EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2021.21093

Case-based Review

Granulomatosis with polyangiitis: The trigger cannot be long hidden

Shameek Gayen[1], Diana Zhang[1], Eliza Sternlicht[1], Daniel Bulanowski[1], Maher Tabba[2,3]

Abstract

Granulomatosis with polyangiitis, or GPA, is a form of vasculitis that affects multiple organs especially the respiratory tract and the kidneys. The diagnosis is suspected with the clinical presentation and elevated serum titer of antineutrophil cytoplasmic antibodies and confirmed with the biopsy of the affected organ. Viral infection has been described as one of the triggers of the immune system in developing GPA. In this report, we describe a rare case of GPA that developed following cytomegalovirus infection in a patient with unknown immunocompromised medical condition.

Keywords: Granulomatosis polyangiitis, Wegener's disease, cytomegalovirus, pneumonia

ORCID iDs of the authors:
S.G. 0000-0002-5076-8419;
D.Z. 0000-0001-7411-0091;
E.S. 0000-0001-6108-9748;
D.B. 0000-0002-8084-7767;
M.T. 0000-0001-6058-7948.

Cite this article as: Gayen S, Zhang D, Sternlicht E, Bulanowski D, Tabba M. Granulomatosis with polyangiitis: the trigger cannot be long hidden. *Eur J Rheumatol.* 2021;9(1):54-57.

[1]Department of Medicine, Tufts Medical Center, Tufts University School of Medicine, Boston, Massachusetts, USA

[2]Department of Medicine and Surgery, Tufts University School of Medicine, Boston, Massachusetts, USA

[3]Division of Pulmonary & Critical Care and Sleep Medicine, Tufts Medical Center, Boston, Massachusetts, USA

Address for Correspondence:
Maher Tabba, Medicine and Surgery, Interventional Pulmonology, Critical Care Medicine-Melrose Wakefield Health System, Division of Pulmonary & Critical Care and Sleep Medicine, Tufts Medical Center, Tufts University School of Medicine, Boston, Massachusetts, USA

E-mail: mtabba@tuftsmedicalcenter.org

Submitted: July 12, 2020
Accepted: : January 19, 2021
Available Online Date: December 27, 2021

Introduction

The 2012 Chapel Hill Consensus Conference defines granulomatosis with polyangiitis (GPA), formally called Wegener's disease, as a systemic, necrotizing vasculitis affecting predominantly small to medium vessels. Necrotizing granulomatous inflammation commonly involves the upper and lower respiratory tract and kidneys.[1] A wide variety of clinical presentations and potential organ involvement often confounds diagnosis. GPA shares several clinical manifestations and laboratory abnormalities with microscopic polyangiitis (MPA), another systemic vasculitis with multiorgan involvement.

GPA commonly has upper and lower airway, renal, and cutaneous involvement and affects a wide age distribution without gender preference.[2] It is more common in Caucasians, particularly the Northern European population, rather than Asian and African populations. The yearly incidence of the disease in Europe is 2.1-14.4 cases/million.[3]

The pathophysiologic origin of the autoimmune disease in general has been linked to multiple factors including immune system disturbance, genetic susceptibility, hormonal effect, infectious trigger, and environmental exposure.[4]

The ensuing case involves a patient who failed standard empyema treatment with appropriate intravenous antibiotic therapy and chest tube drainage. The concomitant diagnosis of GPA was made after linking the biopsies obtained from nasal and endobronchial lesions with serology results.

