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Concurrent IgG4-Related disease and clear cell renal cell carcinoma

Kar Ven Cavan Chow [1], Shahadat Hossain [*]

Bundaberg Base Hospital, 271 Bourbong Street Bundaberg Central, Queensland, 4670, Australia

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ABSTRACT

We report a case of a 54-year-old man with a concurrent diagnosis of IgG4-related disease (IgG4-RD) and clear cell renal cell carcinoma (ccRCC) following asymptomatic submandibular lymphadenopathy with an incidental finding of a left renal mass. Partial nephrectomy revealed ccRCC with surrounding lymphoplasmacytic infiltrate, storiform fibrosis and a strong positivity for IgG4 on immunoperoxidase staining. The IgG4+:IgG + ratio was >40% and serum IgG4 levels were elevated at 159mg/dL. This case highlights the concurrent diagnosis of a unique dual pathology within the same organ and emphasises the importance of malignancy screening in patients with IgG4-RD and vice versa.

1. Introduction

IgG4-related disease (IgG4-RD) is an immune mediated condition with multisystem involvement characterised by high serum IgG4 levels and IgG4 plasma cell infiltration into solid organs leading to the classical histopathologic findings of storiform fibrosis, lymphoplasmacytic infiltrates and obliterative phlebitis.[1]

Common major organ involvement includes the salivary glands, lymph nodes, pancreas, retroperitoneum and biliary tract.[2,3] Renal involvement occurs in approximately 15% of cases with tubulointerstitial nephritis and glomerular involvement being the most common manifestations.[1,4] The multiorgan nature of the disease makes IgG4-RD a known mimicker of many conditions. With recent associations between IgG4-RD and malignancies, making this distinction is crucial as the treatment options and prognosis differ significantly. We report an unusual case of the concurrent diagnosis of IgG4-RD and clear cell renal cell carcinoma (ccRCC) existing within the same organ.

2. Case presentation

A 54-year-old man presented with a 2-month history of painless left submandibular lymphadenopathy with no systemic symptoms, on a background of type 2 diabetes mellitus and asthma. Excisional biopsy showed reactive lymph nodes with follicular hyperplasia, non-necrotising granulomas and increased number of plasma cells within the germinal centres. The IgG4+:IgG + ratio was >40% with >100 IgG4 positive cells seen per high powered field. Serum IgG4 levels were elevated at 159mg/dL (<135mg/dL) satisfying the criteria for IgG4-RD.[1] His renal function remained normal throughout the course of the illness.

Radiological imaging with CT chest, abdomen and pelvis, and renal doppler ultrasound scan revealed multiple mediastinal and hilar lymphadenopathy ranging from 10 to 11mm in size, and a heterogenous, predominantly hypodense exophytic mass (64 × 43 × 43mm) with internal vascularity arising from the medial border of the lower pole of the left kidney (Fig. 1) suspicious for a renal cell carcinoma (RCC).

A partial left nephrectomy was performed whereby histology showed microscopic evidence of conventional ccRCC of WHO/ISUP nucleolar grade 2 with no extracapsular extension or vascular invasion. Interstitial fibrosis and chronic inflammation were evident in the surrounding renal parenchyma. The perirenal soft tissue was infiltrated by a dense lymphoplasmacytic inflammatory infiltrate with storiform fibrosis but no obliterative vasculitis (Fig. 2). Immunohistochemical staining showed strong diffuse positivity for IgG4 plasma cells with a IgG4+:IgG + ratio of >40% (Fig. 3), in keeping with probable IgG4-related kidney disease.[1] Staging investigations including a hilar lymph node biopsy showed reactive granulomatous changes only, and therefore the tumour was staged as T1bNxM0 ccRCC.

The patient was managed with prednisolone 0.25mg/kg daily. The lower dose was chosen because the patient was a diabetic and asymptomatic. Prednisolone was subsequently weaned off following minimal response to the sizes of the hilar and mediastinal lymphadenopathy over two months, coupled with compromised diabetes control. The patient remains asymptomatic and is currently being followed up regularly by

* Corresponding author.
E-mail addresses: ckv2047@gmail.com (K.V.C. Chow), shahadat.hossain2@health.qld.gov.au (S. Hossain).
[1] Present address: Princess Alexandra Hospital, 199 Ipswich Road Woolloongabba QLD 4102, Australia.

