Coincidence of Idiopathic Hypereosinophilic Syndrome in End Stage Renal Disease Patients Subjected to Maintenance Hemodialysis

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Abstract

Hypereosinophilic syndrome (HES) is defined as the presence of: 1- peripheral blood eosinophilia >1.5 x 10^9/L for at least one months, 2- evidence of eosinophil-mediated organ damage and/or dysfunction, and 3- exclusion of other potential causes for eosinophilia. In hemodialysis patients, hypereosinophilic syndrome has been associated with hemodialysis intolerance because of intradialytic hypotension or digestive symptoms. However, there have been few case reports of idiopathic hypereosinophilic syndrome in patients undergoing hemodialysis, and its clinical features remain unclear. Here we report 2 cases of idiopathic hyper eosinophilic syndrome in patients undergoing hemodialysis. The first patient presented with unexplained persistent pruritis and intradialytic hypotension, which started 10 minutes after dialysis session initiation. Hematologic studies revealed hypereosinophilia which remarkably improved on steroids therapy. The second patient was accidentally discovered with asymptomatic persistent hypereosinophilia. His blood counts improved initially on interferon treatment before achieving full remission on steroid therapy.

Neither of the two patients did report any past history of allergy nor atopic manifestations. Our case series shed the light on the possible occurrence of HES in hemodialysis patients which may confuse with other dialysis related complications. Although steroids remain the mainstay of treatment, the optimal dose and duration of treatment is still unknown.

Categories: Nephrology, Hematology
Keywords: hypersensitive reaction, peripheral eosinophilia, systemic steroids, hyper-eosinophilic syndrome, hd (hemodialysis)

Introduction

The term Hypereosinophilia (HE) was first introduced 50 years ago by Hardy and Anderson to describe three cases with marked eosinophilia associated with cardiopulmonary involvement. Since then, the definition of HE has evolved with the introduction of modern molecular diagnostic techniques and the invent of effective therapeutic modalities [1].

Hypereosinophilia (HE) is defined as an absolute eosinophil count (AEC) >1.5 x 10^9/L in the peripheral blood on two occasions separated in time by at least one month (instead of 6 months as previously defined by Chusid et al. [2]) and/or pathologic confirmation of tissue HE [1]. Hypereosinophilic syndrome (HES) was defined by as the presence of: 1- peripheral blood eosinophilia >1.5 x 10^9/L for at least one months, 2- evidence of eosinophil-mediated organ damage and/or dysfunction, and 3- exclusion of other potential causes for eosinophilia. Damage to multiple organs, including the lungs, heart, skin, nervous system, and gastrointestinal tract can be irreversible up to death; therefore, urgent assessment and management are necessary [1, 2].

Symptoms and signs of hypereosinophilic syndrome are highly variable depending on the affected organs. Skin affection was reported in 37% of cases in the form of eczema, erythroderma, generalized thickening of the skin (lichenification), dermatographism, recurrent urticaria, and angioedema [3]. Pulmonary manifestations (cough and breathlessness) were seen in 25% of cases, while gastrointestinal manifestations (weight loss, abdominal pain, vomiting, and/or severe diarrhea) in 14% in the form of eosinophilic gastritis, enteritis, and/or colitis [4]. Hepatic involvement may take the form of chronic active hepatitis, focal hepatic lesions, eosinophilic cholangitis, or the Budd-Chiari syndrome. In 4% of cases, cardiac manifestations develop due to eosinophilic myocarditis which is the major cause of morbidity and mortality among patients with hypereosinophilic syndrome (HES) [4, 5]. Neurologic disease in HES is rare (5%) and presents as cerebral thromboembolism, encephalopathy, peripheral neuropathy, or longitudinal and/or transverse sinus thrombosis. Six percent of the patients present with incidentally detected and clinically asymptomatic hypereosinophilia (HE).
In hemodialysis patients, hypereosinophilic syndrome has been associated with hemodialysis intolerance because of intradialytic hypotension or digestive symptoms. However, there have been few case reports of idiopathic hypereosinophilic syndrome in patients undergoing hemodialysis, and its clinical features remain unclear. [6] Here we report 2 cases of idiopathic hyper eosinophilic syndrome in patients undergoing hemodialysis.

