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Minireview

Renal involvement in idiopathic hypereosinophic syndrome

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Abstract
The hypereosinophilic syndromes (HESs) are a group of disorders marked by the sustained overproduction of eosinophils, in which eosinophilic infiltration and mediator release cause damage to multiple organs. In idiopathic HES, the underlying cause of hypereosinophilia (HE) remains unknown despite thorough aetiological work-up. Kidney disease is thought to be rare in HES. Renal manifestations described include eosinophilic interstitial nephritis, various types of glomerulopathies, thrombotic microangiopathy (TMA) and electrolyte disturbances. The diagnosis must be made in time, because a recovery of renal function can be obtained if treatment is initiated promptly.

Keywords: eosinophil; glomerulopathy; hypercalcaemia; thrombotic microangiopathy

Introduction

Hypereosinophilic syndrome (HES) was first recognized as a distinct clinical entity in 1975 [1]. HESs are a group of disorders characterized by persistent and marked hypereosinophilia (HE, >1500/μL) not due to an underlying disease known to cause eosinophil expansion (such as an allergic drug reaction or parasitic infection), which is directly implicated in damage or dysfunction of at least one target organ or tissue [1–3]. Its true prevalence is unknown varying between 0.36 and 6.3 per 100 000 [4]. HESs are further sub-classified according to the pathogenic mechanisms resulting in eosinophil expansion: primary, secondary or idiopathic. In idiopathic HES, the underlying cause of HE remains unknown despite thorough aetiological work-up.

Idiopathic HES has a poor prognosis with a median survival time in untreated cases of 12 months [5]. The associated organ damage generally warrants therapeutic intervention. HESs most commonly involve the heart, lungs, nervous system and skin. Heart failure is the main cause of death [6, 7]. The prognosis has changed dramatically with corticosteroid therapy, although the response varies widely. An association between HES and kidney damage is not well documented. Renal involvement is rare and little is known about their clinicopathological expression and response to treatment [1, 8]. This review describes kidney-defined disorders related to idiopathic HES and discusses their relationship.

Classification of eosinophilic disorders and related syndromes

Eosinophilia is an important indicator of various neoplastic and nonneoplastic conditions. Depending on the underlying disease and mechanisms, eosinophil infiltration can lead to organ dysfunction, clinical symptoms or both. Peripheral blood eosinophilia has been divided into mild (0.5–1.5 3 109/L), marked (>1.5 3 109/L) and massive (>5.0 3 109/L) eosinophilia and can be transient, episodic or persistent (chronic). The term HE should be used when marked and persistent eosinophilia has been documented or marked tissue eosinophilia is observed (Table 1) [9]. The term persistent applies to peripheral blood eosinophilia recorded on at least two occasions with a minimum time interval of 4 weeks (except when immediate therapy is required because of HE-related organ dysfunction). Tissue HE should apply when one or more of the following is fulfilled: (i) the percentage of eosinophils >20% of all nucleated cells in BM sections; (ii) a pathologist is of the opinion that tissue infiltration by eosinophils is extensive (massive) when compared with the normal physiological range, compared with other inflammatory cells, or both or (iii) a specific stain directed against an established eosinophil granule protein (e.g. major basic protein) reveals extensive extracellular deposition of eosinophil-derived proteins indicative of local eosinophil activation [9]. On the basis of the initial patient evaluation, HE can be divided into variant types: hereditary HE variant, HE of undetermined significance (HEUS), primary (clonal/neoplastic) HE produced by apparently clonal (neoplastic) eosinophils and secondary (reactive) HE, (Table 2) [10].

Renal involvement

Kidney disease is thought to be rare in HES [11]. In 55 patients evaluated at the National Institute of Health, no cases of renal disease were seen [7]. The prevalence of

Table 1. Definition of HE and HES. Adapted from ref [9]

Terminology	Definition and criteria
Blood eosinophilia	>0.5 Eosinophils × 10^9/L blood
HE	>1.5 Eosinophils × 10^9/L blood on two examinations (interval ≥1 month) and/or tissue HE defined by the following: (i) Percentage of eosinophils in the BM section exceeds 20% of all nucleated cells and/or (ii) Pathologist is of the opinion that tissue infiltration by eosinophils is extensive and/or (iii) Marked deposition of eosinophil granule proteins is found (in the absence or presence of major tissue infiltration by eosinophils).
Hypereosinophilic syndrome (HES)	(i) Criteria for peripheral blood HE fulfilled and (ii) Organ damage and/or dysfunction attributable to tissue HE and (iii) Exclusion of other disorders or conditions as major reason for organ damage.
Eosinophil-associated single-organ diseases	(i) Criteria of HE fulfilled and (ii) Single-organ disease.

renal involvement varies from 7 [12] to 36% [1]. A review of case reports in the medical literature identifies four kidney-defined disorders related to idiopathic HES: parenchymal diseases, vascular disorders, electrolyte disturbances and Charcot–Leyden crystals (Table 3) [13–32].

