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A Case of Granulomatosis with Polyangiitis Complicated by Ganciclovir-Resistant Cytomegalovirus Central Nervous System Infection

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ABSTRACT

This case report describes a 72-year-old female with a confirmed diagnosis of Granulomatosis with Polyangiitis (GPA), who developed a complex and ultimately fatal clinical course complicated by refractory cytomegalovirus (CMV) meningoencephalitis. Despite initial immunosuppressive treatment for GPA and subsequent antimicrobial therapies for suspected bacterial and fungal infections, the patient presented with recurrent fevers, delirium, and cerebrospinal fluid (CSF) pleocytosis. Repeated CSF analyses and imaging revealed a perplexing picture, with a final diagnosis of CMV infection of the central nervous system (CNS) confirmed by PCR. The infection proved resistant to first-line antiviral therapy with ganciclovir, necessitating the addition of foscarnet. The patient's condition deteriorated, culminating in aspiration pneumonia, hemodynamic instability, and death.

This case highlights the diagnostic challenges of CNS infections in immunosuppressed patients and the potential for severe, treatment-resistant viral opportunistic infections in the context of GPA and its treatment.

Introduction

Granulomatosis with Polyangiitis (GPA) is a formidable systemic necrotizing vasculitis, characterized by granulomatous inflammation that primarily targets small- to medium-sized vessels. The therapeutic landscape for this potentially life-threatening disease has been revolutionized by B-cell-depleting agents like rituximab, which, alongside glucocorticoids, form the cornerstone of remission induction [1, 2]. However, this potent immunosuppression casts a long shadow, significantly heightening the risk of severe opportunistic infections.

Among these, cytomegalovirus (CMV) reactivation is a well-documented complication, typically manifesting as colitis, retinitis, or pneumonitis. In contrast, CMV meningoencephalitis remains a rare and frequently

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devastating neurological sequela. Its diagnosis poses a particular challenge, as its nonspecific symptoms—such as fever, altered mental status, and cerebrospinal fluid (CSF) pleocytosis can masquerade as other, more common conditions, including bacterial meningitis or even a flare of the primary vasculitis [3]. This diagnostic ambiguity is especially perilous in the context of GPA, where the underlying disease itself can cause central nervous system (CNS) pathology, creating a complex clinical puzzle [3].

We present a poignant case that encapsulates this very dilemma: a patient with GPA who developed a relentlessly progressive neurological decline. The initial clinical picture was confounded by a CSF profile highly suggestive of bacterial meningitis and a partial response to antibiotics, yet the ultimate culprit was ganciclovir-resistant CMV meningoencephalitis. This case serves as a powerful illustration of the critical need for persistent diagnostic reevaluation in immunosuppressed hosts and sheds light on the catastrophic potential of resistant viral infections in the era of advanced immunosuppressive therapies.

Case Presentation

Our patient was a 72-year-old woman diagnosed with Granulomatosis with Polyangiitis (GPA). The diagnosis was strongly supported by the 2022 American College of Rheumatology criteria, fulfilled by positive C-ANCA serology, bilateral mastoiditis, and sensorineural hearing loss [1]. Additionally, the patient presented with acute kidney injury (AKI), characterized by elevated serum creatinine and active urinary sediment with casts, which was highly suggestive of glomerulonephritis a key criterion for GPA. However, a renal biopsy could not be performed due to the patient's clinical status. Initial treatment consisted of oral prednisolone (50 mg daily) and a single dose of rituximab.

Shortly after the initiation of immunosuppressive therapy, the patient was admitted to the infectious disease service with left otalgia. A diagnosis of Aspergillus otitis was made, supported by pathological findings from an ear biopsy, which revealed "few septate fungal hyphae in a necroinflammatory background suggestive of fungal infection." She was successfully treated with intravenous, followed by oral, voriconazole and was discharged.

A subsequent MRI brain revealed several significant findings:

- An acute infarct in the left cerebellar hemisphere.
- Dural and tentorial enhancement adjacent to the left petrous bone, with a 6x12 mm extra-axial focus, suggestive of known dural involvement by GPA.
- Post-mastoidectomy changes on the left side.
- Abnormal signal and enhancement in the right vestibule, cochlea, and semicircular canals, indicative of labyrinthitis.
- Enhancement of the left geniculate ganglion.

