

Case report

Association of granulomatosis with polyangiitis and rheumatoid arthritis: A rare overlap syndrome

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Running title: Case of Granulomatosis with Polyangiitis and Rheumatoid Arthritis

Abstract

Background: Granulomatosis with polyangiitis (GPA) is a type of antineutrophilic cytoplasmic antibodies (ANCA) associated vasculitis that primarily involves upper respiratory tract, lungs and kidneys. It is a rare disease and its association with rheumatoid arthritis is even rarer. Early recognition of such overlaps enables more timely diagnosis and may have impact on disease outcome. **Case presentation:** Here we report a case of 29-year-old female, known case of rheumatoid arthritis (RA) since 2019, presented in February 2023 with complaint of fever and cough for 20 days. On evaluation, patient was having deranged renal function tests. Chest Xray revealed multiple thick wall cavities and nasal cavity examination showed thick crusting. Based on these findings GPA was suspected and antineutrophilic cytoplasmic antibodies directed against proteinase 3 (PR3 ANCA) levels and kidney biopsy was planned. PR3 ANCA levels were raised and kidney biopsy revealed pauci-immune glomerulonephritis. In view of RPGN rituximab therapy was started along with prednisolone. **Conclusion:** ANCA associated vasculitis (AAV) associated with RA may be a rare form of an AAV autoimmune overlap. Its recognition can lead to timely antibody screening of patients with the relevant clinical scenario and a more rapid initiation of appropriate management.

Received: Jun 16th 2025

Accepted: Jan 28th 2026

Published: Jun 30th 2026

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Keywords: granulomatosis with polyangiitis, rheumatoid arthritis, overlap syndrome

1. Introduction

The coexistence of Rheumatoid arthritis (RA) and Granulomatosis with polyangiitis (GPA) represents an exceptionally rare overlap syndrome [1]. While RA is a chronic systemic autoimmune disease primarily characterized by symmetric inflammatory polyarthritis with possible extra-articular involvement, GPA is a necrotizing small- to medium-vessel vasculitis associated with anti-neutrophil cytoplasmic antibodies (ANCA) and characterized by granulomatous inflammation of the respiratory tract and rapidly progressive glomerulonephritis [2]. Although both disorders may share systemic features such as constitutional symptoms, pulmonary manifestations, and elevated inflammatory markers, their underlying pathophysiology and prognostic implications differ substantially [3].

Compared to better-recognized overlap entities such as the RA-GPA association is rarely reported in the literature. This rarity increases the risk of misattributing vasculitic manifestations to severe or extra-articular RA, potentially delaying appropriate evaluation for ANCA-associated vasculitis. Such delay can be catastrophic, as untreated GPA historically carries a mortality rate approaching 80% within the first year of diagnosis. Early differentiation is therefore not merely academic but critical for survival, given the need for prompt initiation of aggressive immunosuppressive therapy [3,4].

The aim of this case report is to improve diagnostic vigilance by highlighting this uncommon overlap, emphasizing the importance of maintaining a high index of suspicion for GPA in patients with established RA who develop atypical systemic or organ-specific features.

2. Case presentation

A 29-year-old married female, mother of two children, presented in February 2023 with chief complaints of fever and cough for the last twenty days, which began two weeks after her last normal vaginal delivery. The patient was diagnosed with RA four years ago when she developed pain and swelling in the metacarpophalangeal joints of both hands, along with high rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) titres. She had been receiving methotrexate and hydroxychloroquine for the treatment of RA and was in remission. However, she stopped treatment for the last year due to conception. For the last 20 days, she had been

experiencing a fever of 100-101 degrees Fahrenheit with an unproductive cough. There was no history of shortness of breath, joint pain or swelling, burning micturition, or foul-smelling vaginal discharge. A history of on-and-off paranasal pain and nasal discharge was present for the last six months. On examination, the patient was conscious and oriented to time, place, and person, with a blood pressure of 128/76 mmHg, a pulse rate of 110/min, and spO₂ of 96% on room air. There was no swelling, deformity, or tenderness appreciable at any joint. Bilateral nasal cavities showed mucopurulent discharge on the nasal floor along with crusting. Chest auscultation revealed coarse inspiratory crackles in the right infra-scapular area.

The patient had received multiple antibiotics from multiple private practitioners before presenting to us, but there was no relief in her symptoms. After admission, the patient's complete blood count revealed a haemoglobin of 7.7 g/dL, a total leukocyte count of 8000/mm³, and a platelet count of 2 lacs/mm³. Her blood sugar, liver function tests, and thyroid function tests were in the normal range. Workup for tropical febrile illness including peripheral blood film for malarial parasite, IgM typhidot, IgM anti-leptospira antibody, IgM anti-scrub typhus antibody, blood cultures, urine culture, and sputum examination were all negative. Markers of inflammation were raised with an erythrocyte sedimentation rate of 145 mm in the 1st hour and a C-reactive protein (CRP) of 14.92 mg/dL. Kidney function tests were deranged with a blood urea of 70 mg/dL and a serum creatinine of 3.6 mg/dL. Urine complete examination showed 2+ albuminuria with 25-30 RBCs per high-power field without any dysmorphic RBCs or casts. Chest X-ray and CT scan revealed multiple thin-walled cavities in bilateral lung field as shown in Figure 1.

