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CASE REPORT

Idiopathic Hypereosinophilic Syndrome in a Patient with End-Stage Renal Disease

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SUMMARY

Background: **Idiopathic hypereosinophilic syndrome (IHES) occurring concurrently with end-stage renal disease (ESRD) is rarely reported, and its diagnosis and management present notable challenges.**
Methods: **This case report describes a 79-year-old male with ESRD, undergoing maintenance hemodialysis for two years, who presented with persistent pruritus, interstitial pneumonia, and decreased muscle strength. Laboratory investigations revealed sustained eosinophilia (4.39 x 10^9/L).**
Results: **Following the exclusion of secondary causes such as infections and malignancies, a diagnosis of IHES was established. A treatment course consisting of low-dose prednisone (0.3 mg/kg/day) for five days led to a 71.2% reduction in eosinophil count ($p < 0.01$) and a 62.5% decrease in pruritus score ($p < 0.05$). Complete remission was attained within one month of initiating therapy.**
Conclusions: **This case underscores the importance of multidisciplinary management in patients with ESRD complicated by IHES and indicates that low-dose glucocorticoids may serve as a safe and effective first-line treatment option.**
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KEYWORDS

end-stage renal disease, glucocorticoids, hemodialysis, idiopathic hypereosinophilic syndrome

INTRODUCTION

Idiopathic hypereosinophilic syndrome (IHES) is an uncommon condition characterized by persistent peripheral blood eosinophilia (≥ 1.5 x 10^9/L) accompanied by multi-organ involvement. The underlying pathophysiology has been associated with T helper 2 (Th2)-mediated immune dysregulation, cytokine-induced eosinophil activation - particularly through interleukin-5 (IL-5) and interleukin-33 (IL-33), and the release of cytotoxic granules [1]. Evidence has indicated that eosinophils contribute not only to allergic disorders and parasitic infections but also to direct extracellular matrix degradation via cathepsin L secretion, potentially resulting in organ damage such as emphysema [2]. Addition-

ally, eosinophils may influence tumor progression by modulating the immune microenvironment [3]. Despite these findings, comprehensive investigations into the clinical characteristics and therapeutic strategies for IHES in the context of end-stage renal disease (ESRD) remain limited.

Patients with ESRD may exhibit enhanced eosinophil proliferation due to factors such as uremic toxin accumulation, a persistent microinflammatory state, and dialysis-associated immune alterations. Elevated serum IL-5 concentrations have been observed in this population, potentially influenced by the biocompatibility of dialysis membranes. Moreover, certain uremic toxins, including indoxyl sulfate, have been demonstrated to impair regulatory T cell (Treg) function and contribute to imbalances in Th2 and T helper 17 (Th17) immune responses. Although eosinophilia has been reported in approximately 5% to 10% of patients undergoing dialysis for ESRD, progression to IHES - defined by strict diagnostic criteria - remains exceedingly rare. The 2022 International Consensus by the International Consortium on Eosinophilic Diseases (ICON-EoE) emphasized the necessity of excluding both clonal and secondary causes to confirm an IHES diagnosis. In patients with ESRD, differential diagnosis is particularly challenging due to the presence of multiple coexisting conditions [1].

Glucocorticoids remain the first-line treatment for IHES; however, patients with ESRD may experience altered pharmacokinetics, including impaired drug clearance and changes in protein binding. Consequently, the traditionally recommended dosage (prednisone 0.5 - 1 mg/kg/day) carries an increased risk of adverse effects such as severe infections and metabolic disturbances. Emerging evidence has indicated that low-dose glucocorticoids (≤ 0.3 mg/kg/day), when administered in combination with high-flux dialysis, may offer a safer therapeutic approach by facilitating the removal of unbound drug and mitigating toxicity.

The present case report describes an older adult diagnosed with ESRD who subsequently developed IHES. This case is notable for several reasons: 1) it systematically documents the multi-organ manifestations of IHES in the context of ESRD, including involvement of the skin, lungs, and musculature; 2) it demonstrates a strong correlation between eosinophil count and pruritus severity ($r = 0.82$); 3) it involved rapid hematologic remission - characterized by a 71.2% reduction in eosinophil percentage within 5 days through an innovative combination of low-dose prednisone (0.3 mg/kg/day) and high-flux dialysis without infectious complications; and 4) it employed a multidisciplinary diagnostic approach to exclude dialyzer hypersensitivity, parasitic infections, and clonal hematologic disorders. These findings provide valuable insight into the individualized diagnosis and management of IHES in patients with ESRD.