Case Presentation

A 63-year-old Cambodian male with no known history of an autoimmune disorder presented initially with a productive cough and fever. Notable physical findings were a lifelong "saddle nose" deformity without history of trauma and decreased breathing sounds on auscultation and dullness on percussion at the right lower lung. A chest X-ray showed right lower lobe pneumonia and parapneumonic pleural effusion (Figure 1). The patient was initially treated with broad-spectrum intravenous antibiotics, followed by ultrasound-guided chest tube placement (Figure 2) with intrapleural instillation of tissue plasminogen activator and DNase therapy. The chest tube initially drained pus (>400 K cells/µL, 97% PMNs, LDH >29 K, protein 5.7, pH 6.91) consistent with empyema. No organism was isolated on a routine microbiological culture of the pleural fluid, and both tuberculosis and fungal stains and cultures were negative. The cytology was also negative for malignancy. CT scan of the chest was performed and showed significant improvement in right pleural effusion. The chest tube was removed, and the patient was discharged on amoxicillin/clavulanic acid combination oral therapy to complete 3-4 weeks treatment for empyema.

The patient returned one week later, complaining of increasingly difficult breathing through his nose. On ENT examination, a large midline nasal mass extending through the septum into the right and left nasal

cavities was found. Head CT of the nasal sinuses with contrast revealed a poorly delineated, mildly expansile mass. The mass was centered along the anterior aspect of the left nasal cavity extending into the nares, and it also extended posteriorly into the left nasal cavity and laterally toward the left maxillary sinus. There was severe mucosal disease of the left maxillary sinus, left frontal sinus, and left mucosal air cells, with hyperostosis of the left maxilla and appearance of bony erosion of the lateral wall of the left maxillary sinus. No evidence of orbital involvement was seen. There was left frontal ethmoidal recess narrowing/obstruction due to mucosal thickening (Figure 3). Chest X-ray showed the persistence of his earlier pleural effusion. Repeated CT chest scans showed obstruction of the right inferior bronchus and resulting postobstructive collapse of the right lower lobe with findings suspicious for superimposed infection or necrosis (Figure 4).

Nasal endoscopy showed a midline nasal mass extending through the septum into the right and left nares. The patient underwent intranasal excision of bilateral nasal masses, left endoscopic total ethmoidectomy, left endoscopic maxillary antrostomies, and left endoscopic frontal sinusotomy. A diagnostic bronchoscopy revealed multiple small, abnormal lesions arising from the mucosa and an area of irregular surface morphology located in the lower part of the trachea just above the carina, at the take-off of the right main stem bronchus and the orifice of the posterior segment of the right lower lobe with complete obstruction of the distal segment.

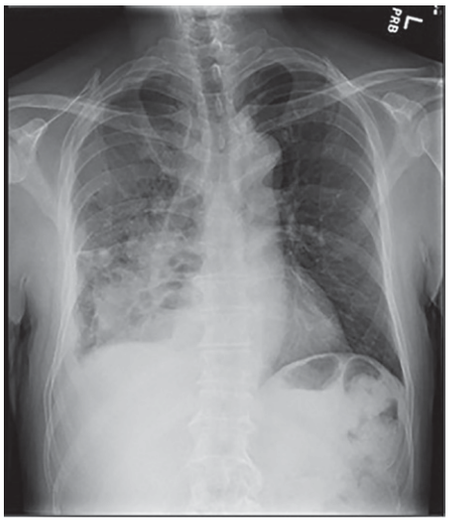

Figure 1. CXR at the time of initial presentation.

Main Points

- CMV viral infection may be the cause of granulomatosis with polyangiitis disease.
- The manifestations of the disease could be masked y other conditions.
- Diagnoses and correlations between infection and disease can be challenging and require extensive investigation.
- Immunocompetent patients remain vulnerable.

The pathological specimens from the nasal, endotracheal, and endobronchial biopsies demonstrated mucosa with marked acute and chronic inflammation with foci of microabscess formation. No well-formed granulomas were observed. Blood vessels contained both neutrophils and lymphocytes within their walls; some vessels showed fibrinoid necrosis. The overall features of the blood vessels were consistent with a vasculitis process (Figure 5). Immunohistochemical stains for cytomegalovirus (CMV) were positive for intranuclear and cytoplasmic viral inclusions in all biopsies. Serum CMV viral load by polymerase chain reaction (PCR) assay was positive at 2.89 log copies/mL, and his serum QuantiFERON and HIV were negative (Figure 6).

