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Case Report

Erdheim-Chester Disease Presenting with Secondary Hypertension as a Result of Bilateral, Proximal Renal Artery Stenosis: A Case Report

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Hypertension · Renal artery stenosis

Abstract
Erdheim-Chester disease (ECD) is a rare, non-Langerhans cell histiocytosis presenting most commonly with bone and central nervous system symptoms, including but not limited to bone pain and diabetes insipidus. We present a known case of ECD, which was referred for secondary hypertension workup and diagnosed with severe, proximal, bilateral renal artery stenosis.

Background

Erdheim-Chester disease (ECD) is an extremely rare non-Langerhans cell histiocytosis. It was first described by Dr. Erdheim and Dr. Chester in 1930 [1]. The disease is characterized by infiltrations of CD68+ histiocytes in multiple organ systems. Bone and the central

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nervous system (CNS) are the most common sites of disease involvement [2]. We present a case of ECD, which was referred to nephrology for resistant hypertension and was diagnosed with bilateral, severe, proximal renal artery stenosis.

ECD has been reported in less than 500 cases in the literature, of which almost half were reported after 2012, probably due to the increase in the awareness of the disease. ECD has been reported in a wide age range (4–77 years), with a median age of 51.5 years at the time of diagnosis in patients with neurologic symptoms [3]. Despite the wide age range, most patients (71%) are diagnosed between the ages of 40 and 70 years [4]. There is also a male predominance with 60% of reported cases [4]. The detailed mechanism and pathophysiology of this condition remain a mystery. However, the basic pathology underlying this condition is the infiltration of CD68+ cells. Based on current data, it seems that a mutation in the BRAF v600 gene plays a role in pathogenesis and has been reported in 51% of patients [5]. The condition has been reported to be seen in almost all of the organ systems. However, the musculoskeletal system (namely bones) is the most common site of the disease, which is reported in 90–98% of patients [5]. The CNS seems to be the second most common site of involvement, which was reported in 25–77% of patients in different studies [2, 3, 5].

Diabetes insipidus (DI) is also an interesting finding. Approximately one fifth of the patients present DI symptoms at the beginning, which seems to be caused by the infiltration of the cells in the hypothalamus and/or the pituitary gland [4]. ECD involves the visceral organs by fibrosis, such as pulmonary fibrosis and retroperitoneal fibrosis [4]. Even though it is rare that the kidneys are directly affected by ECD, chronic kidney disease has been reported in up to 30% of patients. This is caused by either ischemic injury or hydronephrosis as a result of renal artery or ureteral compression from retroperitoneal fibrosis, respectively, which can eventually lead to end-stage kidney disease [6].

Considering the protean signs and symptoms, ECD is a challenging diagnosis. Bone X-rays present characteristic findings including symmetrical diaphyseal osteosclerosis [4]. If the constellation of symptoms raises suspicion for the diagnosis, a biopsy is required to confirm the diagnosis. The biopsy would show foamy CD68+ histiocytes. The biopsy can also differentiate between Langerhans histiocytosis and ECD since these cells will be S-100 and CD-1a negative in patients with ECD [2].

There is no definite treatment for ECD. However, interferon (IFN) alpha is the first line of treatment, followed by options like recombinant human interleukin-1 receptor antagonist, cladribine, tyrosine kinase inhibitors, and autologous hematopoietic stem cell transplantation. These alternatives have been tested with various degrees of success. It has been found that the treatment with IFN alpha leads to improved survival in patients with ECD [2]. The discovery of a possible correlation between the BRAF mutation and ECD has raised hope for a future therapeutic approach [7]. In 1 case, a 1-year treatment with an interleukin 1 receptor antagonist in a patient with chronic kidney disease caused by bilateral hydronephrosis led to an improvement in kidney function and a decrease in creatinine from 3.9 to 2.0 mg/dL [6].

Case Report

Our patient was a 32-year-old white female with ECD who was referred to nephrology for a secondary hypertension workup. Her symptoms initially began at the age of 27 years with a 2-week period of a fever of unknown origin, chills, night sweats, and fatigue. Meanwhile, she was suffering from polyuria, polydipsia, and nocturia. Her mother had a history of melanoma, and the patient was a social drinker and former smoker. She had an extensive workup for infectious disease such as CMV and autoimmune disorders without a definite diagnosis (Table 1).