The mechanisms underlying renal involvement are the same as those implicated in tissue damage of other organs, i.e. eosinophil cytotoxicity, 'mass effect' due to eosinophilic infiltrates and thromboembolic events secondary to cardiac involvement [7, 33]. In previously reported HES cases, renal pathology is either poorly described or nonspecific [16, 21]. However, specific extracellular eosinophil granule major basic protein 1 (MBP1) staining is taken as evidence of eosinophil degranulation. The normal kidney is devoid of eosinophils [34]. In HES, patients are thought to have increased activated blood eosinophils. Activated eosinophils release a number of cytopathic substances especially eosinophil granule MBP1 and the eosinophil peroxidase. Eosinophils also produce other mediators, including reactive oxygen species, leukotrienes, prostaglandins, platelet-activating factor, cytokines and matrix-digesting enzymes [34, 35]. It appears that eosinophil cytotoxicity of those substances induced tissue damage and renal involvement [18].

Glomerulopathies and tubulointerstitial nephritis

About 20% of idiopathic HES patients developed proteinuria and hypertension [1, 8, 13, 36] Renal insufficiency is common as a preterminal event [1] and some authors reported on dialysis treatment in patients with idiopathic HES [37].

Renal manifestations described include eosinophilic interstitial nephritis [16, 22], membranous nephropathy [26, 27], anti-neutrophil cytoplasmic antibody-positive or not crescentic [23, 24] and immunotactoid glomerulonephritis [25], with or without glomerular immune deposits [21].

Date *et al.* [13] provided renal histopathology in autopsic HES patients. The most frequent renal lesions were interstitial nephritis with eosinophilic infiltrates and tubular atrophy and glomerular lesions (mesangial expansion, hypercellularity and thickened basement membrane). In a series of 14 patients, Chusid *et al*. [1] found two cases with glomerular mesangial expansion and thickened glomerular basement membrane and one case with eosinophilic infiltrates in the kidney. In Motellon's case report [16], a renal biopsy showed glomerular abnormalities such as focal mesangial expansion and focal hyalinosis surrounded by wide areas exhibiting chronic tubulointerstitial lesions with focal interstitial eosinophilic leukocytes inflammatory cell infiltrates as well as vascular damage.

The rapid, sustained improvement in renal function and decrease in proteinuria after a course of prednisone suggest that glomerulonephritis secondary to HES may not require aggressive treatment such as cytotoxic drugs and plasma exchange, which have classically recommended as first-line therapy in other causes of vasculitis and progressive glomerulonephritis.

Vascular disorders

Ischaemic renal changes

Most such patients likely have ischaemic renal changes secondary to thromboembolism from endomyocardial disease [8, 11, 13, 16] or atheroembolism [15] which makes the HES-renal insufficiency relationship confused. Spry *et al.* [8] reported ischaemic changes as the most common finding in renal biopsies (2 out of 15 patients) [1] and renal infarcts secondary to thromboembolic events [13, 17] has been recognized in such patients. The patients' symptoms and HE resolved following corticosteroid–hydroxyurea association without anticoagulation [17]. On the other hand, incidental finding of microthrombi in renal vessels [38] or intimal lesions in blood vessels have been reported [22] to be present in renal biopsies and other tissues post-mortem [24]. The mechanisms leading to thrombus formation are unknown, but it has been suggested that eosinophil cytotoxicity could affect the intrinsic coagulation system. Furthermore, massive eosinophil MBP deposition in renal blood vessels intima have been reported, raising the possibility that peripheral ischaemic areas are due to local thrombus formation [22].

Thrombotic microangiopathy

Thrombotic microangiopathy (TMA) is a vasculopathy associated with microangiopathic haemolytic anaemia, thrombocytopenia and renal involvement. The central pathogenic mechanism is endothelial injury secondary to various agents and endothelial shear stress [39]. Thrombotic thrombocytopenic purpura (TTP) is a life-threatening disorder characterized by TMA, neurologic symptoms and fever [40] caused by inherited and/or acquired deficiency of A disintegrin-like and metalloprotease with thrombospondin type 1 motif, 13 (ADAMTS13) [40, 41].

Table 2. Classification and characteristics of HES[a]

HES variants	Characteristics Parameters	Sub types
Myeloproliferative	*Clinical* (i) Hepatomegaly (ii) Splenomegaly *Blood* (i) Myeloid precursors (ii) Anaemia/thrombopenia *Serum* (i) Increased vitamin B12/tryptase *Bone marrow* (i) Fibrosis (ii) Left shift maturation (iii) Atypical mast cells (spindle-shaped) *Cytogenetic abnormalities* *Response to TK inhibitors* (imatinib)	*M-HES:* Features of myeloproliferative disease without proof of clonality *CEL:* Clonal eosinophilia due to autonomous TK activity *FIP1L1-PDGFRA* fusion gene most common other chromosomal rearrangements[†]
Lymphocytic	Eosinophil expansion driven by Th2 cytokine-secreting T cells (IL-5) Exclusion of T-cell malignancies (e.g. lymphoma)	*L-HES:* (i) T-cell subset with abnormal phenotype (ii) CD3−CD4+ (most common) (iii) CD3+CD4−CD8− (iv) CD3+CD4+CD7− (v) Clonal TCR gene rearrangement *Episodic:* (i) Gleich's syndrome (ii) Cyclic angiooedema with eosinophilia (iii) T-cell abnormalities sometimes detected (iv) Suspected role of IL-5
Idiopathic or undefined		*I-HES:* 'True' idiopathic/unexplained hypereosinophilic syndrome. No evidence for M-HES or L-HES

