A Severe Case of ANCA-Associated Small Vessel Vasculitis

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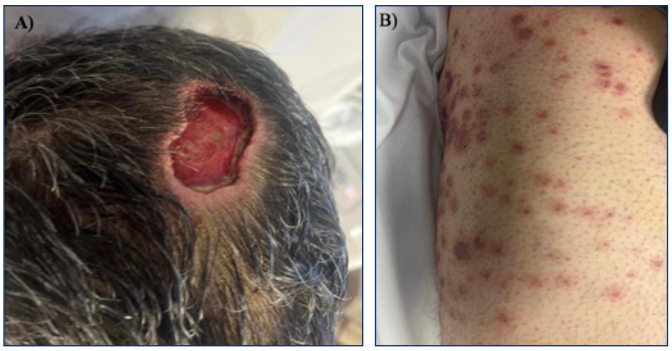
A 31-year-old male with a past medical history of asthma, a recent tooth abscess, and an enlarging scalp wound that grew MSSA and didn't improve with debridement or antibiotics presented with a two-week history of fevers, arthralgias, scant hemoptysis, abdominal pain and a new purpuric rash and associated fingertip discoloration.

Vital signs at triage were significant for a new oxygen requirement of 4 liters. Physical examination was notable for a deep ulcerated scalp lesion (**Figure 1a**), bilateral non-painful scleral injection, numerous small palpable purpuras on the lateral thighs (**Figure 1b**), and splinter hemorrhages of the fingernails.

Figure 1. Physical manifestations of ANCA-associated granulomatosis polyangiitis. [**A**] punched-out ulcer of the scalp [**B**] palpable purpura across the lateral region of the right thigh.



The initial laboratory workup is noted in **Table 1**. CT of the chest showed multiple bilateral pulmonary parenchymal nodules and worsening airspace opacities, some with central cavitation (**Figure 2**). Interferon-gamma release assay for tuberculosis was indeterminate; however, three sputum stains for acid-fast bacilli were negative, and blood cultures yielded no growth. A transthoracic echocardiogram revealed normal left ventricular function without evidence of valve disease or vegetation. The patient declined to have a transesophageal echocardiogram (TTE). His condition failed to improve despite empiric treatment with broad-spectrum antibiotics.

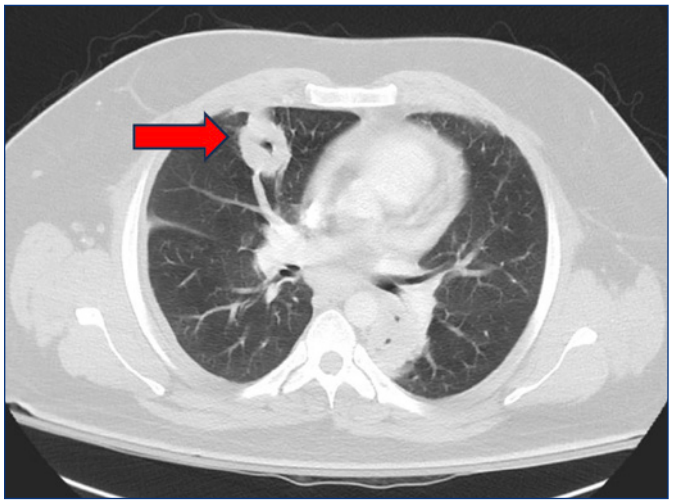
Additional laboratory workup revealed a positive anti-proteinase 3 (PR3) antibody index at 7.1 AI. Immunofluorescence testing for classic anti-neutrophil cytoplasmic antibodies (c-ANCA) was positive. Rheumatoid factor was also elevated at 99 U/mL. The anti-myeloperoxidase (MPO) antibody index was negative, as was the anti-glomerular basement membrane antibody index. CT of the abdomen and pelvis showed splenic infarct and bilateral wedge-shaped kidney hypodensities concerning for renal infarcts (**Figure 3**). A skin biopsy was obtained from the thigh rash, and the final pathology showed exuberant leukocytoclastic vasculitis involving post-capillary venules and medium-sized arteries. Although granulomas were not conspicuous, the findings were consistent with ANCA-associated vasculitis.

Table 1. Initial laboratory workup

Variable	Value	Reference Range
Hemoglobin	8.8 (L)	13.4–16.0 g/dL
Platelet count	562 (H)	168–382 x10exp9/L
White blood cell count	12.3 (H)	4.2–10.0 x10exp9/L
Absolute eosinophil count	0	0.0–0.4 x10exp9/L
Creatinine	0.59 (L)	0.64–1.27 mg/dL
Urinalysis	18 RBC/HPF, Protein: 30 mg/dL (H)	RBC: 0-3/HPF Protein: <10 mg/dL
ESR	120 (H)	<15 mm/hr
CRP	309 (H)	0.00–10.00 mg/L

*Lab values reveal leukocytosis, anemia, sub-nephrotic proteinuria, hematuria, elevated inflammatory markers, and normal eosinophil count. L=low, H=high.

