

CASE REPORT

A case of left foot drop as initial symptom of granulomatosis with polyangiitis: Triggered by COVID-19 disease?

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Abstract

In Granulomatosis with polyangiitis (GPA), involvement of the peripheral nervous system is frequent but its occurrence as an initial presentation is unusual. This case highlights the importance of this occurrence to permit an early diagnosis. Moreover, GPA started after a coronavirus disease 2019 infection and could have been induced by this.

KEYWORDS

ear, nose and throat, neurology, ophthalmology, rheumatology

1 | INTRODUCTION

In recent years, various post coronavirus disease 2019 (COVID-19) syndromes have been described. Moreover, many viruses have been implicated in the pathogenesis of auto-immune diseases, including vasculitis. Here, we report a case of granulomatosis with polyangiitis onset following a COVID-19 disease with an initial presentation of left drop foot.

Granulomatosis with polyangiitis (GPA) is an ANCA-associated vasculitis (AAV) belonging to the primary systemic vasculitis and systemic necrotizing vasculitides (SNV). The disease is characterized by necrosis of small blood vessels (capillaries, venules, arterioles, and small arteries) and by granulomatous formation in multiple organs.¹ It is a rare disease with an annual incidence of about

10 cases per million inhabitants in northern Europe.¹ If untreated, the mortality rate at 1 year is about 70%.² This highlights the importance of a prompt diagnosis, and needs to raise awareness of the most uncommon presentations. It usually presents with ear–nose–throat, pulmonary or/and renal involvement.¹ Nasal and paranasal sinus disorders are observed in 90% of the cases, and are the most common primary manifestations.¹ Pulmonary infiltrates or nodules come second among the most frequent manifestations.¹ Although nervous system involvement is rare at the initial stage,³ neuropathy is reported during the course of the disease in 17% of cases.⁴ The typical presentation is a mononeuritis multiplex, leading to motor and sensory deficits.^{3,5} On the contrary, an isolated peripheral neuropathy, like the one described here, is an unusual finding in GPA.³

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2 | CASE PRESENTATION

In January 2021, a 51-year-old woman was admitted in our department with a worsening chronic polyarticular pain and fatigue but also with a left drop foot that had begun few weeks earlier associated with burning paresthesia. Prior to her admission, she reported redness of the left eye with ocular pain and photophobia (Figure 1). She had no fever, no photosensitivity rashes, no Raynaud phenomenon and no swelling joints. Her past medical history included diabetes, hypertension, osteoarthritis, and chronic non-allergic rhinitis. We noted a diagnosis of mild-form COVID-19 infection 3 months prior without acute respiratory distress syndrome or multiorgan failure. Her chronic treatment included Bisoprolol and Metformine. She had no smoking history, and did not take any drugs.

Physical examination found the left drop foot, and the conjunctival redness of the left eye. Neurological examination revealed a weakness in the dorsiflexion of the left foot, and hypoesthesia of the lateral surface of the distal leg. The rest of her examination, including deep tendon reflexes, was normal. The ophthalmological examination with slit-lamp revealed a diffuse anterior scleritis of the left eye.

An electromyography (EMG) and a lumbar magnetic resonance imaging (MRI) had been performed before the admission and were normal excepted a discal protrusion without radicular conflict. In the past, the patient was known for chronic moderate inflammatory blood test of unknown origin. Laboratory investigation confirmed again the elevation of the erythrocyte sedimentation rate (30/mm) and of C-reactive protein (22 mg/L). The hemogram, renal, and liver functions were normal. She was

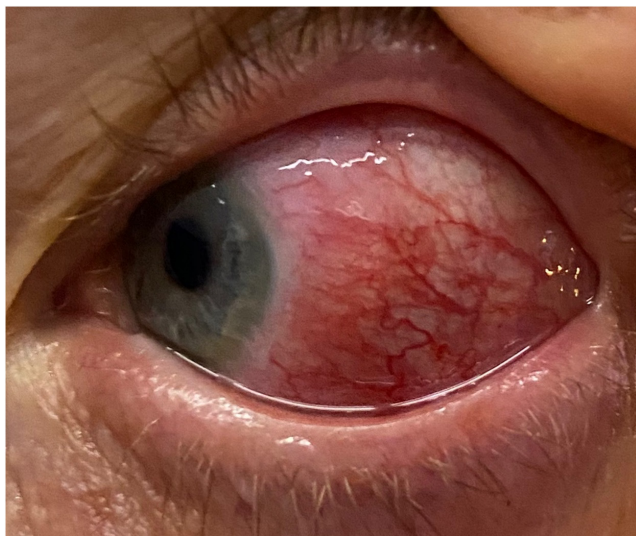


FIGURE 1 External appearance of the diffuse anterior scleritis with widespread inflammation of sclera. The scleral plexus remains visible after phenylephrine.

