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Wegener's Granulomatosis Presenting with Spontaneous Intestinal Perforation: A Diagnostic Dilemma During the COVID-19 Pandemic

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Abstract: ***A 25-year-old woman presented with acute abdominal pain, preceded by fever and polyarthralgia. Emergency laparotomy revealed ileal perforation, necessitating small bowel resection. Postoperatively, persistent respiratory symptoms and prior constitutional complaints led to reevaluation, revealing vasculitis, likely granulomatosis with polyangiitis (Wegener's granulomatosis). Pulse steroid therapy resulted in significant improvement, with a kidney biopsy and rituximab therapy planned. This case highlights the diagnostic challenges during the COVID-19 pandemic, where gastrointestinal symptoms and high false-negative RT-PCR results contributed to delayed diagnosis. [1] It underscores the importance of maintaining a broad differential diagnosis to avoid critical delays in managing non-COVID-related diseases.***

Keywords: Wegener's granulomatosis, granulomatosis with polyangiitis, intestinal perforation, vasculitis, COVID-19

1. Introduction

Granulomatosis with polyangiitis (GPA), previously known as Wegener's granulomatosis, is a systemic autoimmune vasculitis predominantly affecting small to medium-sized blood vessels. It is characterized by necrotizing granulomatous inflammation, with a predilection for the respiratory tract and kidneys. While pulmonary and renal involvement are hallmarks of the disease, extrapulmonary manifestations such as gastrointestinal (GI) involvement are relatively rare but potentially life-threatening. Gastrointestinal complications, when present, may include ischemia, necrosis, or perforation due to mesenteric vasculitis.

The diagnosis and management of GPA are particularly challenging in the context of the COVID-19 pandemic. The clinical overlap between COVID-19 and autoimmune disorders, including symptoms such as fever, joint pains, fatigue, and respiratory complaints, often results in diagnostic delays. Furthermore, false-negative results of reverse transcription-polymerase chain reaction (RT-PCR) tests for COVID-19, coupled with high seroprevalence of SARS-CoV-2 antibodies, complicate the exclusion of COVID-19 as an underlying etiology in patients presenting with multisystem involvement. This case report describes a young woman who presented with acute abdominal pain and intestinal perforation, initially attributed to a gastrointestinal complication of COVID-19. Further investigations revealed the underlying cause to be GPA, highlighting a diagnostic dilemma exacerbated by the pandemic. The case emphasizes the importance of a high index of suspicion for autoimmune vasculitis in patients with multisystemic complaints, even in the backdrop of the COVID-19 pandemic, and underscores the role of timely diagnostic workup and interdisciplinary management in achieving favourable outcomes. This report aims to add to the limited literature on gastrointestinal involvement in GPA, its complex presentation, and the diagnostic challenges posed during the pandemic. It also discusses the significance of c-ANCA testing and histopathological evaluation in confirming the diagnosis, as well as the critical role of immunosuppressive therapy in mitigating disease progression and complications.

2. Literature Survey

Granulomatosis with polyangiitis (GPA) is a rare systemic vasculitis primarily affecting respiratory and renal systems, with occasional gastrointestinal involvement causing ischemia or perforation. The COVID-19 pandemic complicates diagnosis due to overlapping symptoms. Doctors should consider emergent surgical consultation for severe COVID cases with GI manifestations, and empirical vasculitis treatment if tissue diagnosis is delayed.

3. Case Presentation

A 25 year old woman, presented with acute abdominal pain which was diffuse in nature, non radiating, with no relation to meal intake and associated with abdominal distension. She had been obstipated for 3 days, followed by 3-4 episodes of loose motions for 2 days with a slight relief in her abdominal pain. At presentation she was haemodynamically stable with mild tachycardia of 110 beats per minute. General physical examination was non-contributory and there was no joint tenderness or effusion. Abdominal examination revealed a markedly distended abdomen with guarding and tenderness in the lower portion. She also had a sudden skin rash after admission after the test dose of cephalosporins, which was attributed to a drug reaction and subsided with an antihistaminic agent and steroid injection. Contrast CT of her whole abdomen with angiography showed segmental proximal ileal pneumatosis intestinalis with interloop free fluid and mesenteric stranding with a pocket of free air within the fluid collection which was indicative of bowel gangrene with suspected perforation.