Case Presentation

Case 1: A 36-year-old male patient diagnosed with end stage renal disease (ESRD) in 2014 had a living donor renal transplantation in 2015. In 2019, he suffered from acute antibody mediated rejection ending in kidney failure. He was kept on maintenance hemodialysis (3 sessions / week) since January 2020, till now through arteriovenous graft (AVG) using a polysulphone (PSF) membrane. Regarding his past medical history, he suffered from HTN, hereditary thrombophilia, repeated chest infections and he reported family history of acute leukemia (father). Patient’s drug history included apixaban 2.5 mg twice daily, amlodipine/valsartan, clopidogrel 75mg, isopoten 240mg, erythropoietin, and calcium supplements (Table.1).

The condition started in March 2022 with unexplained persistent pruritis not associated with any skin rash. Also, he manifested intradialytic hypotension and vomiting, which started 10 minutes after dialysis session initiation. There was no diarrhea nor abdominal pain. He also denied any history of cough, dyspnea, rhinosinusitis, allergic asthma or any similar symptoms. On examination, there was no skin rash, lymphadenopathy, nor organomegaly. Abdominal examination revealed mild hepatomegaly. Extremities showed no lower limb swelling or clinical signs of deep vein thrombosis (DVT).

His initial work up was ordered, and his blood film revealed hemoglobin 12.5 g/dl (MCV: 89, MCH: 27), platelet: 234 x 10^9/L, WBC: 19 x 10^9/L with absolute eosinophilia (15 x 10^9/L) that was persistent for three months (Fig.1), and CRP as high as 69 mg/l. Stool analysis and serum IgE level were tested normal. Abdominal ultrasonography revealed hepatomegaly (16 cm in span) without splenomegaly. Echocardiography showed hypertensive cardiomyopathy with preserved systolic function. None of his medications was initiated through the last 3 months, and he had no history of drug or food allergy. Bone marrow examination showed moderately hypercellular bone marrow (40% cellularity) with increased in eosinophilic series mainly in the degranulated form (14%) (Fig.1). Genetic analysis for gene mutation of platelet growth factor (PDGF) alpha, beta and fibroblast growth factor receptor 1 (FGFR1) were not done due to financial issues.

Based on these findings, the patient was diagnosed with idiopathic hypereosinophilic syndrome, with involvement of the digestive tract and heart. Therefore, oral prednisolone was started at a dose of 40mg (0.5mg/kg) without change in type of dialyzer. Follow up reassessment after four weeks, there were mild improvement both clinically and laboratory. His follow up CBC showed Hb: 11.5mg/dl (MCV: 82, MCH: 26), Platelets: 204 x 10^9/L, WBC: 9 x 10^9/L with decrease in the absolute eosinophilic count to 5.7 x 10^9L (Fig.2). A significant improvement of the gastrointestinal and pruritic symptoms was reported by the patient. Also, dialysis sessions became more tolerable after the disappearance of the dialysis-associated hypotension and vomiting. After a month, white blood and eosinophilic counts kept declining. The patient’s general condition has remarkably improved since then and he was kept on gradual steroid tapering to reach a maintenance dose of 10 mg daily.

Case 2: A 63-year-old male patient diagnosed with end stage renal disease (ESRD) was kept on maintenance hemodialysis since October 2015. He started dialysis with a frequency of 3 sessions/week, which increased to 4 sessions/week on 2018 after the patient suffered an acute coronary syndrome and reduced ejection fraction (EF 24%) which required coronary artery bypass graft (CABG). Dialysis was performed through a permanent catheter, using PSF dialyzer membrane. Regarding past medical history, he reported long-standing diabetes mellitus and hypertension. His drug history included aspirin 100mg/d, pantoprazole 20mg/d, atorvastatin 20mg, bisoprolol 2.5 mg/d, ticagrelor 180mg/d, (Table.1).
<table>
<thead>
<tr>
<th></th>
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<th>Case 2</th>
<th>Reference</th>
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<td></td>
</tr>
<tr>
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<td>Digestive, skin and hypotension</td>
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</tr>
<tr>
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<td>4h</td>
<td></td>
</tr>
<tr>
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<tr>
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</tr>
<tr>
<td>Blood flow</td>
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<td>500</td>
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<tr>
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<td>22000</td>
<td>4000-11000</td>
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<td>17000 (77%)</td>
<td>0-500 (0-7%)</td>
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<tr>
<td>Treatment</td>
<td>Prednisolone PO 40 mg OD</td>
<td>Pegylated interferon alpha 90 mg, s.c. weekly for a month, then Prednisolone 20 mg PO daily</td>
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**TABLE 1: Clinical and hematologic data for the reported cases.**

