

Lethal giant cell arteritis with multiple ischemic strokes despite aggressive immunosuppressive therapy

Christine Lu-Emerson^a, Melanie Walker^a, Bertrand R. Huber^b, Basavaraj Ghodke^c,
W.T. Longstreth, Jr.^a, Sandeep P. Khot^{a,*}

^a Department of Neurology, University of Washington, Seattle, WA, USA

^b Department of Pathology, University of Washington, Seattle, WA, USA

^c Department of Radiology, University of Washington, Seattle, WA, USA

ARTICLE INFO

Article history:

Received 28 October 2009

Received in revised form 23 March 2010

Accepted 17 May 2010

Available online 17 June 2010

Keywords:

Giant cell arteritis

Temporal arteritis

Brain infarction

Cerebrovascular disease

Immunosuppression

Vasculitis

Extrapyramidal

ABSTRACT

Two patients with giant cell arteritis (GCA) had a malignant course despite aggressive immunosuppressive therapy. A 63-year-old woman presented with symptoms of headache, jaw claudication, scalp paresthesia, and visual disturbances. A temporal artery biopsy showed GCA. While on prednisone, she suffered ischemic strokes, and serial cerebral angiograms demonstrated bilateral, severe and progressive narrowing of distal vertebral and internal carotid arteries. Despite escalating immunosuppressive therapies, she suffered more infarcts and eventually died. Postmortem examination of arteries showed no active inflammation. A 65-year-old man presented with extrapyramidal symptoms though no symptoms typical of GCA. Imaging showed multiple ischemic strokes. Because serial angiograms demonstrated findings similar to the first patient, he underwent temporal artery biopsy that showed GCA. He died 7 months after his presentation with complications of aggressive immunosuppressive therapy. These two patients confirm that GCA can follow a lethal course despite escalating immunosuppressive therapies. Our two patients were unique in that eventually both anterior and posterior circulations were involved bilaterally in a characteristic location where the arteries penetrate the dura. This pattern should always raise the possibility of GCA and, if confirmed, should prompt aggressive immunosuppressive therapy. The dismal outcomes despite this approach may suggest a non-inflammatory arteriopathy, as seen on necropsy in one of our patients. Such an arteriopathy may require novel therapies to be considered for this severe variant of GCA.

© 2010 Elsevier B.V. All rights reserved.

1. Introduction

Giant cell arteritis (GCA), also called temporal arteritis, is the most common form of systemic vasculitis in adults, typically involving large and medium-sized vessels in patients over the age of 50. The majority of patients respond well to treatment with high-dosed steroids. A subset of patients develops a more malignant course with recurrent ischemic strokes from involvement of the distal vertebral or internal carotid arteries. We present two patients with GCA involving both the bilateral distal vertebral and internal carotid arteries with repeated infarcts and death despite escalating immunosuppressive therapies.

2. Case reports

A 64-year-old woman presented with a headache, visual changes, jaw claudication, scalp paresthesia, myalgias, and cognitive decline

over 6 months. Cranial magnetic resonance imaging (MRI) revealed no abnormalities. She was empirically started on high-dose prednisone and a temporal artery biopsy showed GCA. She continued to have episodic neurologic symptoms over the next month culminating in sudden left hemiparesis that quickly resolved. Neurological examination revealed poor attention and delayed recall without sensorimotor deficits. Laboratory studies were significant for an erythrocyte sedimentation rate (ESR) of 36 mm/h, C-reactive protein (CRP) of 40 mg/L and platelet count of 413,000. A repeat MRI showed acute infarcts within the right periventricular white matter and subacute infarcts within the deep white matter. Catheter angiogram demonstrated severe stenoses of both bilateral distal internal carotid arteries (Fig. 1A) and vertebral arteries (Fig. 1B). She was started on low-dose aspirin and 3 days of pulsed methylprednisolone (1 g per day) followed by maintenance of 60 mg of prednisone per day.