Investigation and Treatment:
Laboratory workup revealed a haemoglobin level of 8.9mg/dl and a white cell count of 14430/cumm. The anemia profile was suggestive of iron deficiency. Her serum C reactive protein (80, normal< 6 mg/l) and D-dimer (4.89, normal<0.5mcg/l) were elevated. The serum Procalcitonin was also elevated (9.83; normal <0.5ng/mL). Urine microscopic examination showed numerous RBCs and granular casts. Her urine and blood cultures were sterile. The serum covid antibody titre in the hospital was positive (Total-1790.00 and IgG-5.70). On discussing the CT scan with the radiologist, it revealed localized ischaemic changes in the mid ileal segment with impending perforation and a localized collection. Based on the clinical and radiological findings, a decision was made to take her up for emergency laparotomy.

Our differential diagnoses were
1) COVID-19 related intestinal gangrene
2) Vasculitis with intestinal gangrene
3) CMV enteritis

Exploratory laparotomy was performed under general anaesthesia. Intra operatively, around 500ml of seropurulent fluid with flakes of pus was found in the peritoneal cavity. The distal ileal segment, one foot from the ileocaecal junction had multiple confluent patchy perforations with a localised biliopurulent collection in the pelvis. No changes of gangrene were observed. The mesentery was healthy with normal pulsations in the vessels. We resected the perforated bowel segment (figure1) and brought out a double barrel ileostomy

Outcome and Follow up:
Biopsy of the resected specimen revealed scattered foreign body giant cells with acute serositis (figure-2) with occasional transmural involvement and no evidence of microthrombi in the vessels and no evidence of vasculitis or granulomas. Immunohistochemistry stains were negative for Cytomegalovirus. The immediate post-operative period was uneventful. She subsequently developed continuous, low grade fever, not associated with chills or rigors which was relieved with antipyretic medication. The fever was associated with joint pains and body aches. Computed tomography of her chest was suggestive of viral pneumonitis with a CT severity score of 11/15. She was managed with supportive treatment in the form of oxygen inhalation, intravenous culture specific antibiotics and nebulization. Questioning her further revealed that she had been having fever and joint pains before this episode. Because of the ongoing pandemic, she had herself tested for COVID-19 and stayed at home and had taken symptomatic treatment prescribed by a local physician. Her realtime-PCR (genXpert) however was negative for COVID 19. Physician consultation was taken in view of her long pre-operative history of multiple systemic complaints. The coagulation profile included estimation of Protein C and S, Antithrombin III and homocysteine and anticardiolipin antibody levels which were within normal limits. Based on the long duration of her complaints and associated haemoptysis and haematuria, an autoimmune vasculitis was suspected, and the relevant workup initiated. This revealed a positive c-ANCA (980AU/mL) with a negative p-ANCA, low C3 (619AU/mL) with a normal C4, negative IgM and IgG for beta2 glycoprotein and anti-cardiolipin antibodies, negative anti-ds DNA, negative ANA and weakly positive anti-nucleosome antibody. Based on the above findings, a provisional diagnosis of granulomatosis with polyangitis (Wegener's granulomatosis) was made. Pulse methylprednisolone (methylprednisolone 125mg IV x 3 days) therapy was initiated. High resolution CT of the chest was done which revealed a diffuse ground-glass opacity with nodular infiltrates and peribronchial consolidation in the both lungs (Figure 5) with differential diagnosis being alveolar haemorrhage, fluid overload, an infective aetiology or vasculitis. CMV RT PCR was sent which revealed CMV below the detection range. Patient's repeat investigations revealed a declining trend of serum procalcitonin and other inflammatory markers. Based on the history, laboratory evaluation and interdisciplinary discussion, the working differentials of COVID 19 sequelae or Autoimmune vasculitis (Granulomatosis with Polyangitis, GPA) were made and kidney biopsy planned. Kidney biopsy was deferred as the patient was unwilling to undergo any further procedures at the current time. She improved symptomatically with above line of management and was stable, accepting oral diet with a functional stoma and was discharged on postoperative day 16 on oral corticosteroids. Patient would require re-admission after 1 week for stitch removal, kidney biopsy and possibly initiation of immuno-suppressant (Rituximab) therapy.

4. Discussion

Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis, is a systemic autoimmune disorder characterized by necrotizing granulomatous inflammation and small-to medium-sized vessel vasculitis. It predominantly affects the upper respiratory tract, lungs, and kidneys, but can also involve other organs, including the gastrointestinal (GI) system. The diagnosis is confirmed through the presence of c-ANCA (cytoplasmic anti-neutrophil cytoplasmic antibodies), which are typically elevated in most cases of GPA. In this case, a 25-year-old woman presented with acute, severe abdominal pain, which was associated with a history of fever and polyarthralgia. Initially, the clinical presentation suggested a possible

