

## CLINICAL CASE

Angioinvasive aspergillosis mimicking  
giant cell arteritis in an 81-year-old man  
with jaw pain and vision lossRomain Guemara , Amara Pieren, Laure Brulhart

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**ABSTRACT**

The present case report focuses on an immunocompromised 81-year-old patient initially diagnosed with Waldenström's disease. The patient experienced a gradual vision loss and jaw pain with high erythrocyte sedimentation rate. We first suspected giant cell arteritis, despite inconclusive assessment, including a negative temporal artery biopsy. We rapidly started a corticosteroid pulse therapy followed by high-dose corticosteroid therapy that was followed even after discharge from the hospital. The patient was readmitted 20 days later with severe left retro-orbital pain and progressive left vision loss. Clinical examination revealed complete left eyelid ptosis and unilateral blindness with fixed mydriasis and no eye movement. MRI showed signs of ischaemic optic neuropathy with lysis of the left ethmoid sinus wall; thus, indicating ischaemic optic neuropathy related to lymphoplasmacytic infiltration of Waldenström's disease (Bing-Neel syndrome). Oncological treatment of ibrutinib, a tyrosine kinase inhibitor, was then administered. Despite a favourable prognosis, no improvement was seen. An infectious aetiology was finally confirmed. The left sphenoid sinus biopsy highlighted an angioinvasive aspergillosis with rhino-orbital infiltration observed as ischaemic optic neuropathy. Oncologic treatment was discontinued and antifungal therapy with voriconazole was introduced, leading to a favourable radiological development and analgesic control, without ophthalmological improvement.

**CASE REPORT**

We present the case of an 81-year-old man with a medical history of arterial hypertension and dyslipidaemia. He was recently diagnosed with lymphoplasmacytic lymphoma associated with Waldenström's disease based on IgM Kappa monoclonal gammopathy with IgM level of 20.8g/L (hospital range from 0.5 to 3.0g/L), normal IgA and IgG levels, 60% infiltration by a low-grade B lymphoma with plasmacytic differentiation on the bone marrow biopsy and the L265P mutation of the MYD88 gene. Based on age, his prognostic score was intermediate.<sup>1</sup> Haematological treatment was not started. Medications prescribed were lisinopril, atorvastatin

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

- ⇒ Giant cell arteritis (GCA) is the most common form of systemic vasculitis.
- ⇒ It typically affects people older than 50 years old, causes head and jaw pain, scalp tenderness, vision problems and is closely linked with polymyalgia rheumatica.
- ⇒ Radiological or histological confirmations are mandatory for the diagnosis.

**WHAT THIS STUDY ADDS**

- ⇒ It illustrates how angio-invasive aspergillosis can mimic GCA and its wide range of differential diagnoses, and what can be learnt in similar situation in the future.

**HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY**

- ⇒ Radiological or histological confirmations of giant cell arteritis (GCA) are mandatory for the diagnosis. Unexpected progression of the disease, particularly the persistence of inflammatory markers despite high doses of corticosteroids, should challenge the possibility of GCA.
- ⇒ GCA symptoms in an immunocompromised patient should raise suspicion of infectious neuropathy, including aspergillosis.

and acetylsalicylic acid. The patient did not smoke or have alcohol consumption. Family history was irrelevant.

He initially experienced a gradual left vision loss, jaw pain, without claudication or scalp dysesthesia. There was no weight loss, weakness or paresthesia. Physical examination revealed symmetric hypertension (173/95 mm Hg) without fever. There was tenderness in the left temporomaxillary area, despite normal palpation of the temporal arteries. Joint examination, neurological, cardiac and pulmonary status were otherwise irrelevant. Ophthalmologist examination confirmed visual acuity loss with normal fundoscopic examination.

Biological assessment revealed normochromic normocytic anaemia with a value of



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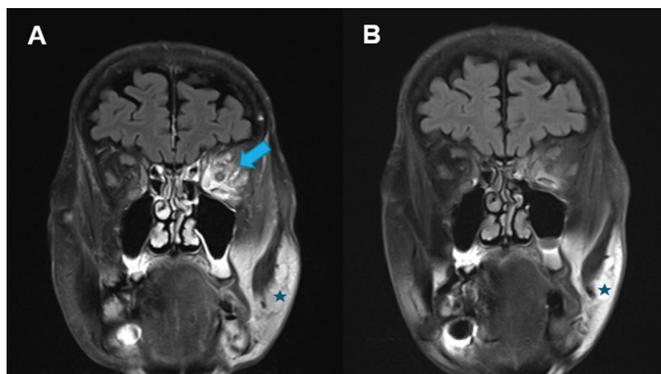
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13.9g/dL (hospital reference range from 14.0 to 16.0g/dL), normal white cell count and erythrocyte sedimentation rate (ESR) up to 65 mm/hour (hospital reference range for men  $\leq$ 15 mm/hour). C reactive protein (CRP) was not assessed initially. Blood electrolyte levels, kidney and liver functions were within normal range.