Despite steroids, a surveillance MRI 2 months later revealed multiple acute and subacute infarcts in the border zone between the anterior and posterior circulations. Another catheter angiogram, performed 3 months after the original study, revealed progression of high-grade stenoses. Intravenous cyclophosphamide (0.75 g/m² for 5 infusions over 6 months) was initiated and subsequently intravenous rituximab (1 g

* Corresponding author. Department of Neurology, Box 359775, Harborview Medical Center, 325 9th Avenue Seattle, WA 98104, USA. Tel.: +1 206 744 3251; fax: +1 206 744 8787.

E-mail address: skhot@uw.edu (S.P. Khot).

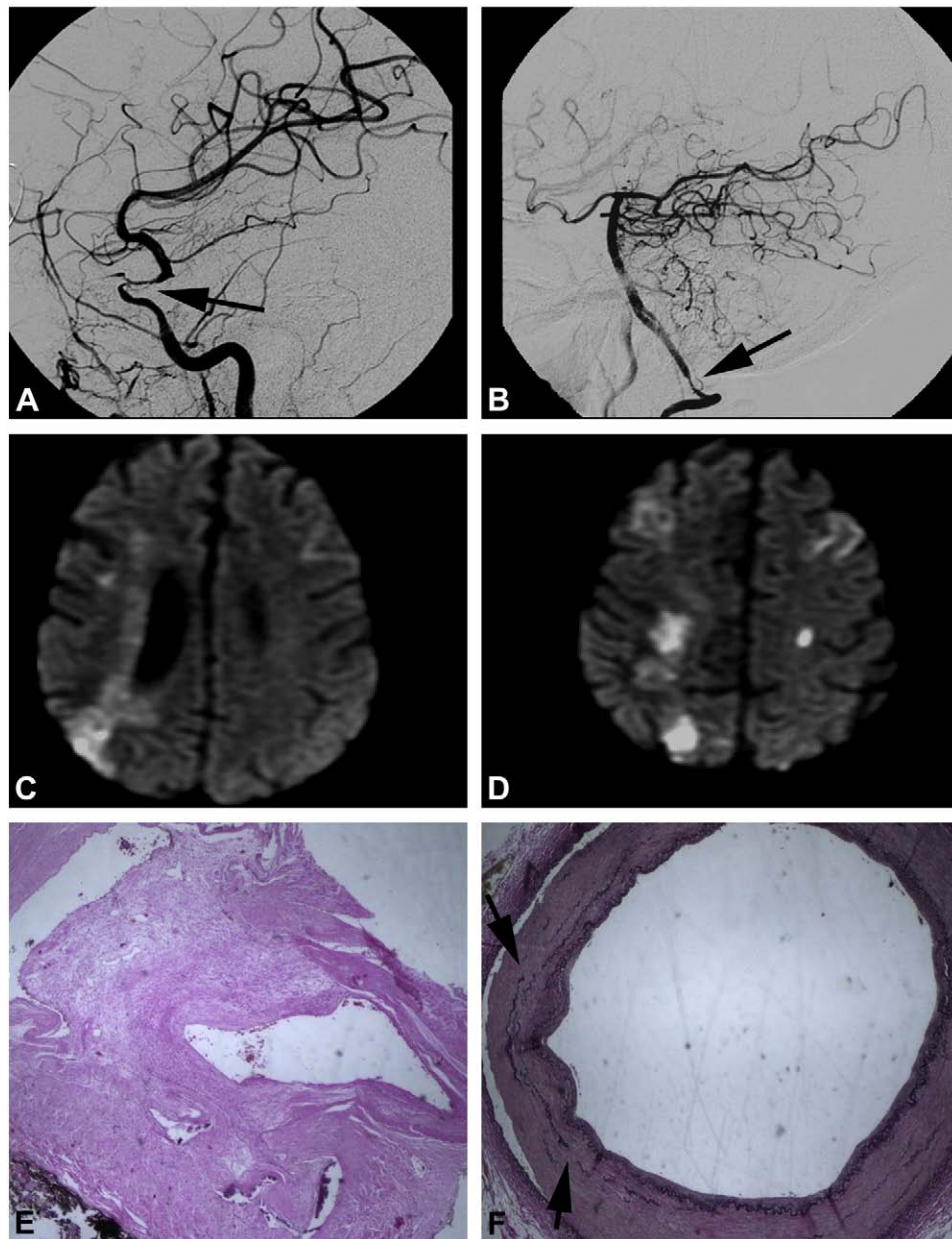


Fig. 1. Case 1: conventional cerebral angiogram performed at the time of patient's initial ischemic stroke (A,B). Anterior circulation injection (A) reveals severe right internal carotid artery narrowing, from just proximal to the ophthalmic artery extending to the level of the posterior communicating artery. Posterior circulation injection (B) shows severe short segment narrowing of the right vertebral artery at the level of the foramen magnum, with normal diameter in the distal intracranial vertebral artery and basilar artery. The contralateral anterior and posterior circulation vessels (not shown) were equally affected in the same regions. Diffusion-weighted MRI sequence following an episode of relative hypotension reveals numerous bilateral acute cerebral infarctions in the border zone between the anterior and posterior circulations (C,D). Postmortem pathology of arterial damage (E,F). Hematoxylin and eosin (H&E) stain of left intracranial distal carotid artery (E) demonstrating severe stenosis with fibrosis and recanalization, within the same affected region seen on cerebral angiography (A). Verhoeff–Van Gieson (VVG) staining of common carotid artery (F) adjacent to the bifurcation demonstrating fragmentation of the internal elastic lamina (arrows), intimal proliferation, and damage of the external elastic lamina.

every 2 weeks over 1 month) was added after worsening of GCA symptoms during tapering of oral prednisone. Even with an 18 month treatment course of oral steroids along with 7 months of intravenous cyclophosphamide plus rituximab, she continued to experience step-wise decline in her cognition and motor function with more infarcts in the right-sided border zone. Extracranial-to-intracranial carotid artery bypass surgery with radial artery graft was considered, but following a final catheter angiogram, she suffered a groin hematoma, relative hypotension, and numerous new bilateral cerebral infarctions (Fig. 1C, D). The family decided to withhold life-sustaining treatments. She died about 2 years after her initial presentation. Postmortem pathology showed severe stenosis in the intracranial distal carotid artery in the same affected regions seen on cerebral angiography. These vessels

