Letter to Editor

Hypereosinophilic Syndrome Induced Cystitis Mimicking Bladder Tumor

Dear Editor,

Hypereosinophilic syndrome (HES) is a rare disorder characterized by overproduction of eosinophils in the bone marrow and persistent peripheral eosinophilia with organ damage due to the release of eosinophilic mediators. HES can affect multiple systems including heart, skin, lungs, gastrointestinal system, kidney, blood, and central nervous system. Bladder involvement in HES is extremely rare. Here, we describe a case of 56-year old previously healthy woman presented with 1 month history of a pruritic ulcerated rash in both lower extremities associated with dysuria and exertional shortness of breath. On presentation, the patient was hypotensive with a systolic blood pressure of 56 mmHg. Temperature was 36.5°C. Physical exam disclosed a displaced point of maximal impulse, an audible 3/6 diastolic murmur and noticeable macular ulcerated rash in both legs [Figure 1a]. Initial labs showed white blood cells count 15 × 10^3 cells/mm^3 (reference range 4.5-11.0), remarkable eosinophilia 88% (reference range 0.0-6.6%) and elevated troponin T at 0.8. Peripheral blood smear showed dominance of eosinophils [Figure 1b]. The patient denied any recent travel outside the United States or recent use of new medications. Serum human immunodeficiency virus, thyroid stimulating hormone, P-antibodies to neutrophil cytoplasmic antigens (P-ANCA), C-ANCA, serum tryptase, serologies for toxocara and stronglyoides and stool study for Ova and Parasites all were negative. Biochemical profile revealed normal kidney and liver function tests. Urine analysis showed 6-10 red blood cells without red blood cell casts. Echocardiography demonstrated impaired left ventricular systolic function with ejection fraction of 45%. Despite broad spectrum antibiotic coverage for presumed sepsis, intravenous fluids and all the initial resuscitative measures, the patient remained critically ill. Two days later, she developed gross hematuria, poor urine output and acute renal failure (obstructive nephropathy due to a blood clot). Bedside bladder scan revealed more than 600 ml urine retention. A urinary catheter was inserted. Computed tomography (CT) abdomen and pelvis showed 5 cm × 4 cm mass at the dome of the bladder with marked bladder wall thickening [Figure 2a]. Cystoscopy revealed a solid mass lesion invading the bladder wall and the entire mucosa appeared hemorrhagic and congested. Biopsy showed infiltration of abundant eosinophils from the submucosa to the muscular layer [Figure 2b]. Bone marrow aspiration revealed marked eosinophilia but no primitive cell predominance. Further evaluation of the eosinophilia included FIP1-like 1/platelet-derived growth factor receptor alfa (FIP1 L1-PDGFRA) fusion gene test and it was negative. Based on the above work up, the diagnosis of HES with cutaneous, cardiac, and bladder involvement was made. The patient was started on prednisone 1 mg/kg/day and hydroxyurea. One week later, the patient made an excellent recovery and his symptoms started to fade away. Eosinophilia on peripheral blood dramatically reduced to 10%. He was discharged with steroid slow tapering regimen. To date, there is no evidence of any other organ involvement.

HES is a rare disorder and defined by three diagnostic criteria: persistent eosinophilia > 1.5 × 10^9/L, organ damage or dysfunction and exclusion of secondary causes of eosinophilia such as parasitic infection or allergic reactions.[1] HES is divided into 6 variants: myeloproliferative, lymphocytic, familial, idiopathic, overlap (blood eosinophilia ≥ 1500/mm^3 in the setting of a single organ involvement), and associated (blood eosinophilia ≥ 1500/mm^3 in association with a distinct second diagnosis, such as inflammatory bowel disease or autoimmune lymphoproliferative disorder, in which

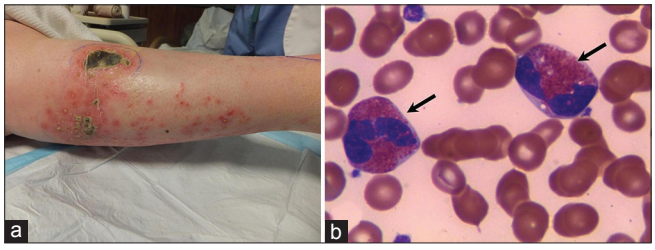

Figure 1: (a) Cutaneous macular ulcerated rash. (b) Peripheral blood smears demonstrating eosinophils (Wright-Giemsa, ×500)

