic antibodies (ANCA). The activated inflammatory cascade can injure or occlude the lumen of the affected vessel resulting in end-organ ischemia and damage. Subsequently, the clinical picture depends on the anatomical distribution of the affected vessels.[12]

The patient in this case presented with bilateral tongue and lower lip necrosis with moderate headache and local tenderness on temporal site. These symptoms are unusual and can be potentially misleading, which emphasizes the

importance of high clinical suspicion in elderly patients with unexplained headache.

A PubMed and google based search for similar situation was performed and we found that bilateral tongue necrosis in GCA has been previously reported in quite few publications. Several reports in the literature echo similar presentations including Sobrinho et al. who reported a case of tongue necrosis in an elderly male as an early manifestation of GCA and Zaragoza et al. whose patient with bilateral tongue necrosis without any visual disturbances or fever. These two reports highlight the diagnostic challenge when GCA presents with atypical symptoms.[4,5] The rarity of tongue necrosis in GCA is because the tongue has rich vascular supply from multiple arteries. However, Schurr et al. and Marcos et al. showed that bilateral necrosis can still occur due to severe luminal narrowing or occlusion of the lingual and external carotid arteries owing to inflammatory vasculitis.[6,7]

Clinical examination is invaluable for early diagnosis of GCA. If there is any high clinical suspicion, high-dose glucocorticoids should be initiated as therapeutic delay increases retinal and cerebral ischemic risk. Initial workup should include full blood count, CRP, and ESR, as most patients exhibit elevated inflammatory markers at presentation. An ESR >50 mm/h, in concordance with typical symptoms, supports further investigation and/or empiric treatment, though up to 4% present with a normal ESR. Kermani et al. reported their result that 7/177 biopsy-proven cases had normal ESR and CRP, with fewer constitutional features and a higher burden of polymyalgia rheumatica symptoms. ESR may be low in concurrent infection, renal impairment, or hypoalbuminemia . Autoantibody testing currently has no diagnostic role in GCA.[13-15]

At present, the gold standard for diagnosis is TAB.[16] However, such inflammation can be shown as skip lesion if inadequate length of artery was sampled, leading to the incidence of false negatives reported to be as high as 42%.[17] A retrospective multi-centre study found that a TAB length of 5 mm or greater to be associated with increased diagnostic sensitivity.[18] Other retrospective multi-centre study concluded that a cut-off point of 15 mm was associated with increased odds of a positive result by 2.25 ($p = 0.003$), where each millimetre increase in TAB length was associated with an increased odds of a positive result by 3.4% ($p = 0.024$).[19]

There are numerous less invasive methods have been proposed, including Doppler ultrasound (CDS), high resolution MRI and FDG/PET CT to detect arteritis. CDS of the temporal artery has been demonstrated in three meta-analyses to have a sensitivity of 68–75% and a specificity of 82–91%, however from the recent prospective multicentre study of 381 new cases of suspected GCA, ultrasound was known to be more sensitive compared to TAB but it came with low specificity (81%). The presence of arterial wall thickening or a dark hyper-echoic area around the vessel lumen referred to as a periluminal halo representing inflammatory change and oedema of the vessel wall can be diagnostic of temporal arteritis. Therefore, CDS also can be used for follow up to see the size of periluminal halo after treatment.[20,21] The same study also concluded that although ultrasound was not able replace TAB, but a combination strategy of US followed by TAB in scan negative patients, combined with CRP and ESR result, increased the likelihood of a firm diagnosis of GCA.[21] MRI is usually used for cases where there is an absolute contraindication to a TAB. It has similar detection rate with CDS.[22] FDG-PET/CT has also been shown to have a high sensitivity, but low specificity.[23] A consensus opinion of experts from the European League Against Rheumatism (EULAR) taskforce recommend early imaging with CDS and MRI, with FDG-PET/CT as an alternative for patients in whom GCA is suspected.[24,25] Despite of physical examination showed tenderness on superficial artery site, CDS and CT angiography from our patient did not detect any vascular abnormality, hence we performed TAB. The histopathology examination revealed features consistent with GCA vasculitis, including the presence of multinucleated giant cells.

The diagnosis of GCA remains clinical and is supported by diagnostic tests according to the American College of Rheumatology (ACR) criteria.[26] In this case, the patient fulfilled all of ACR criteria: age >50 as absolute requirement, new onset of temporal headache, abnormal examination of temporal artery, elevated ESR >50 mm/hr, elevated CRP > 10 mg/L, and a positive TAB. These features confirmed the diagnosis despite the unusual clinical course.