Brain MRA was unremarkable, apart from tortuosity of the basilar and vertebral arteries. An EMG-NCV study revealed subacute to chronic bilateral axonal and demyelinating median and ulnar neuropathies, as well as right peroneal neuropathy (Figure 1).

Following discharge, the patient was readmitted with fever, delirium, and drowsiness. A lumbar puncture (LP) was performed, revealing CSF findings consistent with bacterial meningitis: 700 white blood cells (WBCs)/µL with 90% polymorphonuclear neutrophils (PMNs). However, all cultures (bacterial and fungal) and extensive PCR panels for bacterial, viral, and fungal pathogens including Aspergillus and CMV returned negative. Concurrently, petechial-purpuric lesions developed on her trunk and limbs (Figure 2).

A rheumatology consultation recommended a skin biopsy. The patient was treated with a two-week course of broad-spectrum antibiotics for presumed bacterial meningitis and was discharged.

Two days post-discharge, she was readmitted with weakness, lethargy, and fever. A repeat LP showed 250 WBCs/µL with 85% PMNs, again with negative cultures. Antibiotic therapy was extended for another two weeks (totaling four weeks) for a diagnosis of partially treated meningitis.

Upon completion and cessation of antibiotics, the patient again became febrile. A third lumbar puncture (LP) was performed, which showed 10 white blood cells (WBCs)/µL (90% polymorphonuclear neutrophils [PMNs]). Crucially, on this occasion, cerebrospinal fluid (CSF) PCR returned positive for cytomegalovirus (CMV), with a viral load of 1,300 copies/mL. Intravenous ganciclovir (300 mg twice daily) was initiated. Notably, the skin lesions showed some improvement after starting antiviral therapy. The results of the prior skin biopsy were reported as a "vasculopathic tissue reaction pattern with red blood cell extravasation, in favor of pigmented purpuric dermatoses (PPD)."

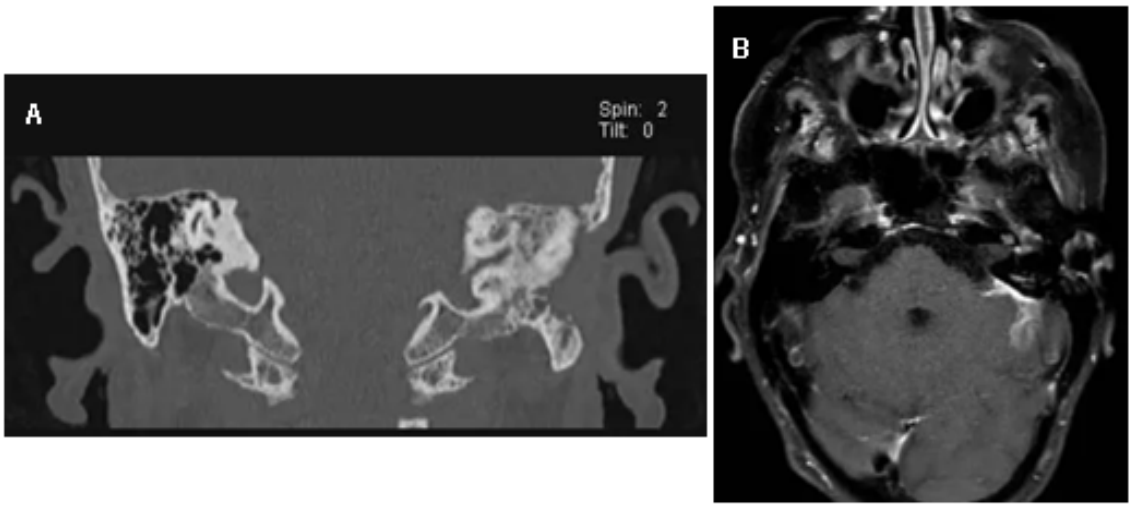

Fig. 1. A. post-surgical changes from a previous tympanomastoidectomy with ossiculoplasty. There was reduced aeration of the left mastoid air cells. The left mastoid cavity was noted to contain non-specific soft tissue opacification. **B.** Dural and tentorial enhancement adjacent to the left petrous bone, with a 6x12 mm extra-axial focus, suggestive of known dural involvement by GPA.

