Pathology (■ xxxx) **xxx(xxx)**, xxx

CORRESPONDENCE

Isolated peri-renal extranodal Rosai–Dorfman disease rich in IgG4+ plasma cells

To the Editor,

We present an unusual case of extranodal Rosai–Dorfman disease arising in the renal hilum which was rich in IgG4+ plasma cells, a rare phenomenon.

Histiocytoses are characterised by accumulations of histiocytes (macrophages, dendritic cells, or monocytic cells). They are classified into five groups: L group [includes Langerhans cell histiocytosis (LCH) and Erdheim–Chester disease (ECD)]; C group (non-LCH localised to skin and mucosa); R group (Rosai–Dorfman disease (RDD) and miscellaneous non-cutaneous non-LCH); H group (haemophagocytic lymphohistiocytosis); and M group (malignant histiocytoses).[1]

Rosai–Dorfman disease, also termed 'sinus histiocytosis with massive lymphadenopathy', is characterised by histiocytes with CD68 and S100 positivity, and CD1a and Langerin negativity.[2] It can present as nodal disease with or without extranodal involvement and may be exclusively extranodal.[3] Histiocytosis involving the kidney most commonly occurs in ECD, and is a rare manifestation of RDD.[1,2] Isolated peri-renal RDD is very rare.

A 55-year-old male presented with acute right flank pain. He denied urinary symptoms, macroscopic haematuria, and systemic symptoms including fever. Comorbidities included obesity (BMI 53.5 kg/m^2), type II diabetes mellitus, ischaemic heart disease, hypercholesterolaemia, and obstructive sleep apnoea. There was microscopic haematuria on urinalysis. Full blood count, urea/electrolytes/creatinine were all normal.

Computed tomography (CT) imaging demonstrated an ill-defined infiltrative 4.7×4.0 cm lesion in the right renal hilum (Fig. 1A) which was isodense to the normal left renal parenchyma, and mildly enhancing after intravenous contrast. Obstruction of the right renal collecting system with vascular involvement was noted. Features of retroperitoneal fat stranding in the perihilar region and along the infrarenal inferior vena cava were evident. The left kidney was normal.

On whole body FDG PET-CT, the right renal hilar mass demonstrated moderate heterogeneously increased FDG activity (SUV 12.9; Fig. 1B). There was no increased activity in the left kidney or FDG-avid lymphadenopathy.

The findings favoured a urothelial malignancy in the renal pelvis. Other considerations included another neoplastic (lymphoma) or inflammatory process.

A right nephrectomy was performed.

Macroscopically, a firm rubbery pale mass was noted in the renal hilum measuring 70×40×35 mm, extending into perinephric fat (Fig. 1C).

Microscopic examination revealed a fibro-inflammatory process (Fig. 2A) with nodular zones of mononuclear cells within a fibrovascular stroma which in areas, particularly toward the perimeter, had a fibro-sclerotic appearance. The inflammatory component was largely lymphocytes and plasma cells with occasional eosinophils and a background of histiocytic cells, some of which had a Touton-like appearance with a peripheral rim of nuclei and many having a spindled appearance (Fig. 2B). In addition, background large histiocytic cells with poorly defined but voluminous pale cytoplasm were noted throughout, obscured in many regions by lymphocytes and plasma cells. Lymphocytes were visible within the cytoplasm of some of the larger histiocytic cells, reflecting emperipolesis.

Infection was excluded via a panel of stains. Periodic acid–Schiff with diastase and Grocott's methenamine silver were negative for fungi, Von Kossa was negative for intracytoplasmic bodies, and Ziehl–Neelsen and Auramine were negative for mycobacterium.

The abundance of plasma cells in a fibroinflammatory background prompted consideration of IgG4-related disease (IgG4-RD). Up to 50 per IgG4+ plasma cells were identified per high power field, with an IgG4:IgG ratio of approximately 35%. There was no light chain restriction on kappa and lambda *in situ* hybridisation. The fibroinflammatory appearance prompted consideration of inflammatory myofibroblastic tumour; expression of SMA was positive in the spindled cells, however ROS-1 and ALK immunohistochemistry were negative.