Corticosteroid is the first and mainstay of treatment for GCA. According to British Society of Rheumatology (BSR), in uncomplicated GCA defined as absence of jaw claudication or visual symptoms, oral prednisolone should be started at a dose of 40–60 mg once daily, followed by intravenous methylprednisolone (500 mg–1 g) daily for three days if there is any visual loss, amaurosis fugax or progressing symptoms. High risk patients may require high dose corticosteroids for 3–4 weeks until both inflammatory markers and patient symptoms resolve.[27] According to the UK National Institute of Health and Care Excellence (NICE) when clinical and laboratory features suggest resolution of active diseases, prednisolone dose can be tapered by 10 mg every 2 weeks until the patient is taking 20 mg daily, then a reduction of 2.5 mg every 2–4 weeks until the patient is taking dose of 10 mg daily, followed by reduction in 1 mg every 1–2 month. Treatment of GCA should be assessed and reviewed on an individual basis alongside clinical input.[28] Majority of patients have improved symptoms within 24–48 h of initiation of corticosteroids; this was seen in our patient. Therapy typically extends over roughly 2 years, but in patients with chronic relapsing disease, long term low dose steroids should be considered. If there is no clinical improvement, the diagnosis should be reevaluated. Despite tapering steroids, 30–50% of patients experience spontaneous flares within the first two years post-diagnosis.[27,28]

Given the elevated risk of large-vessel complications including aortic aneurysm/dissection, large-artery stenosis, and valvular disease such as aortic regurgitation, both the

BSR and NICE advise treatment with low dose aspirin to prevent cerebrovascular complications. This is at present supported by expert opinion and level 4 evidence that show a statistically significant reduction in cranial ischaemic complications although it is currently unclear as to the optimum duration of treatment with aspirin.[27-29]

Steroid sparing agents are being investigated as a method of reducing both total steroid dose and duration of treatment. Methotrexate is currently the most commonly used sparing agent as it reduces the risk of relapse and reduce the total cumulative steroid dose. [30]

IL-6 receptor antagonists have been posited as treatment for refractory GCA unresponsive to steroid therapy including Tocilizumab, an IL-6 receptor-alpha inhibitor, has recently been shown to be of benefit in reducing the total length of steroid course. [31] One recent trial found that when it is combined with prednisolone, steroid treatment was stopped >12 weeks prior to those on steroids alone.[32] A randomised controlled trial by Stone et al. reported that Tocilizumab in either weekly or alternate-weekly administrations alongside a 26 week prednisolone tapered course versus placebo (prednisolone only taper of 26 or 52 weeks) was associated with a significant ($p < 0.001$) increase in remission rates at 52 weeks of up to 42%.[33]

Deep-vein thrombosis (DVT) is a potentially serious complication. The incidence rate ratio for DVT was highest within the first year after diagnosis, declining thereafter independent of age, sex, and other risk factors. This may support consideration of routine thromboprophylaxis. Patients with GCA should be reviewed every three to six months or even more often if relapse is suspected or treatment-related adverse events arise. A comprehensive hematologic, biochemical, and inflammatory panel, and assess large-vessel involvement with chest radiography or echocardiography should be repeated prior to each visit. Repeat FDG-PET/CT may also aid in detecting persistent vascular inflammation during long-term follow-up.[34-36]

Recent data from a multicentre study in France showed that GCA patients presenting with necrosis of the scalp, tongue, or lips had significantly more cranial symptoms and worse overall survival, even though the rates of visual involvement were not different compared to controls. This highlights the prognostic implications of such necrotic complications.[37]

This case demonstrated good response to prednisone 60 mg/day and aspirin, consistent with international guidelines and other case reports. The patient still undergoes three monthly follow up. A reduction of inflammatory marker from laboratory finding is well noted after serial course of high dose of corticosteroid. It is noteworthy that full epithelialization and functional recovery of the tongue occurred within one month of treatment initiation, a favourable outcome that reinforces the need for early intervention.

## CONCLUSION

Necrosis of the tongue is rare and may be caused by a wide array of different pathologies. This paper presents a case of bilateral tongue necrosis as a rare complication of GCA. A high index of suspicion for a vasculitis process such as GCA should be considered, especially in patients above the age of 50 with unusual symptoms, elevated inflammatory markers and normal imaging. The experience highlighted the need of perseverance and multidisciplinary collaboration for early initiation of therapy

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