gastrointestinal (GI) infection, as the patient had abdominal distension and was experiencing obstipation followed by diarrhea. However, the abdominal CT scan revealed segmental ileal pneumatosis intestinalis, free intra-abdominal air, and signs of impending perforation—features indicative of bowel ischemia and gangrene. This complex presentation required urgent surgical intervention. At laparotomy, the diagnosis of multiple ileal perforations was confirmed, and the perforated bowel segment was resected. However, post-operatively, the patient developed respiratory symptoms and persistent systemic complaints, leading to further investigation into the underlying etiology. The presence of c-ANCA and a low C3 level, along with constitutional symptoms (fever, joint pain, hemoptysis), pointed toward a diagnosis of granulomatosis with polyangiitis (GPA), rather than an infectious etiology. This case highlights the diagnostic dilemma faced during the COVID-19 pandemic, where the patient's symptoms initially seemed to be indicative of a COVID-19 infection. The clinical overlap between COVID-19 and autoimmune diseases, such as GPA, complicated the diagnosis and led to a delay in appropriate treatment. The pathophysiology of GPA is driven by autoantibodies against proteinase 3 (PR3), which is a major component of neutrophils. These antibodies activate neutrophils, causing endothelial damage, inflammation, and necrosis of small and medium-sized blood vessels. The gastrointestinal (GI) tract involvement in GPA occurs due to mesenteric vasculitis, which can cause ischemia and necrosis of the affected bowel segment, leading to perforation, as seen in this case. Gastrointestinal perforation in GPA is uncommon but has been reported in a few case series. Yokoyama et al. (2006) and Saad et al. (2014) describe similar cases where vasculitis led to intestinal ischemia, resulting in perforation [5, 6]. In our patient, the perforation occurred in the distal ileum, which was characterized by multiple confluent perforations rather than a single site, suggesting an extensive vasculitic process. During the COVID-19 pandemic, the overlap between symptoms of viral infections (such as fever, fatigue, and joint pain) and those of autoimmune conditions such as GPA became a significant diagnostic challenge. Initially, our patient was suspected to have a COVID-19-related gastrointestinal involvement because of her fever and abdominal symptoms, as COVID-19 has been associated with gastrointestinal manifestations such as diarrhea and abdominal pain. Furthermore, her COVID-19 RT-PCR was negative, but her serum COVID antibody was positive, which suggested prior exposure to SARS-CoV-2. The delay in diagnosis was compounded by the high false-negative rate of RT-PCR testing for COVID-19, especially in the early stages of infection. In a study by Hernández-Rodríguez et al. (2021), it was noted that COVID-19 and autoimmune diseases often present with overlapping clinical features, leading to confusion in diagnosis [4]. For example, respiratory symptoms, fever, and joint pains are common in both COVID-19 and autoimmune conditions like GPA, and thus the clinical overlap can delay the recognition of diseases such as GPA. In our patient, the false-negative RT-PCR test for COVID-19 and the subsequent detection of c-ANCA and low C3 levels prompted a shift toward considering autoimmune vasculitis rather than COVID-19 infection. This is in line with findings from Sreih et al. (2011), who emphasized the importance of c-ANCA testing in patients with systemic inflammatory symptoms, as c-ANCA positivity is highly suggestive of GPA, especially when associated with constitutional symptoms and multisystem involvement [7]. The patient underwent an exploratory laparotomy, which revealed multiple perforations in the ileum, with a local biliopurulent collection in the pelvis but without signs of gangrene. This was consistent with the radiological findings of intestinal ischemia but lacked the widespread necrosis typically seen in more advanced mesenteric vasculitis. A biopsy of the resected bowel showed foreign body giant cells with acute serositis (figure-2) but no granulomas or microthrombi. These findings did not initially confirm vasculitis, and the absence of granulomas made infectious causes (like cytomegalovirus) less likely. The presence of foreign body giant cells was suggestive of a granulomatous process, which led to the further investigation for autoimmune vasculitis, as granulomatous inflammation is a hallmark of GPA. The patient's positive c-ANCA (980 AU/mL) and low C3 levels were key findings that pointed to GPA. The positive c-ANCA confirmed the diagnosis of granulomatosis with polyangiitis, and the negative ANA, anti-dsDNA, and negative cytomegalovirus PCR further excluded other potential causes of systemic inflammation. The treatment of granulomatosis with polyangiitis typically involves pulse corticosteroids and immunosuppressive therapy. In this case, the patient was started on pulse methylprednisolone therapy, which led to an improvement in her inflammatory markers and clinical symptoms. This approach is consistent with treatment protocols for GPA, as outlined in the European League Against Rheumatism (EULAR) guidelines. The patient also requires further kidney biopsy and possibly rituximab therapy, particularly if renal involvement is confirmed in future follow-up [9]. The patient's post-operative recovery was uneventful, though she did develop mild respiratory distress, which was consistent with viral pneumonitis. Given her prior symptoms of hemoptysis and respiratory involvement, high-resolution CT of the chest revealed ground-glass opacities, which are typical of GPA-related alveolar hemorrhage. These findings, along with the patient's ongoing symptoms, further confirmed the suspicion of GPA-related pulmonary involvement. Long-term follow-up will be necessary to monitor the patient's renal function, as glomerulonephritis is a common manifestation of GPA. Furthermore, careful management of her immunosuppressive therapy will be required to prevent relapse, a common issue in patients with GPA.