negative for HIV, hepatitis viruses, and Lyme disease. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies were positive. The patient was tested negative for tuberculosis (TB) by an interferon- γ releasing assay. Immunological tests were negative for antinuclear antibodies, anti-cyclic citrullinated peptide antibodies, rheumatoid factor and for cryoglobulinemia. The complement components 3 (C3) and 4 (C4) levels were normal. However, cytoplasmic anti-neutrophil cytoplasmic antibodies (c-ANCA) titers were elevated (1/160) with presence of Anti-proteinase-3 (PR3) antibodies (744 U/ml [N < 20]). Blood cultures were negative. Urine analysis revealed microscopic hematuria, no red cell casts and no proteinuria. Ultrasound of the urinary tract and cystoscopy were normal. Computed tomography (CT) of the chest showed no abnormalities. A sinus CT described a moderate diffuse pansinusitis with mucosal thickening. A second nerve conduction study was performed and showed an isolated left fibular sensory-motor neuropathy. On the left leg MRI, we visualized a neuritis of the fibular nerve with a denervation edema of the tibialis anterior and the extensor digitorum longus muscles. In the context of hematuria and suspicion of systemic disease, a renal biopsy was also performed and was negative. Nasal mucosa ulcers observed by endoscopy were biopsied and revealed only perivasculitis without necrotizing granulomas. Finally, a combined superficial peroneal nerve/peroneus brevis biopsy according to the electromyography revealed only a perivasculitis (Figure 2).

She was treated with topical prednisolone in her left eye, and a reduced-dose regimen of systemic steroids treatment was initiated with rituximab infusion. This treatment showed a favorable outcome for our patient with pain resolution, and improvement of the drop foot. Physiotherapy was also started. The patient follows a rituximab-based regimen for remission maintenance.

3 | DISCUSSION

We report a case of GPA following a SARS-CoV-2 infection with an isolated drop foot as its first manifestation. Peripheral neuropathies are usual complications of primary systemic vasculitis,^{3,5} but the presentation as first symptom^{4,6} as an isolated mononeuropathy is quite rare particularly for GPA.³ Involvement of other nerves can occur gradually over the course of 1 year or simultaneously. The typical presentation is an acute or subacute painful multifocal neuropathy with asymmetric distribution (15%–24%).⁵ Polyradiculopathy, plexopathy, distal symmetric neuropathy, or exclusive motor neuropathy are less frequent.^{1,3,5,7,8} The peroneal nerve is most often affected (56%–96%), followed by the tibial (11%–86%),

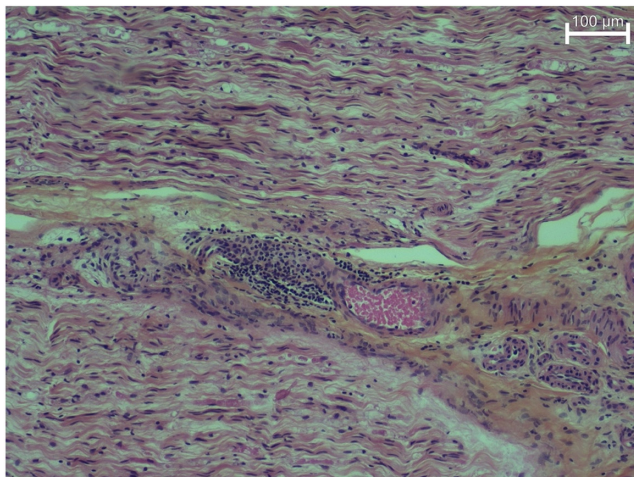


FIGURE 2 Superficial peroneal nerve biopsy with two nerve fascicles demonstrating perivasculitis with mononuclear cell infiltration surrounding small vessels.

ulnar (24%–75%), median (9%–58%), and radial (4%–50%) nerves.⁵ Electrophysiological studies reveal in most cases multifocal axonal lesions with an asymmetric pattern.⁸ In our patient, initial nerve studies and EMG were normal, which is due to the short delay (2–3 weeks) between nerve fibers degeneration and the appearance of fibrillations.⁹ The second nerve studies and EMG of the four limbs described an isolated fibular sensory-motor neuropathy.

