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LESSON FOR THE CLINICAL NEPHROLOGIST

Granulomatosis with polyangiitis mimicking cancer: a diagnostic dilemma

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Case 1

A 56-year-old woman was admitted with a non-healing trophic lesion on a leg, and after admission, her kidney function deteriorated. Rapidly progressive glomerulonephritis (GN) was considered and anti proteinase-3 (antiPR3) Anti-Neutrophil Cytoplasmic Antibody (ANCA) positivity was found. The patient progressed to hemodialysis, with oliguria and macroscopic hematuria. Kidney biopsy confirmed pauci-immune crescentic glomerulonephritis with signs of peri-glomerular granulomatous inflammation (Fig. 1B). Furthermore, chest computed tomography (CT) scan revealed signs of alveolar hemorrhage. The skin defect on the patient's lower limb was considered a vasculitis symptom as well. The patient was diagnosed with GPA (granulomatosis with polyangiitis).

During hospitalization, abdominal CT scan detected a large ($90 \times 80 \times 60$ mm), non-homogeneous solid mass with calcifications in the urinary bladder. CT was followed by sigmoidoscopy, the results of which were normal, and cystoscopy, which showed a fragile, whitish flat tumor changing into a firm scirrhous neoplasm in the vertex of the anterior wall of the bladder. A papillocarcinoma and a pseudotumor were considered in the differential diagnosis; the biopsy confirmed the vasculitic etiology, showing necrotizing granulomatous vasculitis with scarring and vein defects of varying size. The morphology corresponded with the manifestation of ANCA-associated vasculitis. (Fig. 1A).

The patient received pulses of methylprednisolone (MP) and cyclophosphamide (CPA), and plasma exchange (PLEX) which led to clinical and laboratory improvement allowing to discontinue dialysis. A control CT scan, performed 6 months later, showed a significant improvement of the "tumorous" focus, which had shrunk to a mere $20 \times 10 \times 10$ mm (Fig. 2A–C), and later completely disappeared. As the vasculitis went into remission, treatment was changed to maintenance with mycophenolate mofetil (MMF), which was eventually discontinued two years later. She has remained in remission since withdrawal ofimmunosupression [adapted from 1].

Case 2

A 44-year-old woman underwent maxillary sinus surgery in 1999. Carcinoma was diagnosed and treated with chemotherapy and radiotherapy. The patient suffered from epistaxis and hoarseness, as well as having polyarthralgia and necrotizing skin lesions, which were biopsied and showed small-vessel vasculitis. One year later, her father was diagnosed and successfully treated for GPA with renal, musculoskeletal and ear-nose-throat (ENT) involvement. In 2003, the patient's hoarseness worsened, and she developed dry cough, not responsive to antibiotic treatment. The work-up revealed renal failure requiring dialysis; anti-PR3

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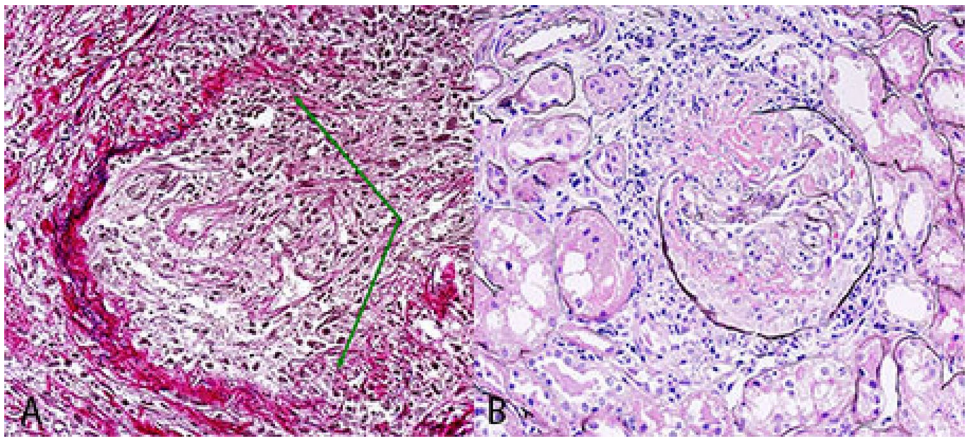

Fig. 1 **A** Urinary bladder, vasculitis of the vein with fibrotic occlusion of the vessel lumen and segmental vasculitis with complete destruction of the vessel wall on the right side of the picture (arrows). **B** Glomerulus showing severe necrosis of the tuft surrounded by crescent formation, as well as fibrinoid necrosis of a hilar arteriole associated with prominent periglomerular granulomatous inflammation (Adapted from [1], with permission)