The generous histiocytic component was highlighted with CD68. CD1a and Langerin (CD207) were negative. S100 stain highlighted the cells with voluminous cytoplasm. Focal subtle emperipolesis was identified using combined S100/CD45 immunohistochemistry (Fig. 2D). The cytoplasmic expression of S100 protein within the Rosai–Dorfman histiocytes was weaker than that of intermingled interdigitating histiocytic cells. BRAF immunostaining was negative. A diagnosis of extranodal Rosai–Dorfman disease was made.

Rosai–Dorfman disease is a non-Langerhans cell histiocytosis characterised by histiocytes with CD68 and S100 positivity, and CD1a and Langerin (CD207) negativity.[3] The lesional histiocytes demonstrate variable emperipolesis (the presence of intracytoplasmic leukocytes); however, emperipolesis is not specific to RDD nor necessary for diagnosis.[3] RDD classically presents as nodal disease with lymphadenopathy, but extranodal forms account for 43% of cases.[1]

Renal involvement is rare, documented between 2% and 9% of cases.[3,4] It is the most common intra-abdominal extranodal site of RDD. RDD involving the kidney occurs with and without nodal involvement.[5] It presents as a discrete mass or diffuse infiltration. Symptoms include flank pain, haematuria, abdominal fullness, renal failure, nephrotic syndrome, and hypercalcaemia. It can cause ureteral obstruction and hydronephrosis.[3] Differential diagnoses include ECD, lymphoma, renal cell carcinoma, IgG4-RD, tuberculosis, and metastatic tumour.[3] RDD with renal involvement has a poor prognosis.[3]

The pathogenesis of RDD is not clearly understood. There are recent reports of MAP-ERK pathway alterations in approximately one-third of RDD patients, suggesting that at least a subset may be neoplastic. These include mutations in *NRAS*, *KRAS*, *MAP2K1*, and *ARAF*.[3,4]

Renal RDD is often seen radiologically as hypoattenuating renal cortical nodules and subcapsular lesions, and peri-renal RDD as ill-defined infiltrative masses of the renal hilum.[6,7] Radiological findings of RDD involving the kidney are

Print ISSN 0031-3025/Online ISSN 1465-3931

Please cite this article as: van Laar Veth A et al., Isolated peri-renal extranodal Rosai–Dorfman disease rich in IgG4+ plasma cells, Pathology, https://doi.org/10.1016/j.pathol.2022.12.351

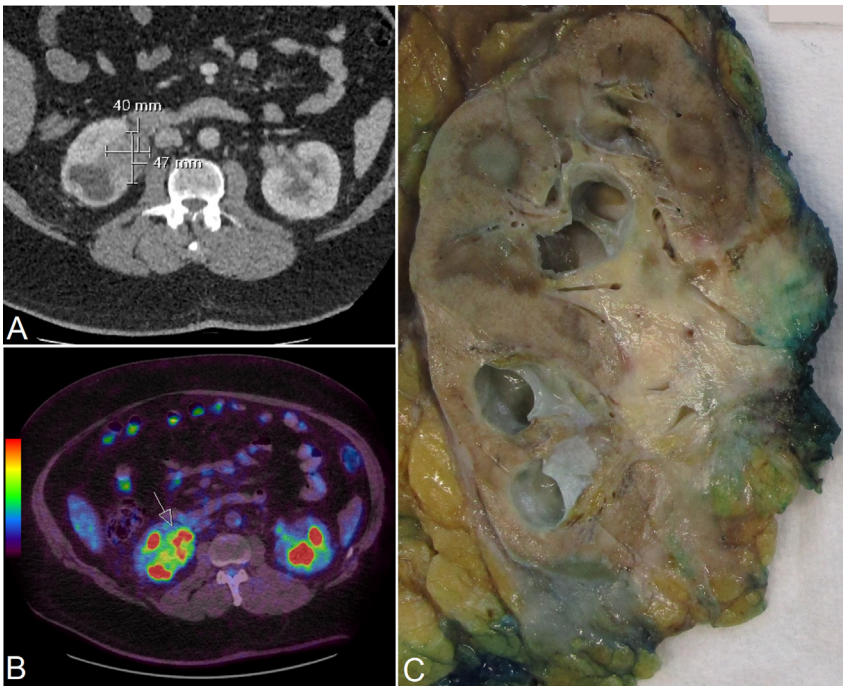

Fig. 1 Radiological and macroscopic features. (A) Axial CT: ill-defined right renal hilar lesion. (B) PET-CT: increased FDG activity in lesion. (C) Longitudinal section of right kidney demonstrating the pale hilar mass.