demonstrated intimal thickening with disruption and redundancy of the internal elastic lamina though no active inflammation (Fig. 1E,F). Intracranial and intraparenchymal arteries were not involved.

A 65-year-old man presented with 5–6 weeks of functional decline and falls. Specifically, he complained of increasing disequilibrium, malaise, positional vision changes, and tremor. His admission examination revealed bradykinesia, diffuse weakness, an action tremor, and impaired balance. Parkinsonism was suspected. An MRI revealed multiple acute left-sided infarcts in the subcortical white matter though no infarction within the basal ganglia. Laboratory studies revealed an elevated ESR of 84. Vascular imaging showed bilateral distal internal carotid artery narrowing at the siphons, presumed to be related to atherosclerotic disease (Fig. 2A). The

elevated ESR was attributed to inflammation after ischemic stroke. He was started on low-dose aspirin and clopidogrel and underwent intra-arterial stent placement in his left cavernous to clinoid internal carotid artery.

He continued to worsen clinically, and another MRI showed acute infarcts on the right. A repeat catheter angiogram approximately 4 months after the original study showed interval progression with an occluded right intracranial distal internal carotid artery and moderate narrowing of the stented left distal carotid artery, as well as new stenosis of the bilateral distal vertebral arteries (Fig. 2 B). Despite lacking typical symptoms for GCA and partly due to the similarity to the first patient's catheter angiograms, the patient underwent a

temporal artery biopsy that confirmed GCA with transmural inflammation consisting of epithelioid histiocytes, multinucleated giant cells, and lymphocytes (Fig. 2E,F). He was immediately started on 3 days of pulse methylprednisolone therapy (1 g per day) followed by 60 mg per day of prednisone. Due to his poor cerebral circulation, immunosuppressive therapy was increased within a month with intravenous cyclophosphamide (0.75 g/m² for 1 infusion) in addition to oral steroids, yet he continued to deteriorate clinically. With further hemispheric infarcts (Fig. 2C,D) in the setting of sepsis related to a line infection 2 months after initiation of pulsed steroids, the family decided to withdraw life-sustaining treatments. He died about 7 months after his initial presentation.