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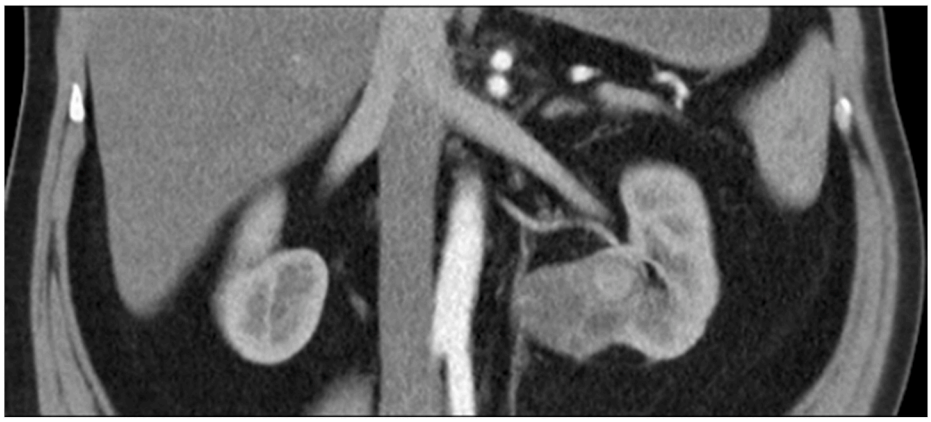

Fig. 1. Coronal section of a contrast-enhanced CT image showing a mass in the lower pole of the left kidney.

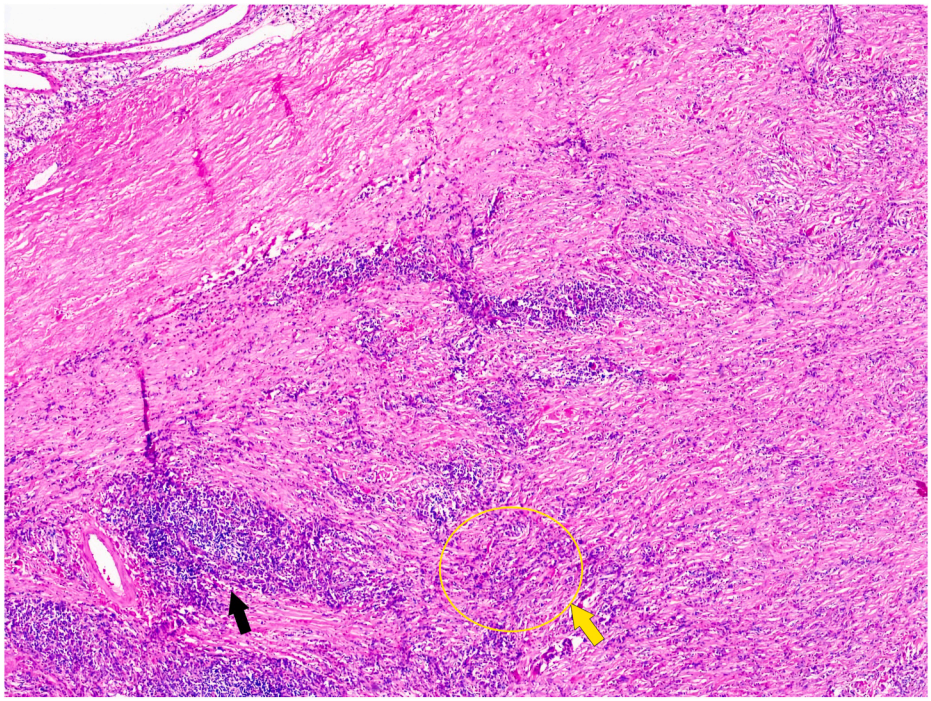

Fig. 2. Histopathology of the left kidney showing a ccRCC (yellow circle and arrow) and areas of lymphoplasmacytic inflammatory infiltrates (black arrow) (×40). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

the nephrology team with no disease recurrence at two years.