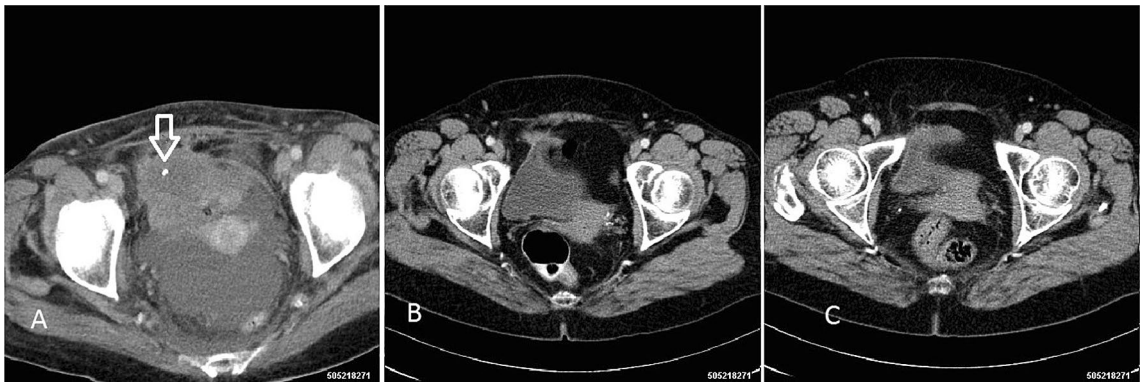

Fig. 2 Pathological CT finding in urinary bladder (granulomatous inflammation **a**), its regression (**b**) and complete disappearance (**c**) (Adapted from [1], with permission)

ANCA were positive. A kidney biopsy showed a pauci-immune crescentic glomerulonephritis. A second opinion was requested on the original maxillary mass; it contained a dense inflammatory infiltration, active 'fibrinoid' vasculitis and no morphological features of carcinoma. The induction treatment with corticosteroids and cyclophosphamide led to remission within 6 months, creatinine dropped to 143 µmol/l and she continued with immunosuppressive treatment (including MMF, Methotrexate, Azathioprine [AZA], Rituximab [RTX]) with a relapsing–remitting course of the disease since then.

Case 3

A 34-year-old male smoker, was referred with polyarthralgia and progressive renal insufficiency (creatinine 412 µmol/l, proteinuria 1.2 g/day). A chest CT scan revealed one granuloma and six areas of ground glass appearance and he was diagnosed with PR3-ANCA-associated vasculitis in March 2012. The diagnosis was immediately confirmed by renal biopsy, which showed florid necrotizing glomerulonephritis with vein lesions leading to diagnosis of ANCA-associated vasculitis. Combined immunosuppressive treatment (CPA + corticosteroids [CS]) was immediately initiated. In June 2012, creatinine level decreased to 130 µmol/l and the patient remained stable for almost two years on maintenance therapy with AZA. In June 2014, a new CT scan revealed a lesion 52 × 45 × 40 mm in size, of unclear etiology, in the apex of the patient's right lung (Fig. 3A). The lesion had small eccentric granular calcifications with aerial stripe zones that resembled bronchograms more than a cavity in a granuloma, and was possibly infiltrating the thoracic wall; on these bases, a malignant lesion was suspected. Due to the unclear imaging features and only a mild increase of his PR3-ANCA levels, upper right lobectomy was performed, leading to the diagnosis of a necrotizing granuloma with a large central necrosis affecting a vessel wall. The pathological analysis confirmed granulomatous polyangitis and excluded tumor and infection (Table 1). Immunosuppression was strengthened. In August 2015, a new right lung granuloma was found on HRCT scan (Fig. 3B). The patient later received two doses of RTX followed by maintenance RTX, leading to stable remission (Fig. 3C).

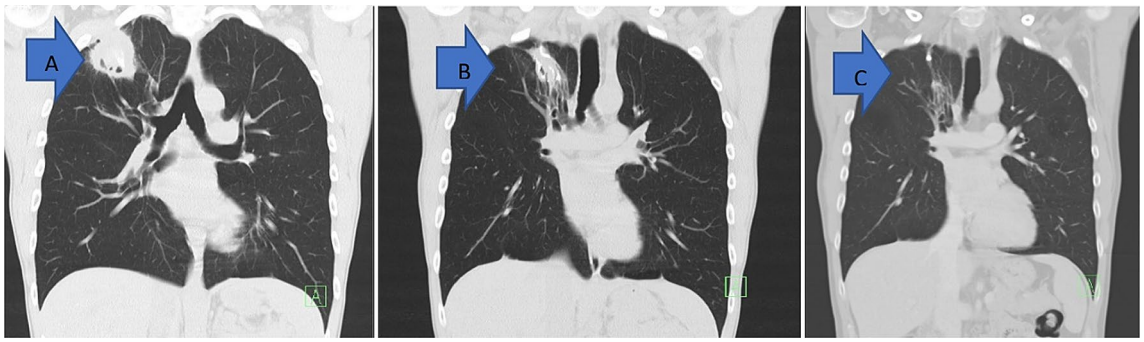

Fig. 3 **A** 2014—Granuloma of the right upper lung lobe. **B** 2015—Suspected recurrence after lobectomy. **C** 2019—Fibrous tissue with calcifications, remission after biological therapy