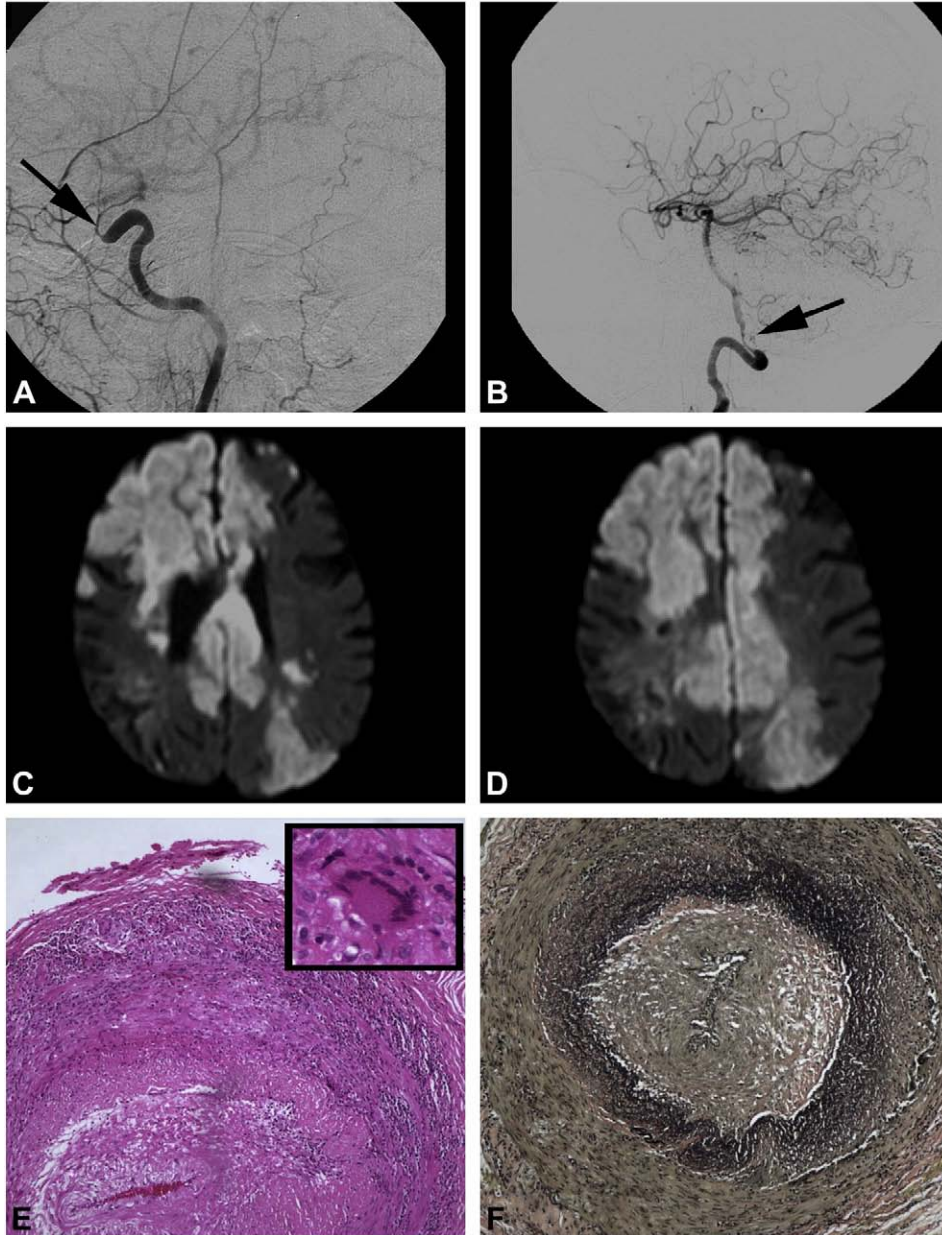


Fig. 2. Case 2: conventional cerebral angiogram anterior circulation injection (A) performed at the time of patient's initial left-sided ischemic infarction shows severe stenosis in the distal left internal carotid artery from the anterior cavernous to the communicating segment. The contralateral distal internal carotid artery was equally affected (not shown) though both vertebral arteries demonstrated normal flow. Repeat cerebral angiogram performed 4 months after the original study revealed new severe short segment narrowing of the left vertebral artery (B) at the level of the foramen magnum, with normal diameter though slow flow in the distal intracranial vertebral and basilar artery. The right vertebral artery demonstrated equally severe focal stenosis and slow flow (not shown). Diffusion-weighted MRI sequence following a line infection and sepsis shows extensive acute infarction in bilateral anterior and middle cerebral artery territories (C,D). Histology of temporal artery biopsy seen obtained after second cerebral angiogram (E,F). H&E stain of a muscular artery (E) showing transmural inflammation including epithelioid histiocytes, multinucleated giant cell (inset), and lymphocytes. The inflammation is most pronounced in the muscular layer and the lumen is markedly narrowed. VVG stain of temporal artery biopsy (F) showing disrupted internal elastic lamina with intimal proliferation.

3. Discussion

Cranial ischemic complications, typically presenting as arteritic optic neuropathy, have been reported in up to one-third of GCA patients, with cerebrovascular events occurring in only 3–4% of patients [1]. The disease can affect both distal vertebral and internal carotid arteries with varying clinical presentations [2–4]. Patients may present with typical symptoms of GCA, including headache and visual changes, with disease progression to involve the cerebrovascular circulation, as in our first patient. Alternatively, our second patient demonstrates the difficulty in diagnosis when patients initially present with ischemic stroke and elevated inflammatory markers but without the characteristic GCA symptoms. In this case, the constellation of slow cognitive decline and profound bradykinesia led to a delay in the diagnosis of GCA. Notably, both patients seemed to suffer from a step-wise cognitive decline, which we postulate was the result of a vascular subcortical dementia, as described previously [5].