It is important to keep in mind that peripheral neuropathy in the presence of elevated markers of inflammation should raise suspicion of a systemic illness.

ANCA testing plays an essential role in the diagnostic process of AAV. GPA is associated with a cytoplasmic pattern of ANCA (cANCA) staining on immunofluorescence (IF) which have an affinity to PR3. Sensitivity of ANCA testing for patients with systemic GPA is around 78% to 96%.¹⁰ The combination of IF and enzyme-linked immunosorbent assay (ELISA) increases this sensitivity.¹⁰ Among patients presenting with vasculitic neuropathy, sensitivity of ANCA testing is around 75%.⁷ In this case, nerve involvement was rapidly followed by an unilateral diffuse anterior scleritis, another unusual manifestation as an initial presentation. In GPA, ocular and orbital (like pseudotumor) symptoms are found in 15% of cases at first assessment, and in approximately 23 to 58% of the cases over the disease course.^{1,11} There is more ocular than orbital involvement, and the most common ocular manifestations are episcleritis and scleritis.¹¹ The most common type of scleritis observed in patients with GPA is diffuse anterior and necrotizing scleritis, more rarely posterior scleritis.¹² Association between ocular and neurological involvement is infrequent.^{8,11} Contrary to our case, Bischof and al observed that in a large cohort study of 955 patients with AAV, the vasculitic neuropathy was

associated with skin and musculo-skeletal involvement instead of renal and ocular involvement.⁸

In case of suspicion of vasculitic neuropathy, extraneural biopsies (renal, nasal) can give inconclusive results, as observed here. Nasal biopsies yield low results, ranging from 16% to 53%.¹³ Nasal biopsies should be guided by nasal endoscopic findings such as bloody submucosal ulcers or persistent white submucosal nodules. These findings have a better reliability when related to histopathologic lesions of active GPA.¹³ Biopsies of the affected nerves may be the key to confirm the diagnosis, even more so when there is no clear evidence of extraneural vasculitis. The patient's nerve biopsy showed perivasculitis, which is compatible with vasculitic neuropathy but not typical. This can be linked to the nerve biopsy sensitivity. Indeed, nerve biopsy yields a sensitivity of about 50%^{8,14} and reaches only 55% when associated with muscle biopsy.¹⁴ Sensitivity remains low due to these lesions being mostly focal.⁸ Hence, in clinical practice, nerve biopsy is not systematically performed.⁸ Typical pathological findings found in nerve biopsies are vessels obstruction with fibrinoid necrosis, inflammation of the vascular structures with structural damage, and granulomas. Axonal degeneration is also an additional suggestive finding.¹⁴ Despite the nonspecific histopathological findings, this case met the Chapel Hill nomenclature criteria for GPA, and the 2022 ACR/EULAR classification criteria. This is a combined score based on clinical, biologic, and histopathologic findings. Five or more points are necessary for the GPA diagnosis, with 93% sensitivity and 94% specificity.^{15,16} Here, this case presented a total score of 9 points. Three points were attribute for nasal congestion history, 5 points for anti-proteinase-3 ANCA positivity, and 1 point for inflammation of the nasal/paranasal sinuses on imaging.¹⁵

Another point of discussion regards COVID-19 association with AAV. We screened the available patient's blood samples. ANCA positivity was found on a serum sample prior to COVID-19 disease. In June 2020, anti-PR3 levels were 120 U/ml. We can support the hypothesis that the SARS-CoV-2 infection acted as a trigger for the GPA development, in a predisposing condition. There are two main processes by which infectious agents may induce auto-immune disease: promoting immune system hyperstimulation and by molecular mimicry mechanisms.¹⁷ SARS-CoV-2 stimulates the immune system by inducing auto-antibodies synthesis and triggers pre-existing auto-immune disease.¹⁷ For example, Vlachoyiannopoulos et al.¹⁸ described the presence of cANCA in 6,9% of patients in a 29-patient cohort with severe COVID-19 disease, and no history of auto-immune disorder. Follow-up studies are required in order to determine whether there is a clinical correlation with these antibodies, or if they are only transitory.

