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EXPLORING ANCA PATHOGENICITY IN ULCERATIVE COLITIS: A CASE REPORT HIGHLIGHTING THE RISK OF PROGRESSION TO ANCA-ASSOCIATED VASCULITIS

Abir Hamid, Frederic Vandergheynst, Maxime Ilzkovitz

Internal Medicine Department, Hôpital Erasme, Hôpital Universitaire de Bruxelles (HUB), Université Libre de Bruxelles (ULB), Brussels, Belgium

Corresponding author's e-mail: maxime.ilzkovitz@hubruxelles.be

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ABSTRACT

Background: The relationship between anti-neutrophil cytoplasmic antibodies (ANCA) and inflammatory bowel disease has attracted significant attention due to shared immunopathological mechanisms and clinical associations.
Case description: This case report describes a 20-year-old African woman with a history of ulcerative colitis who developed diffuse alveolar haemorrhage in the setting of elevated proteinase 3 (PR3)-ANCA. She was treated for ANCA-associated vasculitis with corticosteroids, plasma exchange, and rituximab, leading to a complete resolution.
Conclusion: The case highlights the association between ulcerative colitis and ANCA-associated vasculitis, particularly with PR3-ANCA, and the importance of recognizing this overlap. Although ANCA are frequently present in inflammatory bowel disease, especially ulcerative colitis, their pathogenic role remains unclear. The incidence of ANCA-associated vasculitis is higher in inflammatory bowel disease patients, with ulcerative colitis often preceding ANCA-associated vasculitis. Despite the common presence of ANCA in inflammatory bowel disease, not all patients progress to ANCA-associated vasculitis. This case underscores the need for careful monitoring in ulcerative colitis patients with elevated PR3-ANCA and the role of ANCA in guiding diagnosis and treatment.

KEYWORDS

Anti-PR3, ANCA, ANCA-associated vasculitis, ulcerative colitis, diffuse alveolar haemorrhage

LEARNING POINTS

- High proteinase 3 (PR3)-anti-neutrophil cytoplasmic antibodies (ANCA) titre impacts the severity and management of ulcerative colitis patients.
- ANCA-associated vasculitis is more frequent in ulcerative colitis patients and occurs several years after ANCA positivity.
- Close monitoring of ulcerative colitis patients with PR3-ANCA is essential for early detection of progression to ANCA-associated vasculitis.

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INTRODUCTION

The interplay between anti-neutrophil cytoplasmic antibodies (ANCA) and inflammatory bowel disease (IBD) has garnered increasing attention due to overlapping immunopathological mechanisms and clinical associations. The convergence of ANCA-associated vasculitis (AAV) and ulcerative colitis (UC) presents a compelling case for shared pathogenesis, diagnostic challenges, and therapeutic implications.

CASE DESCRIPTION

A 20-year-old African woman presented to the emergency department for thoracic pain in January 2022. She had a history of UC and two intrauterine foetal death. Her medication consisted of mesalazine 3 g/day. She denied alcohol or toxic abuse. UC was diagnosed in July 2020 following hospitalization for acute bloody diarrhoea without abdominal pain. Abdominal examination and auscultation were normal. Blood tests revealed cytocholestasis, no inflammatory syndrome, and polyclonal hypergammaglobulinemia at 26.2 g/l (8.0 to 13.5 g/l). Autoantibodies screening was positive for proteinase 3 (PR3)-ANCA at 864 (< 20 UI/ml). Stool cultures were negative for aerobic and anaerobic bacteria and parasites.

A colonoscopy revealed severe continuous colic inflammation from the anus to the caecum without any mention of bleeding, ulceration, or images indicative of vasculitis. Systematic biopsies of the colon revealed severe chronic colitis, the inflammation sparing the small intestine. Colonic mucosa revealed modified glandular architecture, abundant mono- and polynuclear leukocytes in the chorion, and basal plasma cells and lymphoid clusters. Mild focal cryptitis was present. No granulomas were observed in the examined sections. Magnetic resonance cholangiopancreatography showed a slight opening of the extrahepatic main bile duct with normal intrahepatic bile ducts. Finally, the patient was diagnosed with severe UC associated with primary sclerosing cholangitis. She was treated with methylprednisolone 8 mg/day and mesalazine 3 g/day, resulting in endoscopic remission.