Figure 2. Cavitary lesion located within the left lung space on CT chest.



A diagnosis of granulomatosis with polyangiitis (GPA) was made. Pulse-dose intravenous methylprednisolone was administered, with clinical improvement in respiratory symptoms, scleral redness, and pain. Despite treatment, the upper extremity digits developed progressive skin changes concerning for dry gangrene. Antiphospholipid antibody testing was negative. Several days later, a repeat CT of the abdomen and pelvis was obtained due to a significant hemoglobin drop and abdominal pain, which demonstrated a right renal hematoma with retroperitoneal bleed (**Figure 4**). Surgical intervention was deferred in the absence of an acute abdomen and hemodynamic stability. The patient was continued on intravenous methylprednisolone and received induction therapy with 1g of rituximab.

Figure 3. Coronal view of bilateral kidney hypodensities on CT abdomen and pelvis.

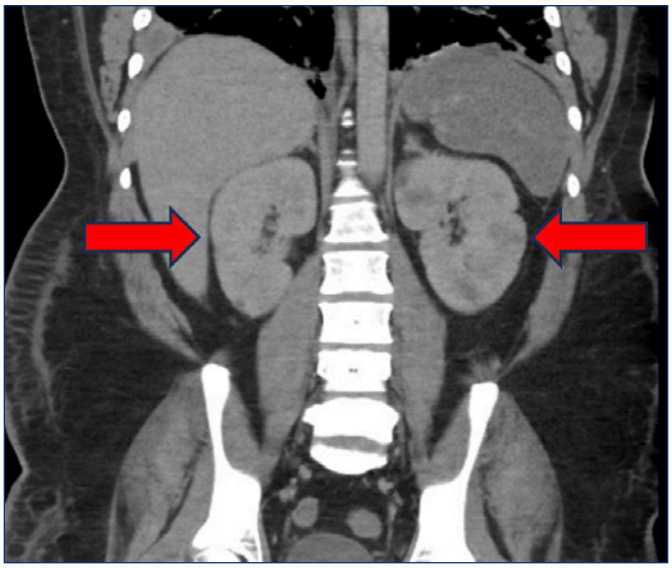
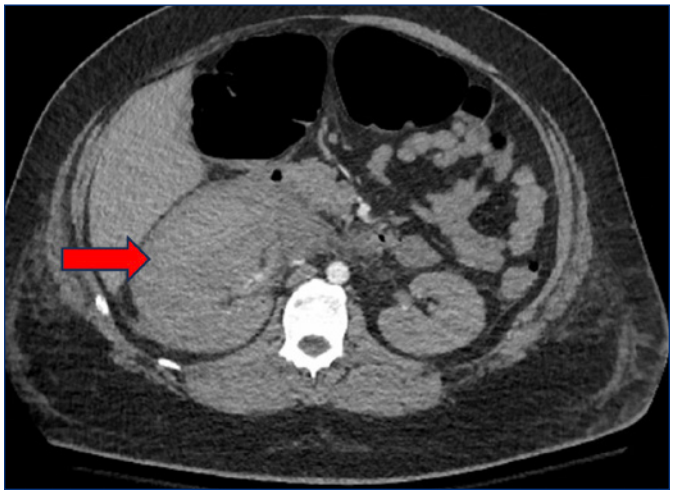


Figure 4. Large right perinephric hematoma decompressing into the retroperitoneum several days later.



DISCUSSION

GPA is a rare disorder classified as small vessel vasculitis that affects the upper and lower respiratory tracts and kidneys and is associated with positive PR3-ANCA. Clinical features often consistent with GPA include arthralgias, petechiae and purpura, splinter hemorrhages, hemorrhagic macules, episcleritis and scleritis, sinusitis, glomerulonephritis, pulmonary fibrosis, pulmonary hemorrhages, and otitis media.[1]

This is an interesting case because of the significant clotting burden without the classic features we would suspect in severe disease like glomerulonephritis or diffuse alveolar hemorrhage. In recent years, there has been more evidence supporting an increased frequency of thrombosis in ANCA-associated vasculitis, including DVT, PE, and myocardial infarction; however, renal and splenic infarcts are rare and often underdiagnosed, ulcerated lesions are only seen in 9.5% to 35.3% of affected individuals.[2-4]

With the patient's poor dentition and recent history of a tooth abscess combined with the appearance of embolic phenomena, we considered infective endocarditis, which can present as GPA[5] and positive rheumatoid factor.[6] Given his recurrent negative blood cultures, normal TTEs, and failure to improve with antibiotics, it was less likely.