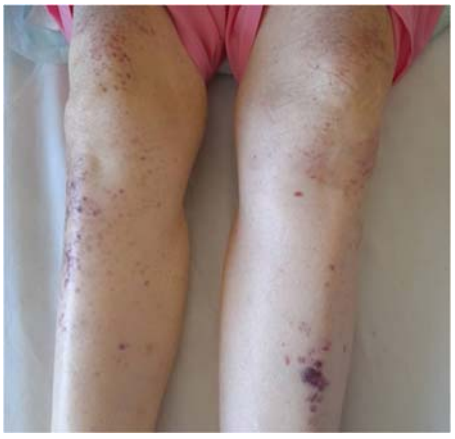

Fig. 2. petechial-purpuric lesions developed on her trunk and limbs. The results of the skin biopsy were reported as "vasculopathic tissue reaction pattern with red blood cell extravasation, in favor of pigmented purpuric dermatoses (PPD)."

Treatment with ganciclovir induced leukopenia, requiring administration of granulocyte colony-stimulating factor (G-CSF). After two weeks of ganciclovir therapy, a fourth LP was performed. It showed 10 WBCs/µL (90% PMNs) and, critically, a persistently positive CMV PCR with a viral load of 930 copies/mL, indicating refractory infection. A diagnosis of ganciclovir-resistant CMV meningoencephalitis was made. Intravenous ganciclovir was continued, and foscarnet was urgently requested and added to the regimen.

Given the persistent CMV infection despite antiviral therapy, profound immunosuppression was suspected. A serum immunoglobulin G (IgG) level was checked and revealed significant hypogammaglobulinemia (395 mg/dL; normal laboratory range for age: 600–1600 mg/dL). Consequently, intravenous immunoglobulin (IVIG) was administered at a dose of 0.4 g/kg for five days. A repeat test showed an increase in the IgG level to 619 mg/dL. Despite this immunomodulatory intervention, the patient's overall clinical condition failed to improve.

Ultimately, her clinical course deteriorated with the development of respiratory distress and a decreased level of consciousness. She was transferred to the intensive care unit (ICU) with a diagnosis of aspiration pneumonia. Despite intensive support, she developed hemodynamic instability and died three days later.

Discussion

This case presents a profoundly complex and tragic neurological evolution in a patient with GPA, underscoring the formidable diagnostic challenges at the intersection of active vasculitis, immunosuppressive therapy, and opportunistic

infections. The patient's course was marked by a sequential unfolding of neurological syndromes: from cranial neuritis and cerebellar cerebrovascular accident (CVA), potentially attributable to GPA, to invasive fungal otitis, and ultimately to fatal meningoencephalitis. The central diagnostic dilemma revolved around the recurrent meningitic picture, where initially convincing evidence for a bacterial process gradually gave way to the confirmed diagnosis of refractory CMV infection.

The initial cerebrospinal fluid (CSF) analysis, demonstrating neutrophilic pleocytosis (700 WBC/µL with 90% PMNs), is a classic presentation of acute bacterial meningitis. The observed transient clinical improvement following antibiotic therapy further supports the possibility of a concurrent bacterial infection. This creates a compelling argument for a dual pathology: an initial bacterial meningitis (possibly related to her otological disease or immunosuppressed state) that responded partially to antibiotics, followed by the unmasking or reactivation of latent CMV in the central nervous system (CNS) as the dominant pathogen later in the clinical course. Alternatively, the inflammatory milieu of a treated bacterial infection may have facilitated the reactivation of CMV [1]. This sequence of events highlights that improvement with antibiotics does not definitively exclude a concurrent or subsequent viral process in immunocompromised hosts.

The neurological manifestations in this patient were multifaceted and reflective of widespread involvement of the CNS. The MRI findings were critical in illustrating the extent of the disease [3]:

- Cerebellar Acute Infarct: Likely secondary to vasculitic involvement of the posterior circulation vessels, a known complication of GPA.

- Dural Enhancement and Labyrinthitis: These findings are highly characteristic of GPA itself, which is renowned for its otological and meningeal involvement.