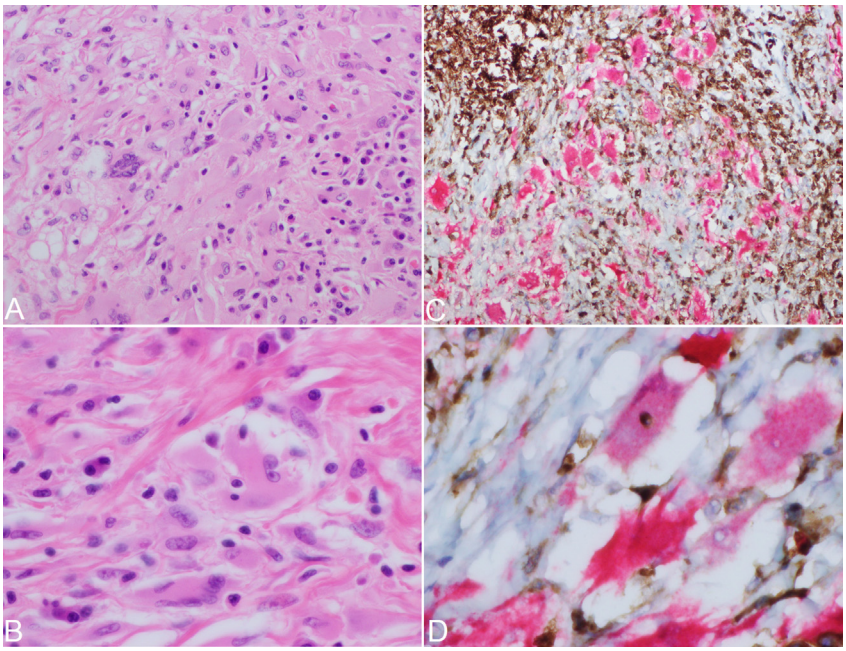

Fig. 2 Histopathological features. (A) Fibroinflammatory lesion with lymphocytes, plasma cells, and histiocytes (H&E). (B) Emperipolesis and Touton-like cell (H&E). (C) Combined S100/CD45 stain (low power). Histiocytes highlighted by S100 (red), and lymphocytes by CD45 (brown). (D) S100/CD45 stain (high power) highlighting emperipolesis.

typically bilateral.[8] Isolated unilateral renal involvement is unusual.[4,5] Our patient had isolated unilateral renal involvement without lymphadenopathy.

The numerous IgG4+ plasma cells in this case prompted consideration of IgG4-related disease. This entity is characterised by a dense lymphoplasmacytic infiltrate, fibrosis with at least focal storiform architecture, and obliterative phlebitis.[9] There was no phlebitis in this case. Some forms of extranodal RDD are associated with an increased number of IgG4+ plasma cells, however studies have shown a low IgG4:IgG ratio (<40%).[3] No clear evidence indicates a shared pathogenesis;[3,10] however, evaluating the IgG4:IgG ratio in all RDD cases is recommended in the most recent classification of histiocytoses.[1] An occasional case of RDD rich in IgG4+ plasma cells has been associated with immune thrombocytopenia.[10]

The diagnosis of RDD in this case was challenging, reflecting the subtle nature of the Rosai–Dorfman histiocytes

Please cite this article as: van Laar Veth A et al., Isolated peri-renal extranodal Rosai–Dorfman disease rich in IgG4+ plasma cells, Pathology, https://doi.org/10.1016/j.pathol.2022.12.351

with slightly weaker S100 protein expression than that of adjacent interdigitating cells and which were obscured in a background of lymphocytes and plasma cells in a fibroblastic stroma. The findings initially prompted consideration of other differentials which included IgG4-related disease and inflammatory myofibroblastic tumour. The lower IgG4:IgG ratio and negativity in ROS-1 and ALK staining dissuaded from these diagnoses. With an optimised S100 stain, the lesional histiocytes were more clearly identifiable, allowing a diagnosis of extranodal RDD.