Other laboratory findings were notable for mild leukocytosis, elevated C-reactive protein (CRP) and serine protease, nonreactive VDRL, and positive c-ANCA (1:20) and PR3-ANCA suggesting a diagnosis of GPA with respiratory and nasal involvement. The patient notably did not have any evidence of renal, skin, or joint involvement. Furthermore, cultures from left septal mass biopsies grew methicillin-sensitive *Staphylococcus aureus* (MSSA).

The patient was started on oral corticosteroid prednisone 60 mg daily with slow tapering. He also later started corticosteroid-sparing agent methotrexate in addition to folic acid. Pneumocystis carinii pneumonia prophylaxis with trimethoprim/sulfamethoxazole was provided to the patient accompanied by close blood count monitoring. After completing the two month course of valganicyclovir, led by the improvement in the CMV viral load to undetectable, the patient was treated with intravenous Rituximab infusion.

Follow-up chest X-rays showed improvement in the right lower lung density. Multiple radiographic studies including CT scans of the head and sinus, and an MRI of the brain, revealed stable postsurgical changes related to the recent sinus surgery, in addition to diffuse, enhancing

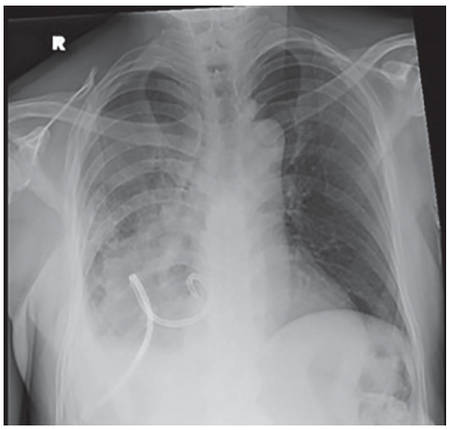

Figure 2. CXR after chest tube insertion and injecting tPA-DNase.

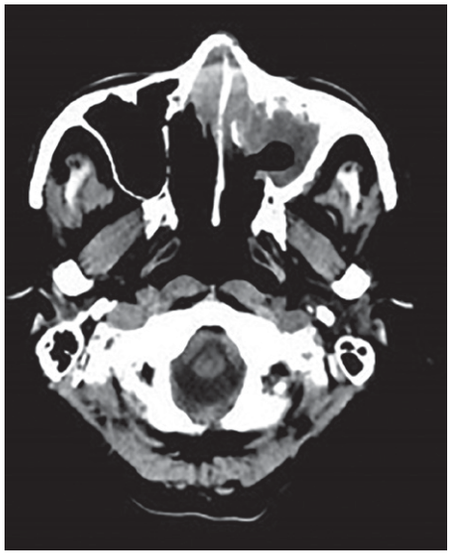

Figure 3. CT scan of the sinus showed a poorly delineated mildly expansile mass, the left nasal cavity and severe mucosal disease of the left maxillary sinus, left frontal sinus, and left mucosal air cells.

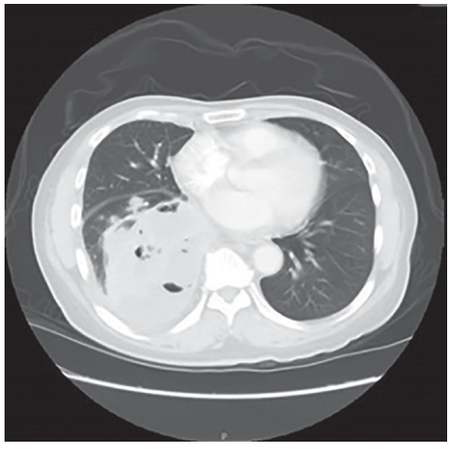

Figure 4. CT scan of the chest showing resolving right pleural effusion with R.L.L. infiltrate.