Therapy for GPA is often initiated with combined corticosteroids and cyclophosphamide for remission induction; however, studies show that combination with rituximab is non-inferior to cyclophosphamide in severe cases of ANCA vasculitis and may be superior in relapsing disease.[7-9] Many clinicians have transitioned to using rituximab in combination with corticosteroids for remission induction to reduce the risks of infertility, bone marrow toxicity, and secondary malignancy predominantly seen in cyclophosphamide use.[8]

Once remission induction is achieved, therapies for maintenance therapy are variable but include transition to rituximab, mycophenolate, methotrexate, or azathioprine. The MAINRITSAN trial demonstrated that rituximab is more effective at sustaining remission than azathioprine and methotrexate.[10] The duration of therapy is widely dependent on the likelihood of relapse. Notably, individuals with positive PR-3 antibodies have higher rates of relapse.[11]

References

1. West SG, Kolfenbach JR. Rheumatology Secrets. 4th ed. Philadelphia, Pennsylvania: Elsevier, 2020.
2. Bottomley MJ, Gibson M, Alchi B. PR3 vasculitis presenting with symptomatic splenic and renal infarction: a case report and literature review. BMC Nephrol. 2019 Mar 6;20(1):84. doi: 10.1186/s12882-019-1266-5. PMID: 30841860; PMCID: PMC6404344.
3. Chen X, Zhang S, You R, Ma Y, Xia P, Shi X, Wu H, Zheng K, Qin Y, Tian X, Chen L. Renal damage, and old age: risk factors for thrombosis in patients with ANCA-associated vasculitis. Thromb J. 2024 Mar 20;22(1):29. doi: 10.1186/s12959-024-00593-9. PMID: 38509585; PMCID: PMC10953224.

4. Qian J, Li J, Li J, Wang G, Zhao H. Cutaneous Deep Ulcerations as Initial Presentations of Granulomatosis with Polyangiitis: Two Case Reports and Differential Diagnosis. *Medicina*. 2023; 59(3), 563. https://doi.org/10.3390/medicina59030563. PMID: 36984564; PMCID: PMC10057340.
5. Peng H, Chen WF, Wu C, Chen YR, Peng B, Paudel SD, Lou TQ. Culture-negative subacute bacterial endocarditis masquerades as granulomatosis with polyangiitis (Wegener's granulomatosis) involving both the kidney and lung. BMC Nephrol. 2012 Dec 26;13:174. doi: 10.1186/1471-2369-13-174. PMID: 23268737; PMCID: PMC3574827.
6. Peechakara B, Kadam A, Mewada M, Nakrani A. Infective Endocarditis Masquerading as Rheumatoid Arthritis. Cureus. 2019 Sep 11;11(9):e5626. doi: 10.7759/cureus.5626. PMID: 31700729; PMCID: PMC6822880.
7. Trandafir CM, Balica NC, Horhat DI, Mot IC, Sarau CA, Poenaru M. Granulomatosis with Polyangiitis (GPA)-A Multidisciplinary Approach of a Case Report. Medicina (Kaunas). 2022 Dec 13;58(12):1837. doi: 10.3390/medicina58121837. PMID: 36557039; PMCID: PMC9785195.
8. Geetha D, Kallenberg C, Stone JH, Salama AD, Appel GB, Duna G, Brunetta P, Jayne D. Current therapy of granulomatosis with polyangiitis and microscopic polyangiitis: the role of rituximab. J Nephrol. 2015 Feb;28(1):17-27. doi: 10.1007/s40620-014-0135-3. Epub 2014 Sep 4. PMID: 25185728; PMCID: PMC4322237.
9. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, Kallenberg CG, St Clair EW, Turkiewicz A, Tchao NK, Webber L, Ding L, Sejismundo LP, Mieras K, Weitzenkamp D, Ikle D, Seyfert-Margolis V, Mueller M, Brunetta P, Allen NB, Fervenza FC, Geetha D, Keogh KA, Kissin EY, Monach PA, Peikert T, Stegeman C, Ytterberg SR, Specks U; RAVE-ITN Research Group. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010 Jul 15;363(3):221-32. doi: 10.1056/NEJMoa0909905. PMID: 20647199; PMCID: PMC3137658.
10. Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaître O, Cohen P, Maurier F, Decaux O, Ninet J, Gobert P, Quémeneur T, Blanchard-Delaunay C, Godmer P, Puéchal X, Carron PL, Hatron PY, Limal N, Hamidou M, Ducret M, Daugas E, Papo T, Bonnotte B, Mahr A, Ravaud P, Mouthon L; French Vasculitis Study Group. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med. 2014 Nov 6;371(19):1771-80. doi: 10.1056/NEJMoa1404231. PMID: 25372085.
11. Thai LH, Charles P, Resche-Rigon M, Desseaux K, Guillevin L. Are anti-proteinase-3 ANCA a useful marker of granulomatosis with polyangiitis (Wegener's) relapses? Results of a retrospective study on 126 patients. Autoimmun Rev. 2014 Mar;13(3):313-8. doi: 10.1016/j.autrev.2013.11.003. PMID: 24225075.

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Disclosures

We confirm that there are no conflicts of interest or disclosures to report for all authors of this study.

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