[a]CEL, chronic eosinophilic leukaemia; HES, hypereosinophilic syndrome; I-HES, idiopathic HES; L-HES, lymphocytic variant HES; M-HES, myeloproliferative variant HES; TK, tyrosine kinase; PDGFR, platelet-derived growth factor receptor-a. Table adapted from Cogan and Roufosse 2012 [10]

Table 3. Renal involvement in idiopathic HES [13–32]

Kidney disorders	References
Thromboembolism	[11, 13]
Atheroembolism	[14, 15]
Ischaemic changes	[16]
Renal infarction	[17]
TMA/TTP	[18–20]
Interstitial nephritis	[16, 21, 22]
Crescentic glomerulonephritis	[23, 24]
Immunotactoid glomerulonephritis	[25]
Membranous nephropathy	[26, 27]
Focal segmental glomerulosclerosis	[16]
Hypercalcaemia	[28–30]
Renal hypouricaemia	[31]
Charcot–Leyden crystals	[32]

To date, two cases of each TMA [18] and TPP caused by an ADAMTS13 inhibitor [19, 20] associated with HES have been reported. Among TTP cases, the ADAMTS13 inhibitor was suspected to be drug-induced [19]. Patients were successfully treated with corticosteroids alone or associated with plasma exchange in TMA and PTT cases, respectively. It is assumed that MBP1 and eosinophil peroxidase injured the endothelium and may have promoted thrombosis by altering the clotting system via platelet activation [35] and thrombomodulin anticoagulant effects impairment [42].

Electrolyte disturbances

Malignant hypercalcaemia

Few reports of hypercalcemia related to idiopathic HES have been described [28–30] It is often a symptomatic (general fatigue, loss of appetite, nausea, and difficulty falling asleep) malignant (11.7–16.4 mg/dL [2.93–4.1 mmol/L]) hypercalcaemia with a low normal parathormone level and without parathyroid lesions. Underlying mechanisms are unclear. In one case, hypercalcaemia was associated with a high 1,25(OH)(2)D concentration in spite of end-stage renal disease and no causal medications. Steroid therapy resulted in the patient's rapid recovery from HE and hypercalcaemia. Since the serum 1,25(OH)(2)D level promptly and markedly decreased, the hypercalcaemia complicated with HES was most likely caused by extrarenal production of 1,25(OH)(2)D [30]. In the other cases, active vitamin D was not the cause of hypercalcaemia [28, 29] Proposed mechanisms include (i) the destruction of bone by an expanding eosinophilic cell

mass with subsequent calcium mobilization as autopsic findings showed eosinophilic infiltration in the bones and marked bone resorption, (ii) the production of a hypercalcaemic humoral substance [28] or three local inflammatory cytokines such as interleukine (IL)-1, tumour necrosis factor and IL-5 [29]. In the case of evolution into severe myelofibrosis requiring bone marrow transplantation, malignant hypercalcaemia could be related to osteolytic lesions [43].

Renal hypouricaemia

A case of renal hypouricaemia [(serum uric acid concentration 1.8 mg/dL [107.1 µmol/L] [range, 1.5–3.0 mg/dL (89.3–178.5 µmol/L)] and 24-h uric acid excretion 816 mg [4.9 mmol/L (normal, 250–700 mg)] related to proximal tubular defect (normoglycaemic glycosuria) has been reported in a patient with idiopathic HES (eosinophil count 4200/mm^3). The striking improvement that followed corticosteroid therapy and the prolonged remission [serum urate levels rose (4.4 mg/dL [261.8 µmol/L]) concomitant with clinical remission (eosinophil count 165/mm^3)] strongly suggests that the severe hypouricaemia was related to the primary disease [31]. This transient tubular defect may be related to a direct toxic effect of eosinophils.

Charcot–Leyden crystals

Crystalluria in acute renal failure caused by hypereo*sinophilic syndrome* has been reported in only one patient so far [32]. Charcot–Leyden crystals, one of the hallmarks of hypereosinophilic syndrome, were found in the renal tubular lumina and in large amounts in the urine. Charcot–Leyden crystals are elongated bipyramids composed of a single acidic protein with a low molecular weight, and are highly insoluble at neutral pH [44].

Conclusion

Although renal involvement in idiopathic HES is rare, the diagnosis must be made in time, because a recovery in renal function can be obtained if treatment is initiated promptly.

Conflict of interest statement. None declared.

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