5. Conclusion

This case underscores the complexity of diagnosing granulomatosis with polyangiitis (GPA), especially in the context of the COVID-19 pandemic, where the overlap of symptoms between these two conditions can lead to diagnostic confusion and delays. Intestinal perforation as a manifestation of GPA is rare, but it should be considered in patients presenting with abdominal pain, systemic symptoms, and gastrointestinal distress. Early recognition and prompt treatment with immunosuppressive therapy, including corticosteroids and rituximab, are crucial for improving patient outcomes. The role of c-ANCA testing and immunohistochemistry in confirming the diagnosis of GPA remains critical in such challenging cases.

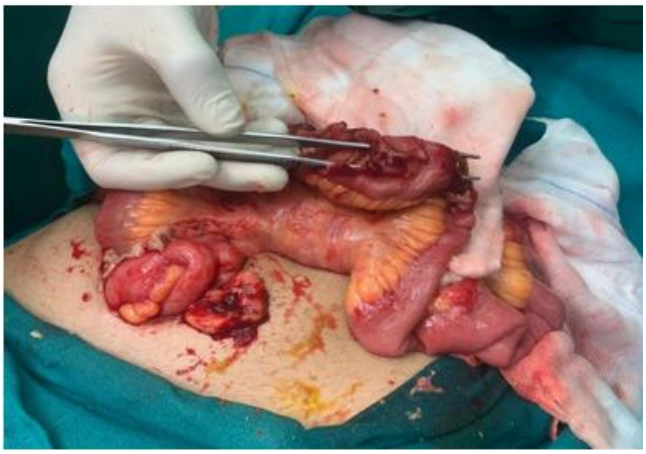

Figure 1: Perforated Bowel Segment

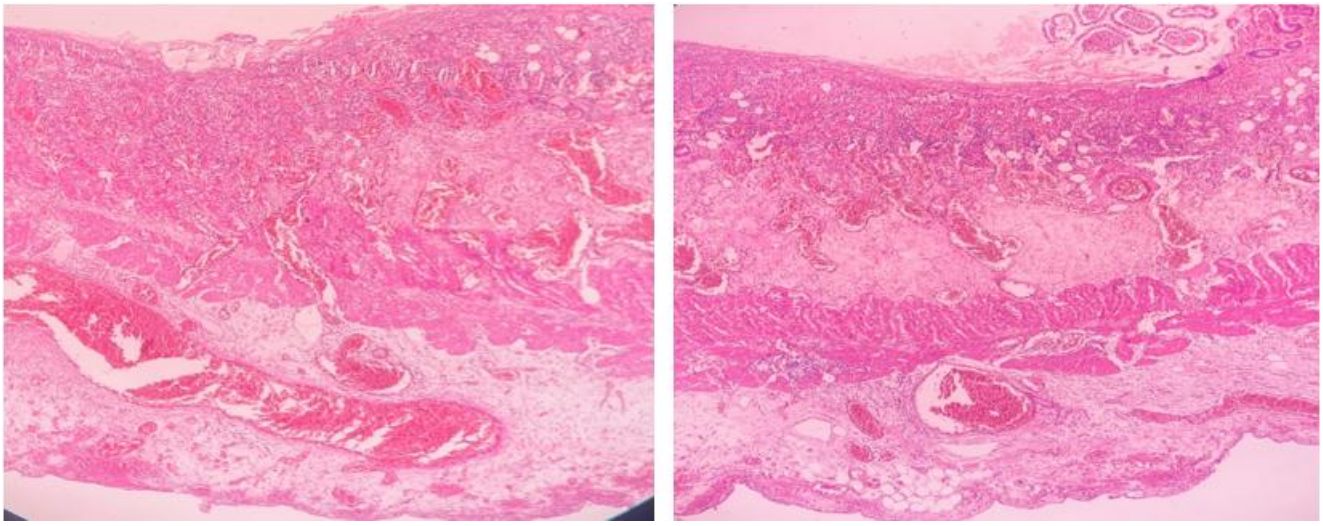

Figure 2, 3: Ulcer with transmural inflammation and serositis

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