Unlike atherosclerotic disease, the areas of stenoses in GCA typically involve the intracranial distal internal carotid and vertebral arteries, with arteritic involvement abruptly ending a few millimeters distal to the site of dural perforation, where the amount of elastic tissue in the vessel drops [4]. In these two cases, the catheter angiograms were consistent with this description showing abrupt changes in luminal size soon after the vessels pierce the dura (A and B in both figures), a pattern that should always raise the possibility of GCA. The brain infarcts in these patients result from hypoperfusion to the border zones or from artery-to-artery emboli, rather than from arteritis of end vessels. A possible relationship between atherosclerotic disease, common in this age population, and GCA has been proposed as a pathogenic mechanism of the intracranial cerebrovascular disease. Though both processes play a role in the inflammatory process, GCA likely contributes to a higher and earlier mortality by accelerating the progression of vascular disease through impeded collateral flow [2].

The characteristic radiographic pattern appears to correlate with the underlying pathologic process. Both the innate immune system and the adaptive immune response orchestrate a complex interplay between cytokines and various cell types, resulting in systemic inflammation and vascular injury due to structural changes, intimal hyperplasia, and luminal occlusion [6–8]. One of the mechanisms appears to be the targeting of elastin by macrophages [8]. The fact that inflammation of GCA diminishes as the vessels perforate the dura may correspond to the thinning of external elastic lamina as the vessel enters the dura with complete loss occurring about 0.5 cm intradurally [4]. The decreased amount of elastin present in intradural vessels may explain the relative sparing of the more distal vessels from the disease.