The patient's serum creatinine level rose to 5.9mg/dl within two days of admission. Due to the rapidly progressing glomerulonephritis (RPGN), multiple cavitary lung lesions, and a chronic history of sinusitis, PR3 ANCA levels were sent and found to be highly elevated with a titre of 1:200. To confirm the diagnosis of GPA, a renal biopsy was performed, revealing necrosis of the capillary loop, extra capillary proliferation with crescent formation, and 30-40% interstitial fibrosis and tubular atrophy without any immune complex deposition on immunofluorescence (IF) microscopy, suggesting pauci-immune glomerulonephritis.

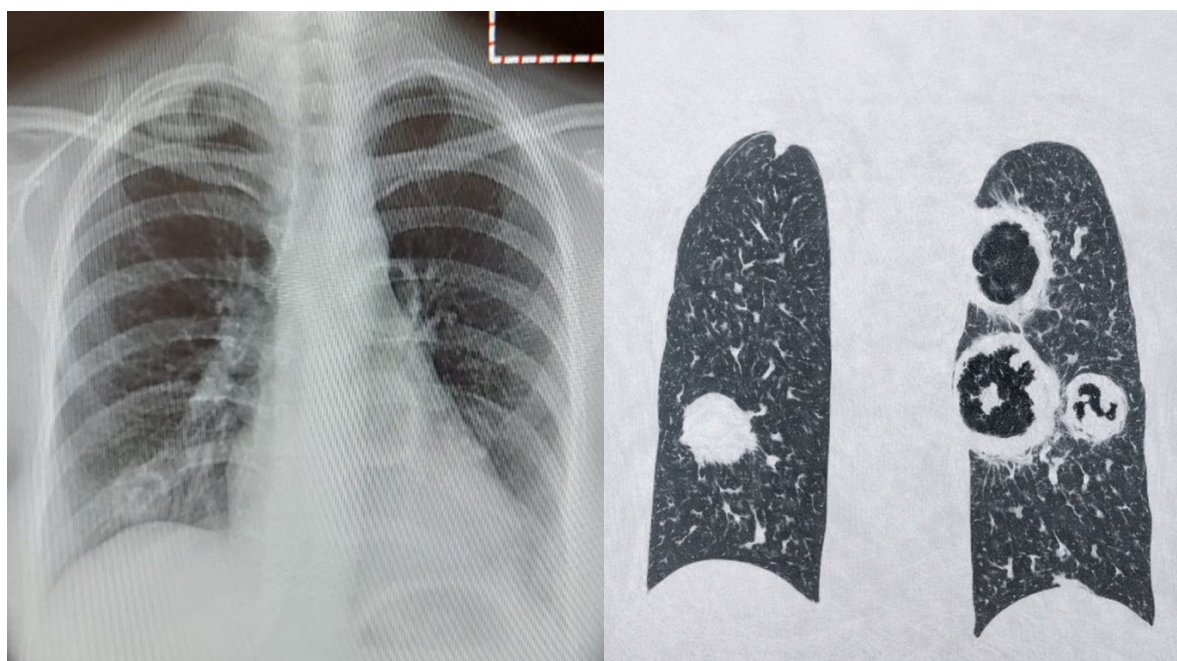


Figure 1. (A), (B) Multiple thin-walled lung cavities bilaterally.

After confirming the diagnosis of GPA and excluding other infections such as infective endocarditis through transthoracic echocardiography and blood cultures, and tuberculosis through bronchoalveolar lavage, the patient was started on rituximab induction therapy (375mg/m² per week for 4 weeks) along with prednisolone (1mg/kg) following European League Against Rheumatism (EULAR) guidelines. The patient also received 3 sessions of haemodialysis due to rapidly progressive renal failure. After 4 weeks of induction therapy with rituximab (500mg), patient renal functions recovered partially with S. creatinine value of 2.5mg/dl.

3. Discussion

The coexistence of RA and GPA may be conceptualized within the framework of a shared autoimmune “common soil.” Both conditions are characterized by loss of immune tolerance, autoreactive B- and T-cell activation, and pathogenic autoantibody production [5]. Genetic susceptibility plays a central role in this overlap. Variants within the HLA region - particularly class II alleles - are strongly associated with RA and have also been implicated in ANCA-associated vasculitis (AAV), influencing antigen presentation and autoreactive T-cell priming [6]. Beyond HLA, non-HLA susceptibility genes further support a convergent immunogenetic background. Polymorphisms in PTPN22, which modulates T-cell receptor signalling thresholds, have been linked to multiple autoimmune diseases including RA and AAV. Similarly, alterations in uteroglobin (SCGB1A1) - involved in anti-inflammatory and immunomodulatory pathways within

the respiratory epithelium - may contribute to susceptibility to pulmonary-predominant autoimmunity. Variants in NF- κ B2, a regulator of B-cell maturation and survival, may amplify aberrant humoral immune responses in both RA and vasculitis [7].

