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Case Report

Granulomatosis with polyangiitis presenting as a renal mass mimicking immunoglobulin G4-related disease

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1. Introduction

Granulomatosis with polyangiitis (GPA, previously known as Wegener's granulomatosis), is a small and medium vessel vasculitis characterised by systemic necrotising granulomatous inflammation, necrotising vasculitis, and necrotising glomerulonephritis [1]. It commonly manifests in the upper and lower respiratory tracts, and kidneys, however can affect various organs including the skin, orbits and gastrointestinal system [2].

IgG4-related disease (IgG4-RD) is a recently recognised fibroinflammatory disease that presents as tumefactive lesions that can affect virtually any organ. Histological features of this entity are storiform fibrosis, a dense lymphoplasmacytic infiltrate rich in IgG4+ plasma cells, and obliterative phlebitis [3,4].

We describe a case of GPA presenting as an inflammatory mass in the kidney, incidentally found on histological examination of a nephrectomy specimen removed for adjacent renal cell carcinoma (RCC). Due to the absence of clinical features of GPA, the absence of typical histological features of GPA in the lesion and the non-neoplastic renal parenchyma, and a high IgG4+ plasma cell count in the lesion, the mass was misdiagnosed initially as IgG4-RD.

2. Case report

A 46 year-old otherwise healthy male was incidentally found to have a left renal mass on abdominal ultrasound done as part of a workup for mildly deranged liver tests. Computed tomography (CT) of the abdomen and pelvis showed a lobulated mass in the left kidney with perinephric stranding, highly suspicious for RCC (Fig. 1a). Preoperative chest X-ray revealed numerous nodules in the right lung, largest 2.7 cm (Fig. 1b). These were thought to be suspicious for pulmonary metastases. No pulmonary or constitutional symptoms were present at this stage. Laparoscopic assisted left radical nephrectomy was carried out.

Histological sections of the renal mass confirmed the presence of a clear cell RCC of Fuhrman grade 3, confined to the kidney (stage pT2a) (Fig. 2a). In addition to this, centered in the perirenal fat but merging with the tumour was a fibroinflammatory lesion, characterised by storiform spindle cells in sheets and a prominent inflammatory component, comprising lymphocytes, plasma cells, histiocytes, eosinophils and multinucleated giant cells (Fig. 2b–d). The spindle cells had bland cytology in most areas, but displayed occasional atypical cells. These were negative for cytokeratins (Cam5.2 and CK AE1/3). Large areas of basophilic necrosis were present (Fig. 2e). The inflammation extended into the non-neoplastic kidney interstitium, entrapping normal glomeruli and tubules. Tubulitis was seen where there was entrapment of tubules (Fig. 2f), however no tubular obliteration was seen. There was no evidence of glomerulonephritis; in particular, no evidence of changes of membranous glomerulonephritis on Periodic acid Schiff (PAS) stain and no glomerular capillary wall deposits on trichrome

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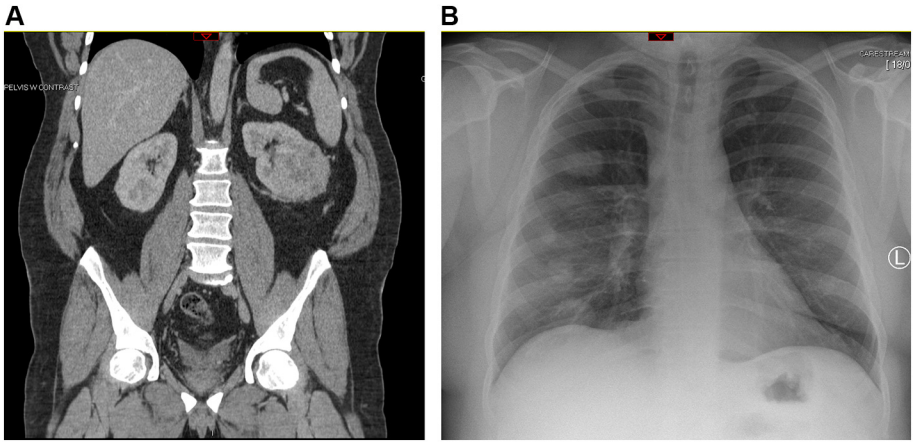

Fig. 1. Pre-operative imaging. (A) Computed tomography of chest, abdomen, and pelvis showing lobulated mass in the left kidney with perinephric stranding. (B) Multiple lung nodules seen on preoperative chest X-ray, largest 2.7 cm.

stain (Fig. 2g–h). The inflammatory process extended into surrounding veins which showed intimal proliferation, but no obstructive venulitis was seen (Fig. 2i–j). No arteritis was seen, and neither did the granulomatous inflammation with necrosis surround arteries. Medullary capillaritis was not identified. The necrotising process did not involve vessels and vasculocentricity could not be demonstrated on elastic stains. No fungal or acid-fast microorganisms were identified on PAS and Ziehl-Neelsen stains. IgG4 stain showed positive staining of plasma cells up to 90/high power field (hpf), distributed in focal, dense clusters (Fig. 2k). The diagnosis of probable IgG4-related disease (IgG4-RD) coincident with Fuhrman grade 3 clear cell RCC was favoured. The patient had no previous history of IgG4-RD involvement of other organs. Serum IgG4 was not measured at this stage.