Patients presenting with GCA, but without cranial ischemic complications, typically respond to steroid monotherapy. Several long-term studies have shown that treatment has an overall preventative effect on vascular complications [9,10]. Our two patients and others reported in the literature were characterized by a steroid-resistant form of the disease with poor outcomes [2,3,5]. Glucocorticoid therapy may represent a double edged sword in the management of systemic vasculitis, with progression of vascular occlusion even after control of inflammation [11]. The possibility of a “burned-out” vasculitis has been described in Takayasu’s arteritis, another large vessel vasculitis that is characterized by neoangiogenesis with adventitial and intimal thickening resulting in fibrosis, despite the paucity of inflammation seen on histologic examination [12]. Mediators of the intimal hyperplasia and ischemic complications in GCA include proinflammatory cytokines and growth factors such as platelet derived growth factor and vascular endothelial growth factor [13]. In Takayasu’s arteritis, it remains unclear whether steroids alone can completely eradicate inflammation, as there is little angiographic evidence of any attenuation of arterial stenosis despite clinical

improvement [14]. Interferon- γ also plays a key role in the pathogenesis of inflammatory cerebrovascular disease and steroids do not typically affect interferon- γ expression [11,15]. Thus despite clinical improvement in the systemic signs of GCA with steroid therapy, local disease activity and post-inflammatory remodeling may well persist within the intracranial vessel wall even after inflammation has been quelled. The relative lack of inflammation at the site of severe distal intracranial stenosis noted on necropsy in our first patient may reflect such a “burned-out” stage of disease.

Though GCA may lead to a protracted course with multiple disease flares, these two patients and others described in the literature demonstrate how aggressive the disease may become despite escalating immunosuppressive therapies [2,3,5]. Neither patient appeared to benefit from antithrombotic and immunosuppressant therapy. Both were treated with antiplatelet agents as the infarct distribution was more consistent with a border zone pattern rather than an embolic one. Anticoagulants were withheld due to bleeding complications while on antiplatelet medications in both patients. Elderly patients may also have an increased susceptibility to adverse events from steroids and immunosuppressant drugs due to the increased likelihood of comorbidities and drug interactions. This population warrants vigilant monitoring, especially for myelosuppression and secondary malignancies.

Ongoing research into the development of new treatments for GCA appears to focus on targeting the mediators of the disease pathogenesis [16]. A recent study demonstrated that the presence of CD68 antigen-presenting cells and the extent of glucocorticoid receptor staining in GCA can suitably predict complete remission, possibly helping to identify the subset of patients who are unlikely to benefit from further immunosuppression [17]. Because of documentation of successful use in GCA [18], presumed steroid-sparing properties, and benefit in refractory cases of small to medium vessel arteritis, rituximab was used in our first patient. A few case reports describe the successful use of tissue necrosis factor- α blockade in GCA as well [19,20], and the crucial role played by interferon- γ and other cytokines may lead to further studies of clinical improvement, especially in a “burned-out” vasculitic phase of the disease. Nonetheless, despite multiple clinical trials, there is currently limited data regarding effective glucocorticosteroid sparing therapies in refractory GCA [21]. Whether other aggressive approaches, such as extracranial-to-intracranial bypass using arterial grafts, endovascular stenting of arteritic vessels, or autologous hemopoietic stem cell transplant, should be considered in these patients requires further study. We argue that because a subset of GCA patients is resistant to usual therapies, other approaches such as these should be considered in an attempt to halt the seemingly inexorable progression to disability and death.

References

- [1] Caselli RJ, Hunder GG, Whisnant JP. Neurologic disease in biopsy-proven giant cell (temporal) arteritis. *Neurology* 1988 Mar;38(3):352–9.
- [2] Ruegg S, Engelter S, Jeanneret C, Hetzel A, Probst A, Steck AJ, et al. Bilateral vertebral artery occlusion resulting from giant cell arteritis: report of 3 cases and review of the literature. *Medicine (Baltimore)* 2003 Jan;82(1):1–12.
- [3] Salvarani C, Giannini C, Miller DV, Hunder G. Giant cell arteritis: involvement of intracranial arteries. *Arthritis Rheum* 2006 Dec 15;55(6):985–9.
- [4] Wilkinson IM, Russell RW. Arteries of the head and neck in giant cell arteritis. A pathological study to show the pattern of arterial involvement. *Arch Neurol* 1972 Nov;27(5):378–91.
- [5] Solans-Laquer R, Bosch-Gil JA, Molina-Catenario CA, Ortega-Aznar A, Alvarez-Sabin J, Vilardell-Tarres M. Stroke and multi-infarct dementia as presenting symptoms of giant cell arteritis: report of 7 cases and review of the literature. *Medicine (Baltimore)* 2008 Nov;87(6):335–44.
- [6] Krupa WM, Dewan M, Jeon MS, Kurtin PJ, Younge BR, Goronzy JJ, et al. Trapping of misdirected dendritic cells in the granulomatous lesions of giant cell arteritis. *Am J Pathol* 2002 Nov;161(5):1815–23.
- [7] Weyand CM, Goronzy JJ. Giant-cell arteritis and polymyalgia rheumatica. *Ann Intern Med* 2003 Sep 16;139(6):505–15.
- [8] Weyand CM, Goronzy JJ. Pathogenic principles in giant cell arteritis. *Supplement 1 Int J Cardiol* 2000;75:S9–S15.