In February 2022, leukocytosis was incidentally discovered during his routine CBC follow-up (TLC: 22x 10^9/L, AEC: 17 x 10^9/L) (Fig.1). At this time the patient was clinically asymptomatic, with no reported pruritis, urticaria, rhinosinusitis, allergic asthma, intradialytic hypotension nor gastrointestinal complaints. The sepsis work-up was done and found negative. His blood film revealed normocytic normochromic anemia (Hb: 10 gm/dl), normal platelet count (371 x 10^9/L), leukocytosis (TLC 18 x 10^9/L) with absolute eosinophilia (AEC: 13 x10^9/L, 69% of TLC). Stool analysis was found normal. Serum IgE level 2271 IU/ml (normal up to 100).

On examination, there were no pallor, skin lesions nor lymphadenopathy. Abdominal examination confirmed by ultrasonography revealed no hepatosplenomegaly. Extremities showed no lower limb swelling nor clinical DVT. By thoraco-abdominal computed tomography, there were no abnormalities detected in the lung fields. On electrocardiography and echocardiography there were no abnormalities, except for those caused by the previous myocardial infarction. Bone marrow aspirate and trephine biopsy revealed hypercellular bone marrow, normal megakaryopoiisis, granulocytic hyperplasia with marked increase in the eosinophilic series, normal neutrophilic series, erythroid hyperplasia with no increased in the blast count and no lymphoid infiltration (Fig.1). JAK2 (V617F) mutation by PCR was negative. FISH for FIP1L1- PDGF alpha fusion gene was negative as well.
Accordingly, he was diagnosed with idiopathic hyperesinophilic syndrome. However, due to concerns about corticosteroids’ exaggeration of his previously existing renal osteodystrophy, diabetes mellitus, and hypertension, a second line of treatment was initiated in the form of pegylated interferon alpha (90 mg subcutaneously post dialysis once weekly for 3 weeks). Follow-up CBC after 4 weeks of treatment showed partial decrease in the TLC 19.9 x 10^9/L with absolute eosinophilic count 13 x 10^9/L. The patient was kept on interferon treatment until he started to suffer from severe anorexia and weight loss (7 Kg in one month). As a result, interferon was stopped, and the patient was shifted to low dose prednisolone 20 mg/day. One month later, his follow up CBC showed marvelous improvement regarding TLC and eosinophil counts, and both dropped to normal by the third month of treatment (Fig.2). Eventually, steroids were gradually tapered, and the patient was maintained on low dose oral prednisolone (5 mg per day).

**FIGURE 1: Diagnostic peripheral blood and bone marrow morphology for the reported cases.**

Case 1 (a-c) and Case 2 (d-f) peripheral blood eosinophils (red arrows)(a,d), bone marrow aspirates (b,e) and bone marrow trephine (c,f) histopathologic morphology.

**FIGURE 2: Blood cells count trends after treatment initiation.**

Case 1 (a) and Case 2 (b) peripheral blood total leukocytic count (TLC) and absolute eosinophil count (AEC) trends after the start of treatment.

**Discussion**

Hemodialysis is considered the most common treatment modality for end stage renal disease (ESRD) worldwide. Despite the great advances in hemodialysis machines and dialyzers, hypersensitivity reactions are still inevitable. Hemodialysis associated hypersensitivity reactions was and is still the big challenge to all dialyzers manufactures. Although dialyzers have been used since 1950, yet trials to improve its efficacy together with increasing its biocompatibility never stopped over the decades. Although recent technologies had greatly decreased the incidence of such reactions, they are being frequently reported in clinical practice.