Four weeks following nephrectomy, the patient presented with fever, worsening polyarthralgia, and haemoptysis. Blood tests revealed anaemia (haemoglobin 106 g/L), leucocytosis with neutrophilia (white cell count 16.9 × 10^9/L; neutrophil count 15.7 × 10^9/L), raised C-reactive protein (100 mg/L), and stable creatinine which was unchanged from a year ago (142 μmol/L). Chest X-ray revealed significant growth in the right lung lesions, comprising at least five opacities, largest 3.8 cm that had previously been 3.0 cm. Core biopsy of the lung lesions revealed severely inflamed lung tissue comprising mixed inflammatory cells including lymphocytes, histiocytes, giant cells, polymorphs and a few plasma cells (Fig. 3a). There were areas of necrosis surrounded by palisading histiocytes, as well as suppurative granulomas (Fig. 3b). Vessel walls appeared to be targeted by the inflammatory cells within the background inflammatory process; however no fibrinoid necrosis of vessels were seen (Fig. 3c). Blood tests promptly revealed a positive c-ANCA (titre 1:160) with a raised level of antibody to PR3 (36 U/mL), consistent with GPA. Bronchoscopy and bronchial biopsy showed focal superficial erosion of the bronchial epithelium with an acute inflammatory exudate, consistent with ulcerative bronchitis. Prednisolone 50 mg daily was commenced. Four days following the bronchoscopy, the patient was admitted due to worsening haemoptysis, rash and polyarthritis. A three-day course of intravenous methylprednisolone was given, followed by oral prednisolone 80 mg daily and a single dose of intravenous cyclophosphamide. During admission, his haemoptysis resolved, and he remained haemodynamically stable and afebrile until discharge. Since discharge he has had four infusions of rituximab. Serial chest X-rays done up to sixteen weeks following discharge showed progressive reduction in size and density of lung nodules. Renal function remained stable at a creatinine level of 138 μmol/L. The patient remains well at last review.

3. Discussion

The initial manifestations of GPA are protean and the classic triad of necrotising granulomatous inflammation of the upper and/or lower respiratory tracts, systemic or focal necrotising vasculitis, and focal necrotising glomerulitis is often not present. The presentation of GPA as a renal mass is rare and less than twenty cases have been reported in the literature [5–13]. The radiological appearance of GPA-associated masses is indistinguishable from renal neoplasms [7,8]. The recognition of GPA as the aetiology for these inflammatory masses is arrived at by a combination of clinical and histological features. In addition to respiratory tract and/or renal manifestations, constitutional symptoms such as fever or malaise may be present. Histologically, GPA shows necrotising vasculitis and irregular basophilic parenchymal necrosis with associated palisading granulomas, neutrophilic abscesses, and multinucleated giant cells [2]. A positive serum anti-neutrophil cytoplasmic antibody (ANCA) and anti-PR3 antibody strongly support the diagnosis, however a small percentage of patients are seronegative [1].

In our case, the inflammatory mass in the kidney was found incidentally during examination of the nephrectomy specimen for suspected RCC. The patient was completely asymptomatic at this stage. The renal mass was seen on ultrasound as part of a workup for mildly deranged liver tests detected on routine health screening. The lung masses detected preoperatively were interpreted as metastases, but this was not known to the pathologist or mentioned in discussions with clinicians. Due to the lack of systemic manifestations of an inflammatory disorder, the initial histological examination of the inflammatory mass was perplexing. The lesion was also mainly centered in the perinephric fat with some extension into the renal interstitium and no glomerular involvement. The coexistence of a spindle cell proliferation with Fuhrman grade 3 RCC raised the possibility of sarcomatoid RCC, however negative staining for cytokeratin disproved this. The lack of membranous glomerulonephritis, which can be seen in association with IgG4-RD in a minority of cases [14] and the lack of crescentic glomerulonephritis, often seen in association with ANCA-associated vasculitis, provided no clues toward the underlying aetiology. Focal tubulitis was present, however this can be seen in both GPA and IgG4-RD in the kidney. There was no evidence of medullary capillaritis to support ANCA-mediated disease [15] nor was there arteritis. The predominantly perirenal location of the lesion, focal storiform fibrosis, dense lymphoplasmacytic infiltrate and a high IgG4+ plasma cell count misled the authors to a diagnosis of IgG4-RD in the first instance. In retrospect, the presence of geographic basophilic necrosis and granulomatous inflammation, though mostly extrarenal, were inconsistent with IgG4-RD, and should have raised the alternative diagnosis of GPA [4]. In addition, sclerosis was focal and tubular elements were still identifiable in the midst of sclerosis, in