CLINICAL VIGNETTE

Transient Kidney Injury in a Patient with Erdheim-Chester Disease

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Case Presentation

A 60-year-old woman presented to primary care clinic with renal insufficiency and poorly controlled hypertension. Ultrasound revealed bilateral renal artery stenosis and she underwent renal artery stent placement with subsequent improvement in her blood pressures and renal function. One year later she developed flank pain, acute kidney injury and uncontrolled hypertension. Computerized tomography (CT) scan revealed bilateral hydronephrosis and retroperitoneal fibrosis (Figure 1). Bilateral ureteral stents were placed and she was treated with high-dose prednisone. She subsequently developed fevers, night sweats, and diarrhea. Positron emission tomography/ computed tomography (PET/CT) demonstrated diffuse retroperitoneal and peritoneal soft tissue thickening involving thoracic vessels and the pericardium. A T11 lytic bony lesion was also noted without significant metabolic activity. Omental biopsy revealed an atypical histiocytic infiltrate, positive for Fascin, CD163 and CD68 and negative for S100, CD1a, BRAF and Langerin (Figure 2). Histopathology was consistent with Erdheim-Chester disease. Cladribine 0.14 mg/kg was initiated but discontinued after 3 of 5 doses due to worsening renal failure.

The patient was admitted to the hospital for further evaluation when her creatinine increased to 3.16 from baseline creatinine 1.5-2.0. Physical examination was significant for blood pressure elevated to 163/74 mm Hg and mild right flank tenderness. Nuclear medicine scan suggested diminished kidney perfusion and partial obstruction. Further CT imaging revealed stable dilated calyces with normal renal pelvis, concerning for bilateral sinus involvement. Surgical intervention was not recommended and her acute kidney injury resolved without intervention. However, three weeks later, she was readmitted for an elevated creatinine to 4. She remained asymptomatic and renal ultrasound revealed patent renal arteries without ureteral obstruction. Her urine electrolytes were consistent with an intrarenal process. She underwent kidney biopsy which showed nonspecific glomerulosclerosis and tubulointerstitial scarring. No specific offending agent was identified. She was discharged from the hospital after improvement in her creatinine.

However, within the next three months, she was admitted to the hospital twice for acute renal failure without improvement of her renal function. Her acute renal failure was managed with intravenous fluids and tapering of prednisone. She was started on cobimetanib and received one cycle of therapy before passing away from a cardiopulmonary arrest.

Discussion

Erdheim-Chester disease (ECD) is a rare non-Langerhans histiocytosis with only several hundred cases reported in the medical literature. Diagnosis requires identification of CD68+ and CD1a/S100- histiocytes on biopsy. Although the pathophysiology of ECD is not fully understood, it has been categorized as a clonal neoplastic disorder, often with hyperactivation of mitogen-activated protein kinase signaling and elevated inflammatory markers.[1] ECD has the highest incidence in the fifth decade of life with slight predominance in males and an average survival of 2.3 years after diagnosis.[2]

ECD is clinically diverse disorder with manifestations ranging from asymptomatic bone lesions to multiorgan involvement. Renal involvement is reported in up to 30% of patients, although many are asymptomatic.[3] Hydronephrosis and renal insufficiency, are rare and affect approximately 6%.[2] In the present case, the etiology of renal failure was likely the bilateral proximal renal artery stenosis leading to renovascular hypertension and involvement of the bilateral renal sinuses and ureters causing obstructive uropathy. In a cohort study by Villatoro-Veillar et al., renal artery involvement was frequently observed (left 27%, right 18%) with stenosis present in 16% on the left and 6% on the right.[4] The obstructive uropathy is associated with retroperitoneal fibrosis in 79% of cases and renal histiocytic infiltration in 21% of cases.[5] While most patients can be managed medically for these urological manifestations, a subset require stent placement.[6]

Renal biopsy may be helpful in identifying the etiology of kidney injury. André et al described a patient with bilateral enlarged kidneys in the setting of systemic ECD who underwent renal biopsy. Pathology was characteristic of ECD with perirenal fibrosis and perirenal infiltration by Touton-type giant cells and foamy histiocytes that were CD68+ and S100-.[7] The etiology of our patient's recurrent kidney injury, however, is unclear with biopsy revealing glomerulosclerosis and acute tubular necrosis. Her renal injury was thought to be related to renal hypoperfusion, transient obstructions or an adverse effect of cladribine.