CASE PRESENTATION

History and examination

A 79-year-old male was admitted to the hospital on November 28, 2024, due to a 15-year history of intermittent bilateral lower extremity edema and elevated serum creatinine levels persisting for approximately two and a half years. Medical history indicated a diagnosis of stage II membranous nephropathy with ischemic kidney injury, confirmed by renal biopsy 15 years prior. Progression to ESRD was noted two years before admission, at which point maintenance hemodialysis was initiated (three sessions per week), corresponding to an estimated glomerular filtration rate (eGFR) of 8 mL/minute/1.73 m^2. At the time of admission, the primary presenting symptoms included bilateral lower limb weakness necessitating wheelchair use, persistent pruritus (visual analogue scale [VAS] score of 8), and production of white, viscous sputum. These symptoms were occasionally accompanied by chest tightness and dyspnea. Physical examination revealed mild pitting edema in both lower extremities, diminished muscle strength (grade III) in the limbs, and the presence of excoriations and lichenification of the skin. Additional findings included a red and fissured tongue with yellow coating, and a small, wiry pulse.

Laboratory and imaging tests

The results of laboratory tests (November 28, 2024) demonstrated the following: blood routine examination indicated a white blood cell count (WBC) of 10.02 x 10^9/L, hemoglobin (HGB) level of 141 g/L, eosinophil percentage (EOS%) of 43.8%, and an absolute eosinophil count of 4.39 x 10^9/L. Biochemical indices revealed elevated alkaline phosphatase (ALP) at 157 U/L(↑), decreased albumin (ALB) at 35.05 g/L(↓), elevated blood urea nitrogen (BUN) at 43.4 mg/dL(↑), and elevated serum creatinine (Scr) at 603 μmol/L(↑). Thyroid function tests demonstrated suppressed thyroid-stimulating hormone (TSH) < 0.01 μIU/mL(↓), decreased free thyroxine (FT4) at 10.5 pmol/L(↓), normal thyroid peroxidase antibody (TPOAb) at 12 IU/mL, and a negative thyrotropin receptor antibody (TRAb). Cardiac enzyme analysis revealed elevated hydroxybutyrate dehydrogenase (HBDH) at 254 U/L(↑) and lactate dehydrogenase (LDH) at 331.07 U/L(↑). Iron metabolism testing demonstrated a ferritin (FER) level of 49.5 ng/mL and a reduced iron/total iron-binding capacity (Fe/TIBC) ratio of 14.84%(↓). Additional results included serum vitamin B12 at 375.6 pmol/L, serum phosphorus at 1.27 mmol/L, and parathyroid hormone (PTH) at 76.62 pg/mL.

Imaging examination revealed patchy ground-glass opacities in the upper lobe of the right lung and interstitial grid-like changes in the lower lobes of both lungs on lung computed tomography (CT) (Figure 1). Cardiac ultrasound demonstrated pulmonary artery systolic blood pressure of 42 mmHg and decreased left ventricular diastolic function. Magnetic resonance imaging

(MRI) of the pituitary gland demonstrated a partially empty sella.

Exclusionary investigations demonstrated negative results for fecal parasite microscopy, no pathogenic bacteria in sputum culture, normal tumor markers (e.g., CEA, CA19-9), negative anti-neutrophil cytoplasmic antibody (ANCA), and a normal serum κ/λ light chain ratio.

Diagnosis and differential diagnosis

Basis for diagnosis

This case is consistent with the diagnosis of IHES based on the following criteria:

Persistent eosinophilia, as indicated by a peripheral blood eosinophil count greater than 1.5 x 10^9/L (maximum 4.39 x 10^9/L) for four consecutive months (July-November 2024), which meets the core hematological criterion for IHES according to the 2022 ICON-EoE consensus [4].

Evidence of multi-organ involvement includes: skin lesions, with intractable pruritus (VAS score 8), excluding hyperphosphatemia (serum phosphate 1.27 mmol/L), uremic pruritus (PTH 76.62 pg/mL), and dialyzer allergy (no improvement with cellulose membrane replacement); pulmonary involvement, as demonstrated by lung CT presenting interstitial lesions along with chronic cough and sputum production, consistent with eosinophilic pneumonia; and muscle dysfunction, with grade III muscle strength in the lower extremities, which improved after hormonal therapy, indicative of eosinophil-mediated muscle injury.

The secondary causes were systematically excluded: Infection was ruled out based on negative results in microscopic stool examination, sputum culture (no pathogenic bacteria), and lack of exposure to endemic areas; allergic disease was excluded with a normal serum IgE level (85 IU/mL) and negative allergen screen; drug-induced eosinophilia was ruled out as the patient had not been on sensitizing medications like ACE inhibitors, antibiotics, or antiepileptic drugs; malignancy was excluded with normal tumor markers (CEA, CA19-9) and no evidence of mass lesions or lymphadenopathy on imaging; vasculitis was excluded with a negative ANCA test and absence of characteristic symptoms such as purpura or hematuria; and endocrine causes were excluded with normal adrenal ultrasound and serum cortisol levels (356 nmol/L at 8 a.m.).