At the serological level, the coexistence of rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA) in RA raises intriguing mechanistic questions when PR3-ANCA-mediated pathways are superimposed, as seen in GPA. Chronic immune complex formation driven by RF and ACPA may enhance neutrophil priming and Fc receptor engagement, potentially lowering the threshold for ANCA-mediated neutrophil activation. PR3-ANCA binding to primed neutrophils induces respiratory burst, degranulation, and endothelial injury - processes that may be potentiated in a milieu already characterized by systemic inflammation and circulating immune complexes. This immunological interplay could theoretically intensify vascular injury or modify disease phenotype in overlap cases [8-10].

A major clinical challenge in RA-AAV overlap is the “masking” effect. Extra-articular RA can involve the lungs (interstitial lung disease, rheumatoid nodules, pleuritis) and kidneys (secondary amyloidosis, drug-induced nephrotoxicity), potentially delaying consideration of superimposed AAV when new pulmonary infiltrates or glomerulonephritis emerge. Constitutional symptoms and elevated inflammatory markers further compound diagnostic ambiguity. In such scenarios, the development of haematuria, rapidly rising creatinine, alveolar haemorrhage, or ENT involvement should prompt evaluation for ANCA-associated vasculitis rather than attribution solely to RA progression [11].

Currently, there are no validated clinical or serological criteria specifically defining RA-AAV overlap. Diagnosis relies on fulfilment of established criteria for each individual disease and careful clinicopathologic correlation, particularly renal biopsy demonstrating pauci-immune crescentic glomerulonephritis in the appropriate serological context.

Management is equally complex due to the absence of standardized guidelines for this overlap. Therapeutic decisions must address both the vasculitic process and the underlying RA while minimizing cumulative toxicity. B-cell depletion with rituximab represents a rational strategy in this setting. By targeting CD20-positive B cells, rituximab reduces PR3-ANCA production in GPA and suppresses autoantibody-mediated synovitis in RA. Its steroid-sparing potential and avoidance of cyclophosphamide-related gonadotoxicity are particularly relevant in patients of reproductive

age. Thus, rituximab offers a unified, mechanistically coherent approach for controlling both pauci-immune glomerulonephritis and systemic RA activity [8,12].

There is a pressing need for multicenter registries dedicated to autoimmune overlap syndromes, incorporating standardized phenotyping, genetic profiling, and longitudinal outcome tracking. Such collaborative efforts would clarify prognostic indicators, optimize immunosuppressive strategies, and determine whether tailored management algorithms are required for RA-AAV overlap as opposed to conventional treatment paradigms used for isolated ANCA-associated vasculitis.

4. Conclusions

In summary, RA-GPA overlap likely reflects converging genetic and immunologic pathways within a shared autoimmune substrate. Heightened clinical suspicion, early histopathologic confirmation, and strategically selected B-cell-targeted therapy are central to improving outcomes in this rare but high-risk entity.

Declarations

Author Contributions

Conceptualization: all authors; Methodology: all authors; Formal analysis: all authors; Investigation: all authors; Writing: original draft preparation: all authors; Writing: review and editing: all authors.

Funding

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/ have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Data Availability Statement

The data presented in this study are available on reasonable request from the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest.

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Асоциация между грануломатоза с полиангиит и ревматоиден артрит: рядък припокриващ синдром

Резюме

Въведение: Грануломатозата с полиангиит (ГПА) е вид васкулит, свързан с антинеутрофилни цитоплазмени антитела (ANCA), който засяга предимно горните дихателни пътища, белите дробове и бъбреците. Това е рядко заболяване, а съчетанието му с ревматоиден артрит (РА) се среща още по-рядко. Ранното разпознаване на подобни припокриващи се синдроми позволява по-навременна диагностика и може да окаже значително влияние върху изхода от заболяването. **Клиничен случай:** Тук докладваме за случай на 29-годишна жена с диагностициран ревматоиден артрит (РА) от 2019 г., постъпила през февруари 2023 г. с оплаквания от фебрилитет и кашлица с давност от 20 дни. При параклиничните изследвания бяха установени отклонения в показателите на бъбречната функция. Рентгенографията на гръдния кош разкри множество дебелостенни каверни (кухини), а при прегледа на носната кухина се установи наличие на плътни крусти. Въз основа на тези находки възникна съмнение за ГПА, поради което бяха планирани изследване на нивата на антинеутрофилни цитоплазмени антитела срещу протеиназа 3 (PR3 ANCA) и бъбречна биопсия. Нивата на PR3 ANCA бяха повишени, а бъбречната биопсия потвърди пауци-имунен гломерулонефрит. С оглед на клиничната картина на бързопрогресиращ гломерулонефрит (RPGN) бе започната терапия с ритуксимаб в комбинация с преднизолон. **Заключение:** ANCA-свързаният васкулит (AAV), асоцииран с РА, може да бъде рядка форма на автоимунен овърлап синдром. Неговото своевременно разпознаване е от ключово значение за инициране на антителен скрининг при пациенти със съответната клинична симптоматика и за по-бързото започване на адекватна терапия.

Ключови думи: грануломатоза с полиангиит, ревматоиден артрит, овърлап синдром