Symptoms such as intradialytic hypotension, abdominal cramps, itching and chest tightness should not be
overlooked by physicians or regarded as a usual intolerance to dialysis, especially if they occur during the early minutes of dialysis initiation. Nevertheless, asymptomatic eosinophilia can be the only sign of hypereosinophilic syndrome.

Dialyzer membrane materials have been the principal cause of hemodialysis associated hypersensitivity reactions [6, 7]. Non-synthetic membranes derived from natural materials are less biocompatible than synthetic membranes. Biocompatibility can be improved by substituting hydroxyl groups with other polymers to reduce complement activation and hence more biocompatibility. Although PSF may be the primary polymer, it is blended with other polymers to give each membrane its specific characteristics. Polymers that have been added include acetate, diethylaminoethyl (DEAE), benzyl, polyethyleneglycolic, and vitamin E. The resultant membranes are referred to as modified cellulose membranes [8]. Examples include but not limited to, polysulphone (PES) a blend of hydrophobic base polymers with good biocompatibility and less albumin loss, cellulose triacetate (CTA) with increased solute permeability especially for beta-2 microglobulin, polymethylmethacrylate (PMMA) with increased adsorption properties to enhance removal of some inflammatory molecules, PES plus polarylare (PEPA) with enhanced endotoxin protection, ethylene vinyl alcohol copolymers (EVAL) with low inflammatory impact, and polycrystonitrile (PAN) with good biocompatibility and enhanced fluid removal due to hydrophilic properties. Polysulphone based dialyzers are widely used as they provide low complement activation, good biocompatibility, optimal solute removal and low thrombosis reactions. Lately, a new model of PSF-based dialyzer with advanced helixone membrane named FX-class was launched, that was used for the three cases mentioned above [8].

Idiopathic Hyper-Eosinophilic Syndrome is a systemic disease during which the eosinophil count increases in the peripheral circulation, which results in multiple-organ damage. It is diagnosed by the identification of hypereosinophilia (persistently increased eosinophil count > 1500/mL for more than a month), multiple organ involvement (2 or more organs), and the exclusion of secondary causes of eosinophilia, including malignancy, eosinophilic leukemia, eosinophilic granulomatosis with polyangiitis, parasite infection, and drug reaction.

In the present cases (Table 1), the patients presented with hypereosinophilia and multiple-organ involvement (intra-dialytic hypotension, digestive symptoms, and allergic dermatitis). Any specific cause for the hypereosinophilia was not identified using systemic computed tomography, electrocardiography, echocardiography, bone marrow examination, or blood tests. Therefore, these 2 patients were diagnosed with idiopathic hypereosinophilic syndrome. In the first case patient had intradialytic hypotension and GIT symptoms. Intradialytic hypotension has previously been reported in hemodialysis patients with hypereosinophilic syndrome. This is the result of the large number of eosinophils being activated by contact with the dialyzer membrane, leading to degranulation and the release of various cytokines, which increase vascular permeability and dilate capillaries [9, 10]. Major basic protein is also released by the eosinophils, and this is cytotoxic and induces tissue damage, including the heart [11]. On the other hand, the second patient was asymptomatic and eosinophilia was incidentally discovered. Asymptomatic hypereosinophilia was reported in about 6% of cases of HES.

Early intervention is important to slow the progression of HES and hence improves our patient’s quality of life and tolerance to dialysis. Corticosteroid is recommended as the first-line therapy for hypereosinophilic syndrome [12]. A previous study showed that approximately 80% of patients with hypereosinophilic syndrome had a favorable outcome following this treatment, but delayed intervention could lead to irreversible organ damage, disability, or death [13].

Conclusions
In conclusion, hemodialysis can be associated with idiopathic hypereosinophilia which confuses with other dialysis related complications including hypersensitivity reactions. Here, we report two patients who developed manifestations of idiopathic hypereosinophilia during their dialysis sessions. While corticosteroids remain the main treatment modality in this patient category, which led to a remarkable symptom improvement and blood count normalization, further studies are still required to determine the most appropriate corticosteroid dose and duration of treatment.

Additional Information
Disclosures
Human subjects: Consent was obtained or waived by all participants in this study. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References