On subsequent haematological review, there was no systemic manifestation of the disease (nodal or in other organs). Currently it is recommended that next generation sequencing for mutations should be performed only for refractory or severe cases,[3] not applicable in this patient and thus not performed.

Extranodal RDD is uncommon in the renal hilum, and the presence of IgG4+ cells makes for a challenging differential diagnosis particularly in a setting of unilateral involvement. Extranodal RDD should be considered on imaging studies in the setting of renal hilar soft tissue density masses. In the histopathological assessment of fibroinflammatory lesions, careful attention should be given to background histiocytic cells. Optimised immunostaining with S100 protein to facilitate recognition is recommended.

Acknowledgements: Constantine Theocharous, Leon Vonthethoff, and Veli Marjoniemi (Anatomical Pathologists, St George Hospital), and Anthony Hutton (Urologist, St George Hospital).

Conflicts of interest and sources of funding: The authors state that there are no conflicts of interest to disclose.

Alexander van Laar Veth[1], Joanne Brown[1], Nicholas Chen[2], Fiona Bonar[3]

[1]Anatomical Pathology Department, SEALS Pathology, St George Hospital, Kogarah, NSW, Australia; [2]Radiology Department, St George Hospital, Kogarah, NSW, Australia; [3]Anatomical Pathology Department, Douglass Hanly Moir Pathology, Macquarie Park, NSW, Australia

Contact: Dr Alexander van Laar Veth.
E-mail: a.vanlaarveth@gmail.com

1. Emile J, Abla O, Fraitag S, *et al*. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. *Blood* 2016; 127: 2672−81.
2. Focuar E, Rosai J, Dorfman R. Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease): review of the entity. *Semin Diagn Pathol* 1990; 7: 19−73.
3. Abla O, Jacobsen E, Picarsic J, *et al*. Consensus recommendations for the diagnosis and clinical management of Rosai-Dorfman-Destombes disease. *Blood* 2018; 131: 2877−90.
4. Goyal G, Ravindran A, Young J, *et al*. Clinicopathological features, treatment approaches, and outcomes in Rosai-Dorfman disease. *Haematologica* 2020; 105: 348−57.
5. Wang C, Al-Hussain T, Serrano-Olmo J, Epstein J. Rosai-Dorfman disease of the genito-urinary tract: analysis of six cases from the testis and kidney. *Histopathol* 2014; 65: 908−16.
6. Karaosmanoğlu A, Onur M, Shirkhoda A, *et al*. Unusual benign solid neoplasms of the kidney: cross-sectional imaging findings. *Diagn Interv Radiol* 2015; 21: 376−81.
7. Gumeler E, Onur M, Karaosmanoglu A, *et al*. Computed tomography and magnetic resonance imaging of peripelvic and periureteric pathologies. *Abdom Radiol* 2017; 43: 2400−11.
8. Mar W, Yu J, Knuttinen M, *et al*. Rosai-Dorfman disease: manifestations outside of the head and neck. *Am J Roentgenol* 2017; 208: 721−32.
9. Deshpande V, Zen Y, Chan J, *et al*. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol* 2012; 25: 1181−92.
10. Razanamahery J, Humbert S, Emile J, *et al*. Immune thrombocytopenia revealing enriched IgG-4 peri-renal Rosai-Dorfman disease successfully treated with rituximab: a case report and literature review. *Front Med* 2021; 8: 678456.

DOI: https://doi.org/10.1016/j.pathol.2022.12.351

Please cite this article as: van Laar Veth A et al., Isolated peri-renal extranodal Rosai−Dorfman disease rich in IgG4+ plasma cells, Pathology, https://doi.org/10.1016/j.pathol.2022.12.351