Differential diagnosis

Clonal eosinophilia

The patient declined bone marrow puncture and FIP1-L1-PDGFRA fusion gene testing. However, the case exhibited idiopathic features: the peripheral blood smear demonstrated no blast cells (< 1%), there was sensitivity to glucocorticoid therapy (with a 71.2% decrease in eosinophil percentage within 5 days), and imaging did not reveal splenomegaly or myelofibrosis.

Dialysis-related complications

Dialyzer allergic reactions: Despite replacing the polysulfone membrane with a cellulose membrane, eosinophil levels continued to rise, and no signs of allergy, such as urticaria or hypotension, were observed, ruling out an allergic reaction; Uremic pruritus: Serum phosphorus (1.27 mmol/L) and parathyroid hormone (PTH 76.62 pg/mL) levels were within normal limits. Pruritus demonstrated a positive correlation with eosinophil levels ($r = 0.82$, $p < 0.01$), and symptoms improved concurrently with glucocorticoid therapy [5].

Other secondary causes

Parasitic infection: Stool tests were negative on three occasions, and no larvae were identified in the peripheral blood.

Eosinophilia associated with nifedipine: The incidence of nifedipine-induced eosinophilia was reported to be less than 0.1%, despite the long-term use of nifedipine controlled-release tablets.

Occult tumor: Positron emission tomography-computed tomography (PET-CT) did not reveal any metabolic abnormalities, and serum interleukin-2 receptor (IL-2R) levels were normal (458 U/mL).

Treatment and efficacy

The treatment approach included glucocorticoid therapy and optimization of hemodialysis. Oral prednisone was administered at a dosage of 20 mg/day (0.3 mg/kg) in the morning. This dosage was selected based on the finding that free prednisone concentrations increase by 1.8-fold in patients with ESRD, while dialysis eliminates approximately 30% of the free drug, thereby reducing the risk of cumulative toxicity [6]. Hemodialysis was performed three times per week, with each session lasting four hours, using an FX80 dialyzer (ultrafiltration coefficient: 46 mL/hour/mmHg). This regimen was chosen because high flux membranes are capable of removing medium molecular uremic toxins, such as interleukin-6 (IL-6) and beta-2 microglobulin (β2-microglobulin), which helps improve the microinflammatory state.

Treatment outcomes

Short-term efficacy: Following 5 days of treatment, laboratory results indicated a decrease in EOS% from 43.8% to 12.6% (a 71.2% reduction, paired *t*-test, $p < 0.01$). LDH levels decreased from 331.07 U/L to 198 U/L (a 40.2% reduction). In terms of symptom improvement, the VAS score for pruritus decreased from 8 to 3 points (a 62.5% reduction, Wilcoxon test, $p < 0.05$), and the muscle strength of the lower limbs improved from grade III to grade IV, as assessed by manual muscle testing.

Long-term follow-up (after one month): Hematologic remission was confirmed by a decrease in eosinophil count to 0.06 x 10^9/L, which met the criteria for complete remission [7]. Functionally, the patient ceased using a wheelchair, and the 6-minute walking distance im-

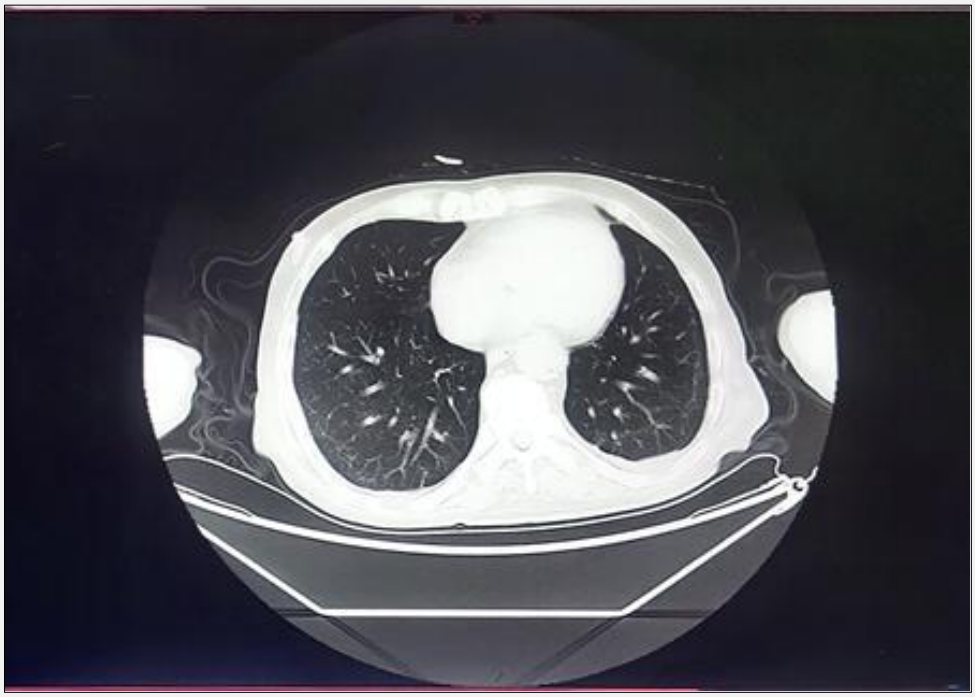

Figure 1. Ground-glass opacity in the right upper lobe, reticular changes in the interstitial of both lower lobes.

proved from 80 m to 210 m. Safety was also maintained, with fasting blood glucose levels kept within the range of 4.8 - 5.6 mmol/L, and no infection events occurred.