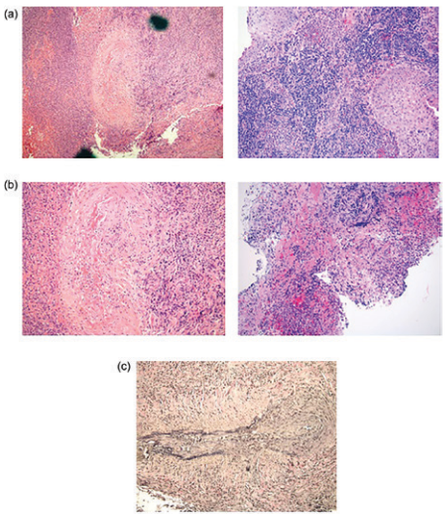

Figure 5 a-c. The pathologic characteristics of nasal biopsy (left) and the endobronchial lesion biopsy (right). (a) Low power showing disrupted architecture of large blood vessel with fibrinoid necrosis and adjacent fibrinopurulent exudate. There is no granuloma. (b) High power showing dark pink fibrin, damaged large vessel wall, and mixed inflammation in vessel wall. (c) Elastic stain shows disrupted elastic internal lamina, which proves blood vessel is injured, that these are not just transmigrating neutrophils in a sea of pus and granulation tissue.

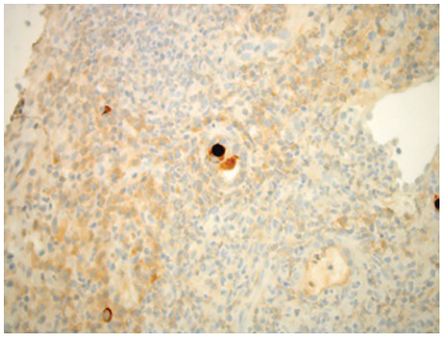

Figure 6. The immunohistochemical stains of the nasal biopsy for cytomegalovirus.

mucosal soft tissue within bilateral ethmoid air cells and nasal turbinates. This finding remains of concern for the possibility of new granuloma formation. There was mucosal thickening seen throughout the maxillary sinus. There was no evidence of an intracranial extension of the GPA and no acute intracranial abnormalities.

Discussion

GPA has a wide variety of clinical presentations, but patients typically present with prodromal symptoms like malaise, fever, weight loss, and other nonspecific symptoms like rhinosinusitis, cough, dyspnea, and urinary abnormalities. Notably, our patient presented with upper airway and pulmonary symptoms.

Diagnosis is usually confirmed with biopsy of the suspected site of active disease. A finding of granulomatous inflammatory changes is diagnostic for GPA. Our patient's nasal and lung biopsies did not demonstrate granulomas, which is the defining difference between MPA and GPA. However, both nasal and transbronchial lung biopsy are limited by high rates of false negative results and nonspecific features given the difficulty in obtaining sufficient tissue samples from these tissue samples. The absence of granulomas on transbronchial specimens is not a sufficient reason to rule out GPA as a possible diagnosis. Given our patient's clinical findings, including the nasal involvement, which is more common in GPA than MPA, and the positive serum c-ANCA, we were confident in finalizing our diagnosis as GPA involving the upper and lower airways.

Pulmonary vasculitis is most frequently seen in small-vessel, namely the ANCA-associated vasculitis: GPA and MPA. Approximately 85% of GPA and MPA patients have pulmonary involvement.[4]

The majority of patients with GPA have upper airway and pulmonary involvement, and 90% of them have nasal, sinus, or ear involvement.[5] Pulmonary involvement in GPA has a broad spectrum of presentation, ranging from asymptomatic to fulminant alveolar hemorrhage with respiratory failure. Typically, the clinical manifestations depend on whether the patient has tracheobronchial disease, lung parenchymal nodules, interstitial lung disease, or alveolar hemorrhage. The most common manifestation of tracheobronchial GPA is subglottic stenosis, but tracheal or bronchial stenosis, tracheobronchomalacia, tracheoesophageal fistulas, ulcerating tracheobronchitis, inflammatory pseudotumor, pulmonary infiltrate, lung nodules or masses, cavitary lesions, pleuritis, and pleural effusion have also been described.[6,7] Associated symptoms of tracheobronchial disease include dyspnea, cough, stridor, and hemoptysis.