As part of her workup, she had an abdominal CT scan, which demonstrated lytic bony lesions in her right femur, neck, and ribs, including a subacute fracture in her right 10th rib. The scan also revealed mild splenomegaly. The patient did not have any bone pain. She was referred to hematology-oncology because of her lytic bone lesions and workup for multiple myeloma. Subsequent imaging showed multiple bony lytic lesions in her humerus, radius, and iliac bones. A biopsy from her iliac bone showed non-Langerhans CD 68+ histiocytosis compatible with ECD.

Her DI was thought to be the result of pituitary involvement, which was also seen in her brain imaging. In the course of her disease, because of an extensive lytic lesion in the right hip bone, she underwent hip stabilization surgery. She also received DDAVP along with radiation therapy to the pituitary stalk and was treated with systemic chemotherapy (cladribine, IFN alpha, and hydrocortisone). She later developed hypothyroidism and adrenal insufficiency secondary to intracranial radiation therapy and pituitary dysfunction.

Five years after the diagnosis, she developed resistant hypertension and was referred to nephrology. Her blood pressures were constantly over 180/120 mm Hg despite treatment with lisinopril 20 mg per day. In the primary workup, her plasma aldosterone and renin activity levels as well as electrolytes were within normal limits (summarized in Table 1 and Table 2). A renal Doppler ultrasound showed no evidence of significant stenosis. Because of high clinical suspicion, magnetic resonance angiography (MRA) of the renal artery was obtained and demonstrated severe, bilateral, proximal renal artery stenosis as shown in Figure 1 and Figure 2. The patient was referred for an angioplasty where the procedure led to a significant decline in blood pressure.

Discussion

ECD is an extremely rare condition with protean manifestations. The most common manifestations are lytic bone lesions, seen in more than 90% of the patients, followed by CNS involvement [3, 8, 9]. DI secondary to posterior pituitary infiltration by CD68+ cells is also a common presentation [3]. Even though our patient primarily presented with nonspecific symptoms such as fevers, chills, and night sweats, she had a history of polyuria and polydipsia. Her bone involvement, including her iliac, femur, and rib, was an incidental finding on her CT scan for which she did not have any complaints. Recently, some studies have proposed a multi-modality imaging method for the diagnosis of ECD [10]. However, biopsy remains the gold standard method for diagnosis [3, 9]. Hypertension is not a common finding in ECD and has not been reported in the past [3, 4, 9–11]. Our patient presented with re-

sistant hypertension and was also evaluated for secondary hypertension. The Doppler ultrasound failed to show bilateral, severe, proximal renal artery stenosis that was later discovered in the renal artery magnetic resonance angiography. This is an extremely rare finding, reported only in a couple of cases in the literature [12]. Angioplasty and stenting were successful in controlling the patient's blood pressure, with a postprocedure blood pressure of 110/80 mm Hg.

The recent discovery of the correlation between the BRAF mutation and ECD has raised hopes in finding a targeted treatment [5, 7]. However, the efforts made so far have not been successful and options like recombinant human interleukin-1 receptor antagonist, cladribine, tyrosine kinase inhibitors, and autologous hematopoietic stem cell transplantation remain the standard of care. Our patient received treatment with IFN alpha, cladribine, and systemic corticosteroids. In addition, she received treatment with DDAVP and intracranial radiation for her DI symptoms.

Conclusion

Only several hundred cases of ECD have been reported in the literature since it was first described in 1930. Even though ECD does not commonly involve the kidneys, the possibility of kidney disease should always be considered. Moreover, hypertension is not reported to be a part of the clinical picture in ECD, and if present, the possibility of renal artery stenosis must be ruled out. We propose magnetic resonance angiogram as the modality of choice to evaluate the vasculature in these patients because Doppler ultrasound is not sensitive enough to detect stenosis, particularly in the more proximal part of the renal arteries.