In January 2022, the patient presented to the emergency department with a 5-day history of diffuse myalgia, asthenia, fever, nausea, vomiting, and right lateral-thoracic pain. She had an arterial pressure of 107/44 mmHg, a heart rate of 104 per minute, a temperature of 35.8°C, and an oxygen saturation of 100%. Physical examination revealed crackles at the base of the right lung. The rest of her examination was unremarkable. Blood tests revealed slight anaemia at 12 g/dl (12 to 16 g/dl), lymphopenia at 600/mm^3 (1200 to 3500 mm^3), and elevated inflammatory syndrome with C-reactive protein (CRP) at 370 mg/l (<5 mg/l). A chest X-ray showed right lower lobe infiltrates suggestive of infectious pneumonia *(Fig. 1A)*. Management was outpatient treatment with amoxicillin-clavulanate 1 g 3 times per day for 7 days.

The patient returned to the emergency department the following day for persistent vomiting, bloody diarrhoea, and odynophagia, preventing the oral administration of antibiotics. Physical examination revealed two ulcerated lingual lesions of 1 cm in diameter and several ulcerated lesions in the oral cavity. Pulmonary auscultation revealed hypoventilation at the base of the right lung. The rest of the physical examination was unremarkable. The chest X-ray revealed an increased right basal pulmonary condensation. The patient was admitted to the pneumology department.

A few hours after admission, the patient developed exertional dyspnoea and chest pain associated with haemoptysis. On admission, blood tests revealed non-haemolytic anaemia at 10.5 g/dl (12 to 16 g/dl), thrombocytopenia at 113,000/mm^3 (150 to 440,000/mm^3), elevated CRP at 410 mg/l (<5 mg/l), and cyto-cholestasis. PR3-ANCA were at 443 UI/ml (< 20 UI/ml). Renal function and urine sediment analysis were normal. Urine and sputum cultures were sterile. Contrast-enhanced chest computed tomography (CT) scan suggested alveolar haemorrhage *(Fig. 1B)*.

The bronchoscopy revealed the presence of abundant foamy blood in the entire tracheobronchial tree. The bronchoalveolar lavage did not reveal any infection. Biopsies of the ulcerated lingual lesions disclosed a herpetic infection without vasculitis. The patient was transferred to the intensive care unit due to hypoxemic respiratory failure. The patient presented a diffuse alveolar haemorrhage (DAH) in the setting of an anti-PR3 ANCA-associated UC. She was treated as if she had ANCA-associated vasculitis alveolar haemorrhage with pulse corticosteroid therapy (15 mg/kg/day for 3 days), plasma exchange (every other day for 5 days), and rituximab (37 5mg/m^2 once a week for 4 weeks). Rapid and complete resolution was observed, leading to patient discharge.

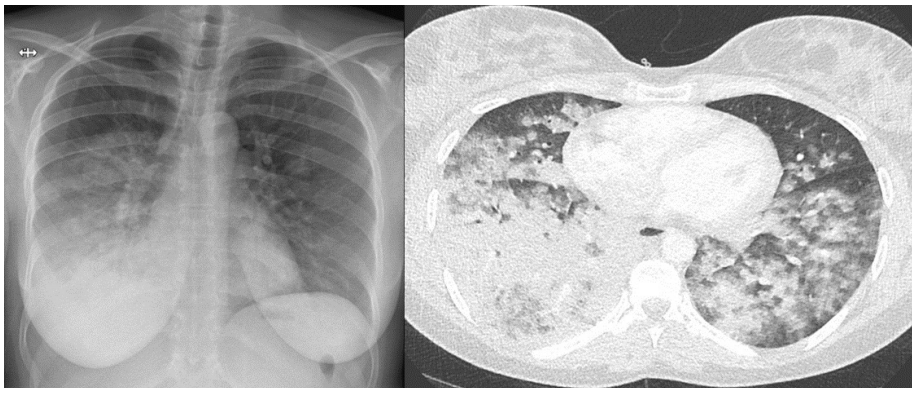


Figure 1. A) Chest X-ray: right lower lobar condensation suggestive of infectious pneumonia; B) Chest computed tomography scan: bilateral perihilar ground-glass opacities with condensations in the right lower lobe without any sign of pulmonary embolism.

DISCUSSION

We report a case of DAH associated with AAV in a patient known for UC associated with elevated PR3-ANCAs. The association between UC and AAV, raises the issue of anti-PR3-ANCA pathogenicity and the importance of having reliable ANCA-associated vasculitis biomarkers.