3. Discussion

Several reports have shown an association between IgG4-RD and malignancy. The overall malignancy rate in IgG4-RD is 2–3.5 times higher than the general population.[2,3] Types of cancer reported in IgG4-RD are varied with the most common cancers reported being prostate, lung and colon cancer. The overall occurrence of RCC is infrequent. Malignancies can occur before, concurrently or after a diagnosis of IgG4-RD, with the highest risk reported to be in the first year following the immune disorder diagnosis.[3] There appears to be no correlation between the IgG4-RD affected organ and the site of malignancy.[2,3]

The exact pathogenesis between IgG4-RD and malignancy remains unclear although several hypotheses have been proposed. One theory suggested that IgG4-RD could be a manifestation of paraneoplastic syndrome. This is supported by regression of IgG4-RD with treatment of the underlying malignancy in some reported cases.[3] Cancer treatment with chemotherapy or radiotherapy has also been implicated as a cause for immune dysregulation, producing neoantigens leading to the development of autoimmune disease.[3] Thirdly, tumour surveillance failure leading to uncontrolled inflammation and loss of tumour suppression has also been proposed as an explanation, and is evidenced by the higher risk of autoimmune pancreatitis (AIP) in pancreatic cancer.[2]

We identified two previously published case reports of IgG4-RD followed by ccRCC diagnosis years later. The first one was a 61-year-old female with a diagnosis of ccRCC seven years after a diagnosis of IgG4-related sialadenitis.[5] The second case described a middle-aged man with a history of mucosa-associated lymphoid tissue (MALT) lymphoma and ccRCC who consequently developed AIP and IgG4-RD two years later.[4]

To the best of our knowledge, there are no known previously reported cases of a concurrent diagnosis of IgG4-RD and ccRCC in the literature. Although the diagnosis was made concurrently in our case, it is difficult to determine the exact temporal relationship. Nevertheless,

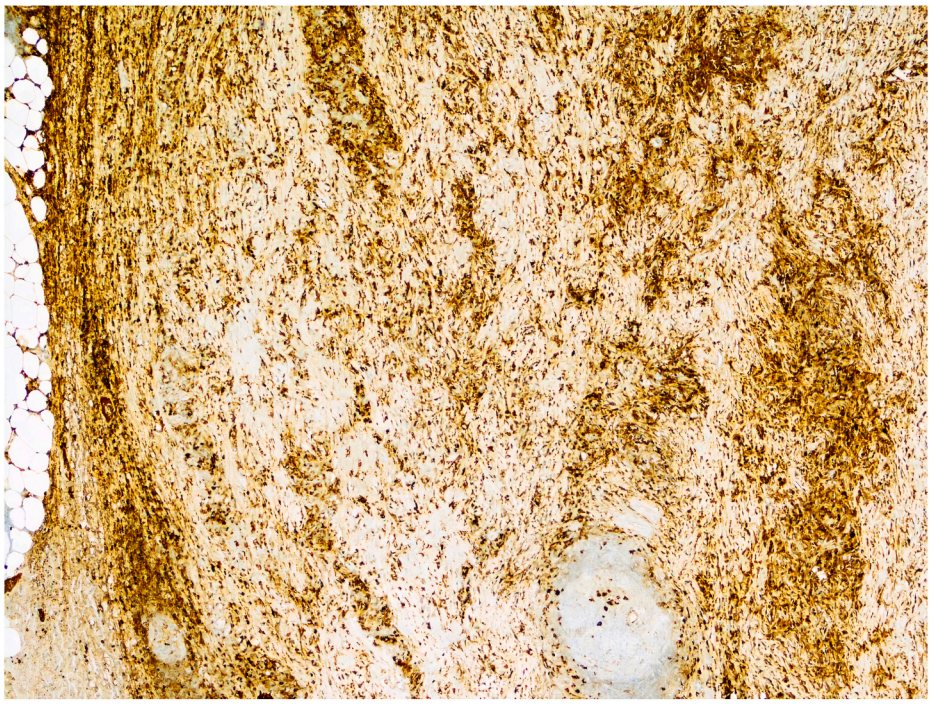

Fig. 3. Immunostaining for IgG4 showing abundant IgG4-positive plasma cells (×40).

the dual pathology of ccRCC and IgG4-RD within the same organ reported here is unique. Our case showed minimal response to corticosteroids, potentially due to the lower prednisolone dose used compared to 0.5–0.6mg/kg/day described in most literatures.[1]

4. Conclusion

RCC can rarely be associated with IgG4-RD and both pathologies can occur concurrently within the same organ. This case emphasises the need for a high index of suspicion for malignancies in patients with IgG4-RD, whilst ensuring long term follow up. Thus, a lower threshold for further investigation of suspicious lesions not responding to conventional IgG4-RD treatment is required. The underlying pathogenesis for the link between malignancies and IgG4-RD remains unclear and further studies are required in this area.

Consent

The patient has provided written informed consent regarding the case manuscript and submission for publication.

Conflict of interest statement

There are no conflict of interests.

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