In this case, pre-existing ANCA antibodies prior to SARS-CoV-2 infection argue against a true seroconversion. Rather, it suggests pre-existing disease activation. A few cases of new onset AAV after COVID-19 disease have been reported, including notably three cases with GPA and lung involvement, and two of them also had other organs damage (e.g., kidneys, skin).¹⁹⁻²¹

Treatment strategy for SNV consists of induction and maintenance therapy. Induction treatment depends on the Five-Factor Score (FFS). This tool assesses the prognosis of systemic necrotizing vasculitis (SNV) at initial diagnosis.²² For GPA, this score takes into consideration several organ involvements like renal, gastrointestinal, cardiac, and ear, nose, and throat (ENT) involvement as well as patient age. Each item is given +1 point. As ENT symptoms are associated with a better outcome, and consequently their absence is consequently scored +1 point. Presence of one or more factors is associated with a higher risk of death.²² Among these patients, a treatment with a combination of glucocorticoids and intravenous cyclophosphamide or rituximab is indicated.²³ However, in GPA, contrasting with other SNV, it is recommended to immediately start a combination of steroids and immunosuppressant agents for systemic forms, regardless of the FFS, as there is a significant risk of relapse.^{1,2,22}

We also consider peripheral neuropathy although it is not life-threatening and not associated with higher mortality rates.⁶ Indeed, peripheral neuropathy can lead to disability and reduced quality of life.⁶ The results from the European Vasculitis Study Group trial show that all patients (MPA and GPA) with active vasculitic neuropathy at baseline achieved remission from their neuropathy with aggressive immunosuppressant therapy (mostly cyclophosphamide). Unfortunately, 65% demonstrated sequelae.⁶ Nerve recovery is known to be slow. For all these reasons, and according to these guidelines, we have treated this patient with a reduced-dose regimen of steroids and rituximab. A reduced-dose regimen of glucocorticoids was motivated in order to avoid frequently reported side effects of steroids, particularly corticosteroid-induced myopathy in a context of neuropathy. In this regard, a recent Japanese randomized non-inferiority trial compared two steroids regimens (reduced vs conventional high dose) in addition to rituximab in 140 patients with AAV. There was no evidence of a difference in remission rates at 6 months, while a lower rate of serious infections was noticed for the reduced regimen.²⁴ Similarly, the PEXIVAS trial is a recent study which included patients with AAV with renal involvement or severe diffuse hemorrhage.²⁵ Patients were randomized to either receive or not plasma exchange, and a standard or reduced-dose regimen of steroids. Walsh and al. did not demonstrate any effectiveness

of the plasma exchange in terms of mortality or incidence of end-stage kidney disease. However, they demonstrated non-inferiority of the reduced-dose regimen of glucocorticoids, and a lower incidence of serious infections at 1 year.²⁵

It is increasingly accepted that total steroids dose during remission induction phase could be reduced in most patients with AAV, regardless of concomitant immunosuppressive therapy. GPA is known to have a high relapse risk,¹ especially with anti-PR3 ANCA positivity.² Hence, maintenance therapy is recommended with Azathioprine or Rituximab. Of note, the MAINRITSAN trial showed rituximab superiority over azathioprine, with reduced disease relapse,²⁶ supporting our choice of Rituximab-based maintenance therapy.

4 | CONCLUSION

ANCA-vasculitis is a systemic disorder characterized by granulomatous inflammation of different tissues, and small vessels necrotizing vasculitis, and has several clinical presentations.¹ This case demonstrates the importance of peripheral neuropathy identification, as an initial clinical presentation of GPA. This allows early diagnosis and prompt immunosuppressive treatment initiation, preventing (or at least, delaying) any life-threatening organ involvement. Diagnosis is usually evident, based on clinical aspects and serological ANCA testing. However, biopsies may be needed, and remain the gold standard.^{1,27} In this case, nasal and nerve biopsies showed perivascularitis without granulomas. Due to these focal lesions, granulomas are frequently missing in the biopsies.^{8,13}

Viral infections can trigger GPA.¹ Here, SARS-CoV-2 infection may have triggered disease development. To our knowledge, there are few published cases of new onset granulomatosis with polyangiitis associated with COVID-19.¹⁹⁻²¹ Most of these findings were published as case reports, cohort, or prospective studies are needed to identify rheumatologic manifestations in the short- and long-term following COVID-19 infection.

AUTHOR CONTRIBUTIONS

Dr Weynand Marjolaine: Substantial contributions to the drafting of the article, acquisition and analysis of the data. Dr Raftakis Ioannis: Critical revising of the article. Dr Chérif Mohammad Yassine: Critical revising of the article. Dr Lecomte Sophie: acquisition of the data and analysis. Pr Badot Valerie: Critical revising of the article and final approval of the version to be published.

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CONFLICT OF INTEREST

There is no conflict of interest for any authors.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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