PR3 and myeloperoxidase (MPO) ANCA are hallmark markers for diagnosing AAV, particularly granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). These markers are incorporated into the American College of Rheumatology classification criteria for AAV[1]. Retrospective studies, such as those by Olson et al., have demonstrated that elevated anti-PR3 ANCAs can precede the diagnosis of GPA by up to 1.5 years in 63% of cases[2]. However, the predictive value of ANCA positivity is influenced by antibody titres, as Bornstein et al. noted that 60.1% of ANCA-positive individuals showed no vasculitis signs, underscoring the importance of quantitative thresholds[3].

ANCA are not specific to AAV and are found in several other conditions like connective tissue disorders, auto-immune liver diseases, cancers, endocarditis, drug exposures, and with IBD[4]. ANCA, predominantly atypical p-ANCAs, are frequently detected in IBD, with UC exhibiting higher prevalence rates (41-73%) compared to Crohn's disease (CD; 0-29%)[5]. PR3-ANCA have emerged as a potential biomarker to distinguish UC from Crohn's disease (CD), with elevated PR3 levels observed more commonly in UC than in CD (29.2% vs. 2.7%)[6]. Moreover, PR3 positivity correlates with more extensive UC, higher endoscopic Mayo scores, and treatment outcomes[7]. These findings suggest PR3's utility in diagnostic stratification, yet the pathogenic role of ANCA in IBD remains poorly understood.

The reported prevalence of AAV is significantly higher in the IBD population (0.71–0.78%) compared to the general population (<0.02%)[1,8]. Moreover, UC generally precedes the occurrence of AAV for several years in 69 to 100% of the cases[8-10].

Shared pathophysiological mechanisms between AAV and IBD might explain this overlap. On the one hand, CD and GPA both involve Th1 and Th17 inflammatory pathways, with similar lymphocytic infiltrate on histology. On the other hand, EGPA and UC share a Th2 profile with eosinophils-enriched infiltrates[8]. Another hypothesis relies on the pathogenic role of neutrophil extracellular traps (NETs), which have been implicated in both UC and AAV models[1,11]. By releasing their contents, NETs—enriched with PR3 and MPO can promote autoantigen exposure, loss of immune tolerance, and subsequent autoimmunity, thus providing a potential link between the pathogenesis of UC and AAV. Nevertheless, not all ANCA-positive IBD cases progress to AAV. According to Mumtaz et al., secondary evolution to AAV occurs in approximately 33.3% and 52.1% of UC and CD cases, respectively[9]. While the overlap between AAV and UC is well documented in the literature, the occurrence of DAH in the context of AAV and UC co-occurrence is rarely reported[12-15].

The aetiologies of DAH are diverse, including congestive heart failure, infections, cancers, barotrauma, clotting disorders, and immune-related or drug-induced causes[16]. Immune-related DAH accounts for 30–40% of cases and includes aetiologies such as connective tissue disorders, antiphospholipid syndrome, and small-vessel vasculitis, with AAV being the most prevalent vasculitis[17]. Epidemiological data from highlight the higher prevalence of pulmonary vasculitis in IBD populations compared to controls (0.08% vs. 0.05%; p=0.032), with UC showing greater association than CD (0.12% vs. 0.05%; p<0.001)[17].

Besides, PR3 positivity can also guide UC management decisions. Elevated PR3 levels are predictive of treatment outcomes UC, with a sensitivity of 75 and 64.7% and a specificity of 69 and 91% for primary failures of steroids and TNF inhibitors, respectively. Multivariate analysis indicates that PR3 positivity is associated with a fivefold increased risk of steroid primary failure and a nineteen-fold increased risk of TNF inhibitors primary failure[18-19].

Finally, one should consider that some cases of early AAV with isolated digestive tract involvement may be misdiagnosed as UC with PR3 positivity rather than AAV developing secondary to UC. Ongoing research is investigating the pathogenicity of ANCA, focusing on factors such as ANCA avidity, epitope specificity, isotypes, and subclasses, as well as Fab/Fc glycovariants. Additionally, new biomarkers are being explored to better address the unmet needs in this field[1,20].

CONCLUSION

The intersection of AAV and UC necessitates a multidisciplinary approach to diagnosis and management. The potential for ANCA positivity to forecast AAV development in IBD underscores the importance of vigilant monitoring, particularly in UC patients with PR3 autoantibody.

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