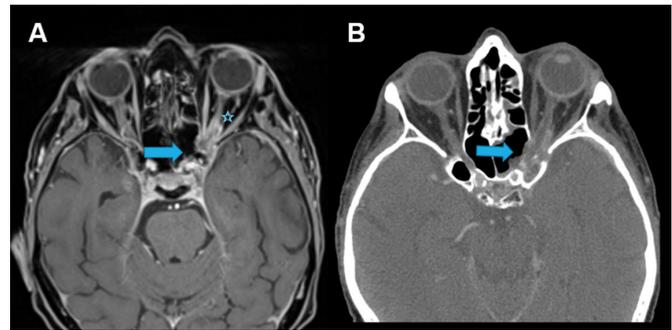
Consequently, giant cell arteritis (GCA) was suspected, prompting intravenous pulse glucocorticoid therapy. Arterial Doppler ultrasound found no halo, compression sign, stenosis or vessel occlusion. The temporal artery biopsy revealed a fibrotic thickening of the intima without any giant cell or lymphocytic inflammation. We then performed cerebral angio-CT and contrast-enhanced MRI, without ischaemic, haemorrhagic or infiltrative lesions. The retinal angiography was normal. The negative results from all these investigations and the haematological context led to further assessment. Microbiological PCR testing, serological examination and immunological markers were negative. In addition, the artery and abdominal fat biopsies showed no sign of amyloidosis, and there was no hyperviscosity. Moreover, lumbar puncture revealed neither hyperproteinorachia nor isolated oligoclonal bands. The patient was discharged from the hospital with 60 mg of prednisone, due to a fairly negative predictive value of the unilateral biopsy for GCA.<sup>2</sup>

After 20 days, he developed severe left retro-orbital pain with left eyelid ptosis, unilateral blindness with fixed mydriasis and a strict absence of eye movement. CRP was up to 20 mg/dL, and ESR was at 90 mm/hour.

A second MRI (figures 1 and 2) showed thickening of the sheath in the left optic nerve, lysis of the wall of the left ethmoid sinus and infiltration of orbital fat and oculomotor muscles. This was suggestive, with the haematological history, for ischaemic optic neuropathy related to lymphoplasmacytic infiltration of Waldenström's disease (Bing-Neel syndrome). The haematological opinion supported the introduction of ibrutinib (tyrosine kinase



**Figure 1** Imaging studies. Coronal images from MRI (T2 weighted fluid attenuated inversion recovery) of the head show signs of ischaemia in the left optic nerve with thickening of the sheath, orbital fat and oculomotor muscles infiltration (A, arrows) and soft tissue oedema (A and B, stars). A control MRI 3 months after antifungal therapy and debulking surgery show great improvement with regression of thickness and local infiltration (B).



**Figure 2** Imaging studies. Axial images from MRI (T2 weighted fluid attenuated inversion recovery) (A) and contrast-enhanced CT of the head (B) show signs of ischaemia in the left optic nerve with thickening of the sheath (A, star) and lysis of the wall of the left ethmoid sinus (A and B, arrows).

inhibitor), with dexamethasone for decreasing the reactive oedema secondary to lymphomatous infiltration in the central nervous system.

Unfortunately, the follow-up radiological assessment 10 days later showed a progressive infiltration of the left orbital apex with parietal necrosis of the ethmoid wall and progression to the sphenoid sinus (figure 2).

### DIFFERENTIAL DIAGNOSIS

Herein, we report a case of an 81-year-old immunocompromised patient with Waldenström's disease. The patient developed progressive unilateral vision loss and temporomandibular pain worsening to unilateral blindness with eye movement loss. The radiological assessment confirmed an optic neuropathy with local infiltration. The elevated CRP and ESR suggested a systemic inflammation caused by autoimmune disease, malignancy or infection.

### Autoimmune diseases associated to optic neuropathy

We first treated GCA due to typical clinical initial examination and the high prevalence of the disease.<sup>2</sup> Optic neuropathy from sarcoidosis, neuro-Behçet, systemic lupus erythematosus, Sjögren's syndrome<sup>3</sup> or chronic relapsing inflammatory optic neuropathy<sup>4</sup> also respond well to corticosteroids. No symptoms, clinical signs, immunological marker or biopsy were suggestive of any other autoimmune disease or ocular involvement from amyloidosis.<sup>5</sup> We excluded the possibility of optic neuritis from multiple sclerosis<sup>6</sup> with both MRI of the brain and lumbar puncture.