Statement of Ethics

As a deidentified case report which did not involve clinical investigation, this report did not require institutional review board review.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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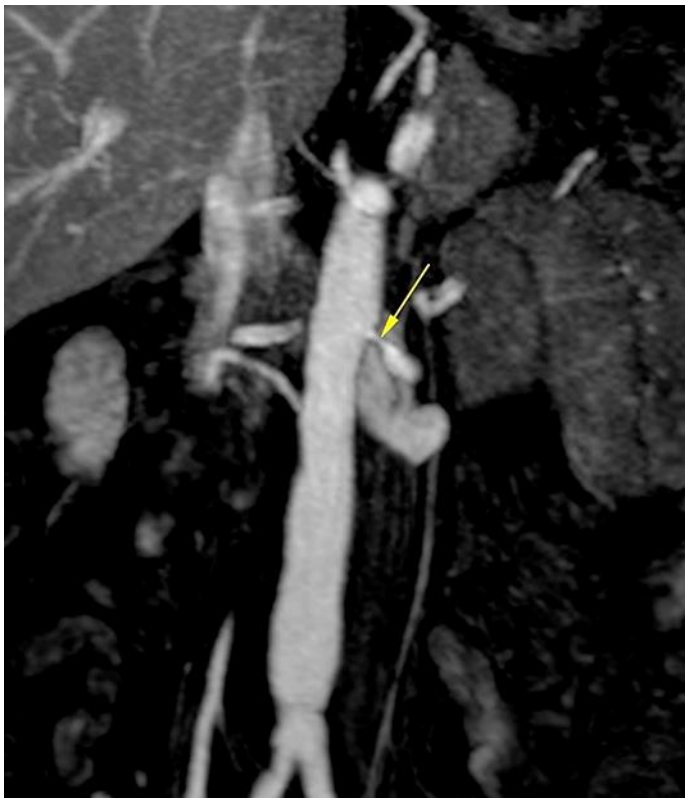

Fig. 1. Bilateral severe renal artery stenosis (incidental finding: duplicate right renal arteries, which are both stenotic).

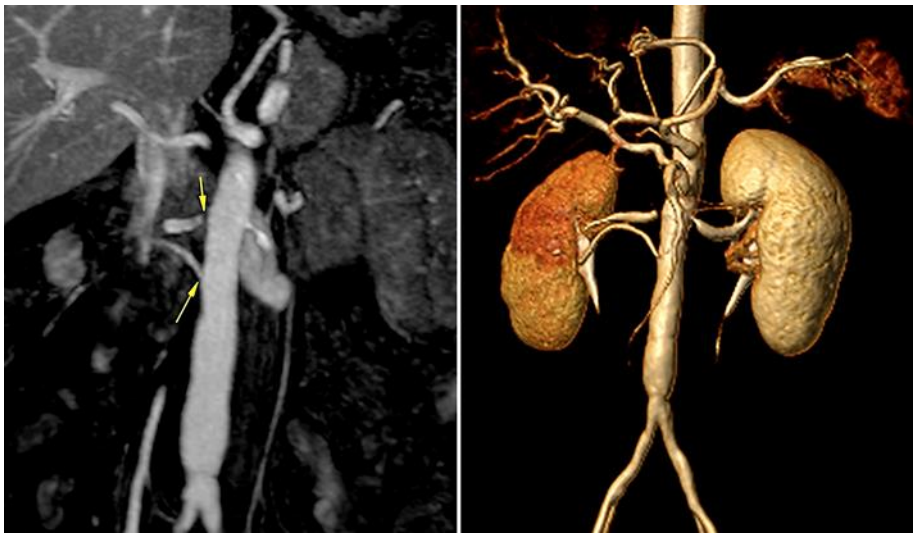

Fig. 2. Erdheim-Chester disease presenting with secondary hypertension.

Table 1. Basic metabolic panel

Sodium, mmol/L	136
Potassium, mmol/L	4.4
Chloride, mmol/L	95
HCO_3, mmol/L	26
Creatinine, mg/dL	0.8
GFR, mL/min/1.73 m^2	84
Calcium, mg/dL	9.4

Table 2. Secondary hypertension workup

Cortisol (8 a.m.), μg/dL	25 (4–25)*
ACTH, pg/ml	31 (4–48)
Plasma renin activity, ng/mL/h	2.12 (0.25–5.82)
Serum aldosterone, ng/dL	5 (<28)
Serum norepinephrine, pg/mL	175 (112–750)
Serum epinephrine, pg/mL	<20 (0–50)
Serum dopamine, pg/mL	<25 (0–29)
Serum norepinephrine, μg/24 h	21 (15–80)
Urine epinephrine, μg/24 h	<3.7 (<21)
Urine dopamine, μg/24 h	<36.9 (65–400)

* Values in parentheses show the normal range.