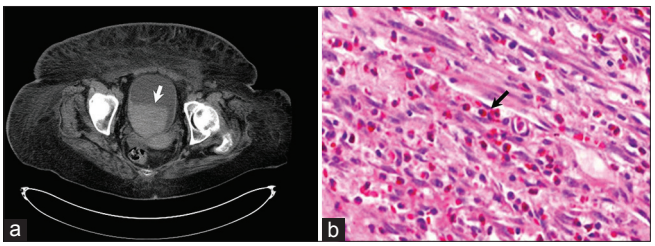

Figure 2: (a) Computed tomography of the pelvis shows focal mass of the bladder mimicking pseudotumor and locally thickened right bladder wall. (b) Bladder mucosa with inflammatory infiltrates composed predominantly of eosinophils in lamina propria

eosinophilia has been reported with increased frequency but rarely leads to end organ manifestations).[1] HES is seen in young to middle age patients and there is a male predominance, with a male-to-female ratio of 9:1. Skin is among the most common organ system involved in HES with more than half of all patients have cutaneous involvement and it can be the only manifestation of HES.[2] Skin eruptions can be angioedematous/urticarial and associated with a benign prognosis or erythematopapular/nodular, with or without ulceration.[2] The heart is commonly involved in HES and result in endomyocardial fibrosis, valvular disease, mural thrombus formation, cardiomegaly, and pericardial effusion. Furthermore, thromboembolic complications resulting from cardiac involvement can lead to distal embolization and multisystem disease.[3]

Eosinophilic cystitis, a rare condition can be associated with allergic and autoimmune diseases such as lupus. It is also believed to be associated with injury; medications (e.g., methicillin, warfarin, anthranilic acid, intravesical mitomycin, and thiotepa); bacterial, viral, and parasitic infections; reactions to food (e.g., vegetables, spices, and chocolate) and systemic peripheral eosinophilia, such as in idiopathic HES.[4] Urinary bladder involvement in HES is very rare. Previous German literature has reported one combination of HES and cystitis.[5] Hypereosinophilic cystitis is characterized by infiltration of the bladder wall with eosinophils. Interleukin 5 (IL-5) plays a significant role in the terminal differentiation, maturation, activation, and stimulation of eosinophils. Eosinohils can also release significant amounts of IL-5. This pathophysiologic cycle can play a significant role in the toxic injury of eosinophils to the bladder tissues resulting in gross hematuria, marked irritation of the lower urinary tract causing dysuria and frequency.[6] CT scan of the abdomen may show a bladder mass if present but cystoscopy with biopsy is the main diagnostic measurement. Thickening of the bladder wall with erythematous edema are the main finding on cystoscopy and may resemble an invasive tumor (pseudotumor), which is commonly mistaken with bladder cancer.[7]

Churg-Strauss syndrome (CSS), or allergic granulomatous angiitis, is a rare vasculitic syndrome can be in the differential diagnosis of HES. It affects medium-and small-sized vessels and is associated with ANCAs. However, the presence of 4 or more criteria out of 6 yields a sensitivity of 85% and a specificity of 99.7%. These criteria include (1) asthma, (2) eosinophilia of more than 10% in peripheral blood, (3) paranasal sinusitis, (4) pulmonary infiltrates, (5) histological proof of vasculitis with extravascular eosinophils, and (6) mononeuritis multiplex or polyneuropathy.[8] Our patient did not meet the criteria to diagnose CSS and his ANCAs antibodies were negative.

There are no recommended treatments for asymptomatic patients with HES as treatment itself is not without risks. Such patients are closely assessed every 3-6 months. In contrast, cases of HES with myeloproliferative features, particularly those with FIP1 L1/PDGFRA mutation, should be treated aggressively, as they carry worse prognosis without treatment. Glucocorticoids are the first-line therapy in all patients without FIP1 L1/PDGFRA mutation; however, about one third of patients do not respond to steroids. In such patients, interferon alpha and hydroxyurea are the second-line drug of choice.[9] For patients with FIP1 L1/PDGFRA mutation, imatinib is the drug of choice with a very good response that approaches 100% in various studies. Supportive management with analgesic and inflammatory drugs in addition to using corticosteroids seem to be a reasonable treatment option for patients with bladder involvement. Patients who have a disease intractable to conservative treatments or presenting with profuse hematuria, contracted bladder, distal ureteral involvement together with renal failure could be considered for partial or total cystectomy, and diversion.[10] In our patient, remission of the disease, multi-organ involvement and the eosinophilia was achieved successfully with steroids and hydroxyurea.

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