### Neurological and ophthalmological involvement in Waldenström macroglobulinemia

Blurring or vision loss, diplopia and headache could suggest hyperviscosity syndrome.<sup>1</sup> The neuropathy associated with Waldenström disease is typically distal, symmetric and slowly progressive with sensorimotor peripheral neuropathy.<sup>7</sup> Cranial nerve neuropathy and mononeuritis multiplex are less common.<sup>8</sup> Infiltration of the central nervous system by plasmacytoid lymphocytes is pathognomonic for the Bing-Neel syndrome.<sup>8</sup>

## Infectious neuropathy

Any infectious meningitis or encephalitis may lead to optic neuropathy, which could be the first manifestation of some indolent infection.<sup>9</sup> Neuroretinitis is associated with cat scratch disease and toxoplasmosis. Postviral optic neuritis is described with measles, mumps, chickenpox, influenza, varicella zoster and Epstein-Barr virus, and usually follow clinical infection in 1–3 weeks.<sup>10</sup> A recent publication highlights SARS-Cov-2 infection that mimics GCA with spontaneous resolution.<sup>11</sup> The absence of uveitis plus the microbial assessment was against tuberculosis. Finally, invasive aspergillosis can lead to dissemination as well as local extension from the paranasal sinuses and even potentially lead to mycotic aneurysm.<sup>12–13</sup>

## FINAL DIAGNOSIS

After multidisciplinary counselling, an invasive mycosis was suspected in the presence of an unfavourable evolution of the infiltration under well-conducted oncological treatment. A biopsy from the left sphenoid sinus did not show signs of malignancy but confirmed the presence of *Aspergillus fumigatus*, and finally led to the diagnosis of angioinvasive aspergillosis with rhino-orbital infiltration presenting as ischaemic optic neuropathy. Oncologic treatment was discontinued. Voriconazole was introduced with a debulking surgery. Jaw pain was finally well controlled under fentanyl and pregabalin. MRI follow-up 3 months later showed stability of the collections and granulations with the regression of left optic neuritis (figure 1C). Unfortunately, there was no neurological recovery on the clinical examination.

## DISCUSSION

This dramatic case illustrates the wide range of differential diagnoses for GCA, what went wrong and what can be learnt in similar situation in the future. With a high annual incidence (15–25 per 100 000 persons) in people aged 50 or above, GCA is the most common form of systemic vasculitis. Temporal biopsy has a sensitivity and specificity of 73% and 94%, respectively, with very few discordances between unilateral versus bilateral biopsy.<sup>14</sup> In a meta-analysis by Duftner *et al*<sup>15</sup>, the sensitivity and specificity values were 77% and 96%, respectively, for temporal arteries ultrasound and 73% and 88%, respectively, for cranial MRI. Moreover, two studies reported a sensitivity of 67%–77% and specificity of 66%–100% for PET-CT-<sup>18</sup>F-DG as compared with clinical diagnosis or temporal artery biopsy.

In the present case, one-sided, localised headache, slowly developing vision loss, the worsening of symptoms despite high doses of corticosteroids with negative unilateral biopsy and Doppler ultrasound should have suggested other diagnoses than GCA. Waldenström's disease in the patient probably explained the initial elevated ESR; thus, we excluded hyperviscosity syndrome and amyloidosis with blood sample and biopsy congo red staining. A total of 1% of patients with Waldenström

macroglobulinaemia manifest Bing-Neel syndrome,<sup>16</sup> which is suggested by MRI abnormalities and confirmed by the presence of clonal lymphoplasmacytic cells in the cerebrospinal fluid. Interestingly, Bouffard *et al* described a very similar case that ended up being diagnosed as Bing-Neel syndrome.<sup>17</sup>

The immunosuppression raises assumptions for an infectious aetiology, principally opportunistic or fungal infections. Risk factors for aspergillosis include prolonged neutropenia, transplanted patients, advanced AIDS and chronic granulomatous disease.<sup>12</sup> Some other cases of aspergillosis that mimicked GCA have been reported.<sup>18–19</sup> Usually, optic neuropathy from angioinvasive aspergillosis leads to severe evolution, and may even be lethal.<sup>19</sup> The patient developed unilateral blindness, and the delay before tapering prednisone and starting antifungal therapy might have contributed to this complication. No radiological finding is pathognomonic of invasive aspergillosis. Despite involving the sinopulmonary tract, cultures of respiratory samples lack sensitivity.<sup>12</sup> The microbiological assessment remains the gold standard. Galactomannan antigen detection provides a relatively high specificity with a wide variation in sensitivity,<sup>20</sup> even before late symptoms occur. The beta-d-glucan assay has a lower specificity for aspergillosis.<sup>12</sup> Nowadays, there is still a lack of other early markers with a good sensitivity, either from radiological or biological assessment, which could highlight aspergillosis before late progression occurs. Thus, future research should focus on the relevance of the antigen-based assays as the diagnostic strategy for an immunocompromised patient with unspecific inflammatory disease.