Recommendations for treatment optimization: A hormone tapering strategy is recommended: the prednisone dose should be reduced by 5 mg every two weeks, ultimately maintaining a daily dose of 5 mg to reduce the risk of adrenal suppression.

DISCUSSION

This case represents a rare clinical presentation of IHES in an older adult with ESRD, offering new insights into the pathogenesis of IHES, the relationship between multi-organ damage, and potential immunosuppressive treatment strategies. The diagnosis of IHES is characterized by a persistent increase in peripheral blood eosinophils to ≥ 1.5 x 10^9/L, along with the exclusion of all secondary causes. In this case, the patient exhibited an eosinophil count of 4.39 x 10^9/L, accompanied by pruritus, interstitial pneumonia, and decreased muscle strength, which met the diagnostic criteria for IHES-related organ damage as outlined in the 2022 ICON-EoE International Consensus [4].

In patients with ESRD, eosinophil activation may be triggered by the Th2 immune pathway due to the accumulation of uremic toxins, a factor that may be confused with dialysis-related complications [8]. Dynamic monitoring of laboratory markers and clinical symptoms is essential in differentiating between the two. In this case, eosinophil levels remained elevated despite the replacement of polysulfone membranes with cellulose membranes, and there were no signs of allergic reactions (e.g., hypotension, bronchospasm). Additionally, serum phosphorus (1.27 mmol/L) and PTH levels (76.62 pg/mL) were well controlled, and the pruritus was strongly correlated with eosinophil levels ($r = 0.82$, $p < 0.01$).

Furthermore, abnormal thyroid function observed in the patient may be linked to IL-1β-mediated inhibition of the hypothalamic-pituitary-thyroid axis, a phenomenon that can occur during chronic inflammatory states.

In terms of glucocorticoid dose optimization, prednisone at a dosage of 0.5 - 1 mg/kg/day is generally recommended as first-line treatment for IHES [9]. However, in patients with ESRD, the loss of glomerular filtration rate and the resulting increase in free prednisone concentration necessitate the adoption of a low-dose regimen (0.3 mg/kg/day), as demonstrated in this case. This reduced dose yielded significant therapeutic efficacy, with a 71.2% reduction in EOS%. The mechanisms underlying this efficacy may involve the inhibi-

tory effects of the uremic microenvironment on T cell activity and the removal of free hormones through dialysis. High flux dialysis (FX80) was demonstrated to eliminate 30% of free prednisone, thereby reducing its half-life to 2.1 hours and minimizing cumulative toxicity. In cases of hormone resistance or dependence, monoclonal antibodies targeting IL-5, such as mepolizumab, may be considered an alternative treatment due to its renal clearance of less than 1% [10].

The multisystem injury observed in patients with IHES is directly associated with eosinophilic toxic mediators. The mechanisms underlying skin pruritus, muscle involvement, and interstitial pneumonia have been explored previously [11,12]. Although the patient refused bone marrow puncture and FIP1L1-PDGFRA fusion gene testing, the absence of blast cells on the peripheral blood smear and the observed sensitivity to hormonal therapy were consistent with the characteristics of IHES. It is estimated that approximately 15% to 20% of patients with IHES may progress to myeloid tumors, such as chronic eosinophilic leukemia [13]. As such, it is recommended to monitor for the Janus kinase 2 V617F mutation (JAK2 V617F), calreticulin gene (CALR) mutation, and perform bone marrow morphology assessments every six months.

CONCLUSION

This case report underscores the importance of evaluating Th2-associated cytokines, such as IL-5 and thymic stromal lymphopoietin (TSLP) in patients with ESRD and eosinophilia to distinguish IHES from dialysis-related complications. The combination of low-dose prednisone and high flux dialysis appears to be a safe and effective initial treatment regimen. Moreover, multidisciplinary collaboration is essential to reduce the risk of misdiagnosis and to guide appropriate management. The primary limitations of this report include the absence of single-cell sequencing to assess eosinophil clonality and the lack of follow-up data beyond one year. Future studies should incorporate extended observation periods to better evaluate long-term outcomes.

Declaration of Interest:
The authors have no conflict of interest.

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