Table 1 Please move to supplemental material

	Key laboratory findings	Imaging ("cancer-mimicking lesions")	Biopsy	Treatment	Remission
Case 1 (at diagnosis)	c-ANCA anti-PR3 > 100 IU/ml sCrea dialysis CRP 1.9 mg/l	Abdomen CT: solid expansion (90 × 80 × 60 mm) with calcifications in the urinary bladder	Bladder: necrotizing granulomatous vasculitis with scarring and vein defects of different age	MP, CS, CPA, Plasma Exchange, later switched to MMF	+
Case 2 (at diagnosis)	c-ANCA anti-PR3 26 IU/ml sCrea dialysis… 332.0 µmol/l CRP 24.0 mg/l	Head CT: osteolytic lesion of maxilla and sphenoid bone	Maxillary mass: [1] inflammatory infiltration, active 'fibrinoid' vasculitis, no signs of carcinoma	CS, CPA, later switched to MMF	+
Case 3 (at relapse)	c-ANCA anti-PR3 5.3 IU/ml Crea 114.0 µmol/l CRP 44 mg/l	Chest CT: lung tumoriform lesion 52 × 45 × 40 mm	Lung: necrotizing granulomas with central necrosis affecting a vessel wall	CS, AZA, later switched to RTX	+

[1]biopsy performed several years prior to diagnosis, 2nd opinion requested at diagnosis

MP methylprednisolone, *CS* corticosteroids, *CPA* cyclophosphamide, *RTX* rituximab, *MMF* mycophenolate mofetil, *AZA* Azathioprine

Lessons for clinical nephrologists

ANCA-associated vasculitides (AAV) are a group of autoimmune diseases that typically affect small vessels. Granulomatosis with polyangiitis (GPA) is the most common among them, and is strongly associated with the presence of ANCA, mainly targeting PR3 (PR3-ANCA) and, much less frequently, myeloperoxidase (MPO-ANCA). The severity of the disease varies from relatively benign to life-threatening. ANCA antibodies are found in around 90–95% of patients with generalized GPA, but the percentage is lower in localized forms. The disease manifestation typically involves the triad of kidney, lungs, and upper respiratory tract. Nevertheless, any organ may be affected.

The standard treatment consists of a combined immunosuppressive therapy with the use of CS and either CPA or RTX in most cases. In non-organ threatening disease, methotrexate or MMF with CS may be prescribed [2]. The addition of PLEX may be considered in severe cases, even though a recent trial failed to prove any significant benefit of adding plasma exchange to standard treatment, and furthermore, the role of PLEX [3] in AAV has been matter of discussion [4, 5]. Relapsing disease should be preferably treated by RTX, whose effect was found to be superior compared to CPA [6].

What are the challenges in AAV diagnostics?

The lesions in GPA may resemble a tumor. Therefore, several GPA patients may be misdiagnosed with cancer, and some of them may even undergo an unnecessary surgical procedure. Our second case included a common manifestation of GPA, with ENT involvement being present in over 87% of GPA patients. However, the patient was originally misdiagnosed with cancer and only when she developed

more severe signs of vasculitis closely resembling those of her father's, was vasculitis diagnosed. Our third case is an example of a typical localization of vasculitic disease in the lungs, highlighting the importance of biopsy in determining the cause of the pathological finding and in guiding complex differential diagnosis.

Urogenital manifestations of AAV

Of the 125 patients with GPA regularly followed-up at our clinic, only 2 were diagnosed with a vasculitic urogenital lesion. One was a necrotizing granulomatous inflammation of a testicle; we describe the second one in this article necrotizing vasculitis with granulomatous edges in the urinary bladder.

Do AAV have a genetic background?

The same disease occurring in both father and daughter raises a question of familial predisposition to AAV, as described in our previous publication in 2006, which also included this family [7]. Most instances of GPA are sporadic and familial clusters are very rare. There are, however, several described familial cases implying genetic predisposition [8], and a significant association of genetic polymorphisms with PR3-ANCA and MPO-ANCA, respectively, was also shown in a GWAS study [9]. Whereas PR3-ANCA positivity was associated with HLA-DP and the genes encoding α1-antitrypsin (SERPINA1) and proteinase 3 (PRTN3), MPO-ANCA was associated with HLA-DQ, suggesting two distinct autoimmune syndromes.

Concluding remarks

GPA is a relatively rare and potentially life-threatening disease, which should be considered in the differential diagnosis of unclear necrotizing inflammation affecting any organ, in patients who suffer from seemingly unrelated problems in a variety of organ systems. Testing for ANCA and clinical imaging may be sufficient in many patients but in case of doubts, performing a biopsy is strongly recommended since it may spare unnecessary surgical interventions or even oncological therapy; complete remission is possible if the correct treatment is administered, as in the three case reported above. On the other hand, continuous vigilance and screening for secondary malignancies is needed in patients with established vasculitis, particularly in patients with new pathological findings without a concurrent increase in ANCA or other signs of disease activity.

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Declarations

Conflict of interest No conflicts of interest reported by any of the authors.

Ethical statement This report was conducted in compliance with the standard Ethical principles.

Informed consent Informed consent was obtained from the participants.

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