Notably, *Staphylococcus aureus* was present in the microbiology culture grown from our patient's left septal mass biopsies. *S. aureus* infection has been implicated in GPA pathogenesis.[8,9] GPA patients are more likely to be chronic carriers of *S. aureus*, and these carriers have a higher relapse rate.[8]

The pathophysiology is still debatable, but it is not primarily attributable to the presence of *S. aureus* but rather to genetically determined factors related to the phenotype of the disease.

Our patient was also positive immunohistochemical stains for CMV in both nasal and lung biopsies. Many viruses have been linked to various rheumatologic conditions. For example, Epstein-Barr virus (EBV) has been linked to numerous autoimmune diseases including GPA, and CMV has been linked to SLE.[9,10] A strong association has been suggested between GPA (formerly known as Wegener's disease) and CMV IgG antibodies.[11]

CMV infection provokes intravascular T cell immune response, which may contribute toward the development of vascular disease. Recent evidence explains this mechanism. The intravascular T cell immune response in CMV infection is mediated by the loss of CD28 expression on CD4+ T cells. The CD4+CD28- phenotype is almost unique to CMV-specific T cells.[12,13] This phenomenon is uncommon, and when it occurs, the CD4+CD28- cells in CMV-seropositive patients with GPA expand, increasing the risk of infection and mortality.[14] Other evidence suggests that the presence of CD4+CD28- cells have been associated with chronic viral infections and that they emerge after cessation of the viral load.[15] This suggests that the vascular effect of the CD4+CD28- T cells occur after the primary infection and in the chronic or latent state.

In general, CMV infection affects 75% of healthy individuals, and CMV pneumonitis typically results from reactivation of early infection in immunocompromised patients, especially after solid organ transplants.[16-18] CMV pneumonia was previously reported as a result of impaired humoral immunity or splenic dysfunction with the pathogens of community-acquired bacteria such as streptococcal pneumonia.[19] Generally, viral–bacterial co-infection results in a higher incidence of mortality and a more complicated clinical course.[20]

This case demonstrates the difficulty associated with making a diagnosis of GPA. Our patient's initial presentation was not particularly suggestive of GPA, as extra-pulmonary symptoms were not evident. He had no renal or cutaneous involvement, and pathology did not illustrate the classical features of granulomatous vasculitis. The association of CMV infection in the sinus and the endotracheal specimens in addition to elevated CMV viral load suggested the potential link between the infectious process and the development of the GPA in this patient and the virus may play a trigger for exacerbation of the underlying autoimmune disease. This case highlights the varied presentation of GPA and the importance of strong clinical suspicion required to establish the diagnosis in patients.

To our knowledge, this is the first case of GPA in a nonimmunocompromised patient with concomitant active CMV pneumonitis and viremia described in the literature. There are also two other important clinical observations that were noticed in our case. First, the potential CMV triggered GPA disease was limited to the lung despite the elevated systemic viral load. Second, the multiple central endobronchial lesions found on bronchoscopy inspection.

Practitioners should be mindful of the value of adequate clinical assessment and proper diagnostic work up of common medical condition which may lead to diagnosis of uncommon disease. A full evaluation is always necessary to establish an accurate diagnosis and provide the patient with appropriate therapy.

Informed Consent: No consent is required according to the insitutional IRB regulations.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - D.B.; Design - S.G.; Supervision - E.S.; Data Collection and/or Processing - D.Z.; Writing Manuscript - M.T.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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