- Geniculate Ganglion Enhancement: Suggesting involvement of the facial nerve (cranial nerve VII), again consistent with granulomatous inflammation from GPA.

This baseline vasculitic-related neurological damage likely created a state of compromised neural integrity, potentially facilitating the subsequent invasion and persistence of CMV within the CNS.

The confirmation of CMV via PCR in the third CSF sample marked a pivotal diagnostic turning point. The persistently positive PCR with a high viral load after two weeks of ganciclovir therapy is a hallmark of resistant infection. Ganciclovir resistance typically arises from mutations in the UL97 gene (phosphotransferase) and, less commonly, in the UL54 gene (DNA polymerase) [4]. In this setting, the addition of foscarnet—which directly inhibits viral DNA polymerase without requiring activation by the UL97 gene—is the standard of care for resistant cases [4]. The improvement of the patient's purpuric skin lesions upon initiation of ganciclovir is an intriguing observation, suggesting a possible CMV-driven vasculitic component. This adds another layer of complexity to the cutaneous manifestations, which could have been misinterpreted as solely due to GPA.

An additional critical layer of complexity in this case was the identification of significant hypogammaglobulinemia (IgG level: 395 mg/dL) during the course of the refractory CMV infection. Rituximab, a B-cell-depleting agent, is a well-established cause of secondary hypogammaglobulinemia, which can persist for months and significantly increase the risk of severe and recurrent infections [5]. The observed hypogammaglobulinemia likely created a permissive environment for the initial CMV reactivation and critically impaired the humoral immune response necessary for its control, contributing to treatment failure. The administration of IVIG was a rational attempt to reconstitute immune defense, as evidenced by the subsequent rise in IgG levels. However, this intervention was ultimately unsuccessful, underscoring the profound and potentially irreversible state of immunosuppression that can occur in such complex cases. This highlights the importance of monitoring immunoglobulin levels in patients receiving rituximab therapy, especially those presenting with severe or opportunistic infections [5].

This case forces a critical re-evaluation of diagnostic approaches in immunosuppressed patients with CNS symptoms. It underscores several key lessons:

1. The Masking Effect of Immunosuppression: Immunosuppression can blunt the typical immunological response to infections. A "partial response" to antimicrobial therapy should not instill false confidence but should instead prompt a search for additional or alternative pathogens.

2. Persistence is Paramount: In cases of recurrent

or deteriorating CNS inflammation, repeating CSF analysis with advanced microbiological techniques (including multiplex PCR panels and, if indicated, next-generation sequencing) is essential, as the yield of tests can evolve over time [6].

3. CMV as a Neurotropic Pathogen: CMV meningo-encephalitis should be elevated on the differential diagnosis in any severely immunocompromised patient presenting with subacute encephalopathy, delirium, and CSF pleocytosis, even if the initial pattern appears bacterial.

4. Therapeutic Vigilance: The development of antiviral resistance must be anticipated. Regular monitoring of CSF viral load is crucial to assess treatment efficacy, and a failure to decline should prompt an immediate switch to second-line therapy [4].

Conclusion

In conclusion, this case exemplifies a perfect neurological storm, where the lines between active vasculitis, bacterial infection, and opportunistic viral reactivation became profoundly blurred. The initial bacterial-mimicking CSF profile and partial response to antibiotics served as a dangerous distractor, delaying the ultimate diagnosis of lethal CMV meningoencephalitis. It powerfully illustrates that, in immunocompromised individuals, the CNS can become a battleground for multiple simultaneous pathological processes. Clinicians must maintain a high index of suspicion for unusual pathogens, practice diagnostic persistence through repeated investigations, and be prepared to escalate therapy aggressively for resistant organisms—even in the face of initial diagnostic ambiguity.

Ethical Considerations

Ethics approval and consent to participate

The authors declare no ethical conflicts. Written informed consent for publication of this case report and any accompanying images was obtained from the patient's legal guardian.

Consent for publication

Informed consent was obtained from the patient's legal guardian for the publication of identifying information in an online open-access format.

Availability of Data and Materials

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Conflict of Interests

The authors declare that they have no conflicts of interest related to this publication.

Author Contributions

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for the manuscript, take responsibility for the integrity of the work as a whole, and gave final approval to the version to be published.

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