The literature on the treatment of ECD is limited as there are no randomized controlled trials and few prospective studies. Possible treatments include high-dose corticosteroids, various cytotoxic agents, and hematopoietic stem cell transplantation. Interferon-alpha has historically emerged as the first-line treatment although with variable efficacy and high rates of adverse effects.[8] Progression of renal impairment on interferon-alpha has been reported.[9] Cladribine, a cytotoxic chemotherapy agent, is an alternative therapy that has been approved by the US Food and Drug Administration for the treatment of hairy cell leukemia. It has also been used in other lymphoid cancers and Langerhans cell histiocytosis. A retrospective study by Goyal et al. suggested that cladribine has moderate clinical efficacy in patients with ECD and can be considered in patients without the BRAF V600E mutation, as in the present patient.[10] However, the literature has not addressed the use of cladribine in patients with renal manifestations of ECD. Renal insufficiency has been described as a side effect of high doses (4-9 times the recommended dose) of cladribine.[11] Though cladribine may have accounted for our patient's renal insufficiency, she was given the recommended dose of 0.14mg/kg/day over two hours.

Renal involvement suggests a poor prognosis in patients with ECD.[5] Given the high rate of progression to end-stage renal disease and mortality from renal impairment, it will be helpful to identify additional therapeutic options in patients with renal manifestations of ECD.

Conclusion

We present the case of a 60-year-old woman with ECD and renal manifestations, highlighting the clinical, radiological and pathological findings. While there is no recommended therapy for ECD, we discuss the use of cladribine in patients with ECD and renal involvement and the need for further exploration of effective treatment options.

Figures

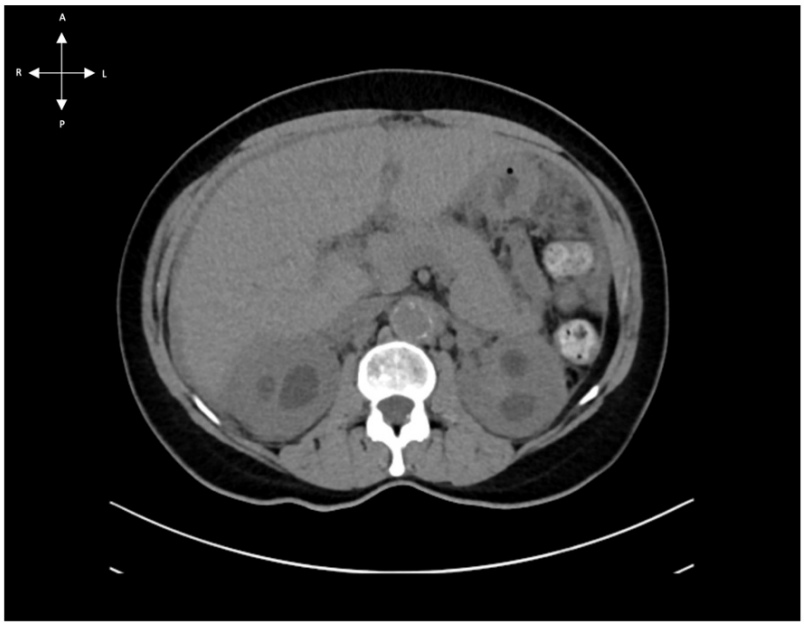

Figure 1. CT abdomen showing bilateral hydronephrosis and retroperitoneal fibrosis.

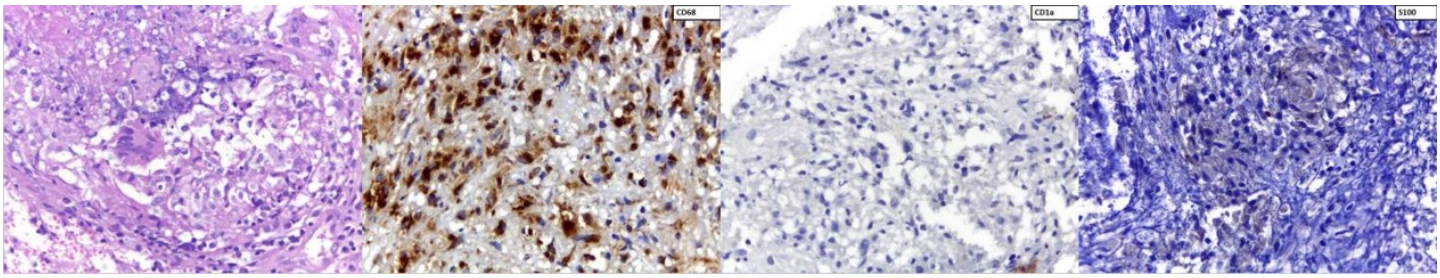

Figure 2. Representative histopathology demonstrating a) atypical histiocytic infiltrate and immunohistochemical staining b) positive for CD68 and negative for c) CD1a and d) S100.[12]

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