- [9] Andersson R, Malmvall BE, Bengtsson BA. Long-term survival in giant cell arteritis including temporal arteritis and polymyalgia rheumatica. A follow-up study of 90 patients treated with corticosteroids. *Acta Med Scand* 1986;220(4):361–4.
- [10] Matteson EL, Gold KN, Bloch DA, Hunder GG. Long-term survival of patients with giant cell arteritis in the American College of Rheumatology giant cell arteritis classification criteria cohort. *Am J Med* 1996;100(2):193–6.
- [11] Conn DL, Tompkins RB, Nichols WL. Glucocorticoids in the management of vasculitis—a double edged sword? *J Rheumatol* 1988 Aug;15(8):1181–3.
- [12] Kerr GS, Hallahan CW, Giordano J, Leavitt RY, Fauci AS, Rottem M, et al. Takayasu arteritis. *Ann Intern Med* 1994 Jun 1;120(11):919–29.
- [13] Kaiser M, Weyand CM, Bjornsson J, Goronzy JJ. Platelet-derived growth factor, intimal hyperplasia, and ischemic complications in giant cell arteritis. *Arthritis Rheum* 1998 Apr;41(4):623–33.
- [14] Ishikawa K, et al. Effects of prednisolone therapy on arterial angiographic features in Takayasu's disease. *Am J Cardiol* 1991 Aug 1;68:410–3.
- [15] Weyand CM, Tetzlaff N, Bjornsson J, Brack A, Younge B, Goronzy JJ. Disease patterns and tissue cytokine profiles in giant cell arteritis. *Arthritis Rheum* 1997 Jan;40(1):19–26.
- [16] Martinez-Taboada VM, Alvarez L, RuizSoto M, Marin-Vidalled MJ, Lopez-Hoyos M. Giant cell arteritis and polymyalgia rheumatica: role of cytokines in the pathogenesis and implications for treatment. *Cytokine* 2008 Nov;44(2):207–20.
- [17] Braun N, Fritz P, Rieth A, Schroth W, Kimmel M, Biegger D, et al. Predictors for treatment success and expression of glucocorticoid receptor in giant cell arteritis and polymyalgia rheumatica. *J Rheumatol* 2009 Oct;36(10):2269–76.
- [18] Bhatia A, Ell PJ, Edwards JC. Anti-CD20 monoclonal antibody (rituximab) as an adjunct in the treatment of giant cell arteritis. *Ann Rheum Dis* 2005 Jul;64(7):1099–100.
- [19] Cantini F, Niccoli L, Salvarani C, Padula A, Olivieri I. Treatment of longstanding active giant cell arteritis with infliximab: report of four cases. *Arthritis Rheum* 2001 Dec;44(12):2933–5.
- [20] Uthman I, Kanj N, Atweh S. Infliximab as monotherapy in giant cell arteritis. *Clin Rheumatol* 2006 Feb;25(1):109–10.
- [21] Nuenninghoff DM, Matteson EL. The role of disease-modifying antirheumatic drugs in the treatment of giant cell arteritis. *Clin Exp Rheumatol* 2003 Nov–Dec;21:S29–34 6 Suppl 32.