In conclusion, we demonstrate the importance of reassessing the diagnosis of GCA, especially when a patient manifests an atypical clinical presentation and unexpected clinical evolution under specific treatment. GCA needs to be confirmed by imaging or histology. As crucial as it is to administer corticosteroids when it is diagnosed, we should also act quickly to rule out the diagnosis and taper the course of treatment if either the radiological or pathological evaluations are unremarkable or the course of the disease does not progress as expected.

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#### REFERENCES

- 1 García-Sanz R, Montoto S, Torrequebrada A, *et al*. Waldenström macroglobulinaemia: presenting features and outcome in a series with 217 cases. *Br J Haematol* 2001;115:575–82.
- 2 Gonzalez-Gay MA, Garcia-Porrúa C, Llorca J, *et al*. Biopsy-negative giant cell arteritis: clinical spectrum and predictive factors for positive temporal artery biopsy. *Semin Arthritis Rheum* 2001;30:249–56.
- 3 Theodoridou A, Settas L. Demyelination in rheumatic diseases. *J Neurol Neurosurg Psychiatry* 2006;77:290–5.
- 4 Kidd D, Burton B, Plant GT, *et al*. Chronic relapsing inflammatory optic neuropathy (CRIION). *Brain* 2003;126:276–84.
- 5 Dammacco R, Merlini G, Lisch W, *et al*. Amyloidosis and ocular involvement: an overview. *Semin Ophthalmol* 2020;35:7–26.
- 6 Balcer LJ. Clinical practice. optic neuritis. *N Engl J Med* 2006;354:1273–80.
- 7 Nobile-Orazio E, Marmioli P, Baldini L, *et al*. Peripheral neuropathy in macroglobulinemia: incidence and antigen-specificity of M proteins. *Neurology* 1987;37:1506–14.
- 8 Minnema MC, Kimby E, D'Sa S, *et al*. Guideline for the diagnosis, treatment and response criteria for bing-neel syndrome. *Haematologica* 2017;102:43–51.
- 9 Lee AG, Brazis PW. Systemic infections of neuro-ophthalmic significance. *Ophthalmol Clin North Am* 2004;17:vii:397–425.
- 10 Mathias M, Nagel MA, Khmeleva N, *et al*. VZV multifocal vasculopathy with ischemic optic neuropathy, acute retinal necrosis and temporal artery infection in the absence of zoster rash. *J Neurol Sci* 2013;325:180–2.
- 11 Riera-Martí N, Romani J, Calvet J. [SARS-CoV-2 infection triggering a giant cell arteritis]. *Med Clin* 2021;156:253–4.
- 12 Segal BH. Aspergillosis. *N Engl J Med* 2009;360:1870–84.
- 13 Riddell Iv J, McNeil SA, Johnson TM, *et al*. Endogenous Aspergillus endophthalmitis: report of 3 cases and review of the literature. *Medicine* 2002;81:311–20.
- 14 Dua AB, Husainat NM, Kalot MA, *et al*. Giant cell arteritis: a systematic review and meta-analysis of test accuracy and benefits and harms of common treatments. *ACR Open Rheumatol* 2021;3:429–41.
- 15 Duftner C, Dejaco C, Sepriano A, *et al*. Imaging in diagnosis, outcome prediction and monitoring of large vessel vasculitis: a systematic literature review and meta-analysis Informing the EULAR recommendations. *RMD Open* 2018;4:e000612.
- 16 Castillo JJ, Treon SP. How we manage Bing-Neel syndrome. *Br J Haematol* 2019;187:277–85.
- 17 Bouffard MA, Chwalisz BK, Romero JM, *et al*. Case 6-2021: a 65-year-old man with eye pain and decreased vision. *N Engl J Med* 2021;384:745–53.
- 18 Murosaki T, Nagashima T, Honne K, *et al*. Invasive sphenoid sinus aspergillosis mimicking giant cell arteritis. *Int J Rheum Dis* 2014;17:476–8.
- 19 Sivak-Callcott JA, Livesley N, Nugent RA, *et al*. Localised invasive sino-orbital aspergillosis: characteristic features. *Br J Ophthalmol* 2004;88:681–7.
- 20 Marr KA, Leisenring W. Design issues in studies evaluating diagnostic tests for aspergillosis. *Clin Infect Dis* 2005;41 Suppl 6:S381–6.