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Hypereosinophilic Syndrome and Proliferative Diseases

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SUMMARY Therapy principles of the last decade and recent advances in the research of polynuclear eosinophil have led to a new approach in the hypereosinophilic syndrome (HES), with important consequences on the development of new and effective therapies. HES is defined by persistent and marked eosinophilia and eosinophil-related organ damage in the absence of any evident cause of hypereosinophilia. Two variants of HES have been characterized, with different prognosis and possible associations with malignant diseases such as myeloid leukemia or T-cell lymphomas. The lymphocytic variant of HES (L-HES) is characterized by the presence of T cell clones, IL-5 expression and possible progression to T-cell lymphoma. Besides steroid therapy, the anti-IL-5 monoclonal antibody mepolizumab is considered as a target therapy for L-HES. The myeloproliferative variant of HES (M-HES) is associated with an increased risk of myeloid leukemia and good response to anti-tyrosine-kinase therapy. The imatinib target is a kinase resulting from an 800-kb deletion on chromosome 4. The fusion gene Fip1-like 1-platelet-derived growth factor receptor alpha (FIP1L1–PDGFRA) has been validated as a marker of response to anti-tyrosine-kinase therapy. Early identification of HES variants is crucial for the rapid introduction of early and appropriately adjusted therapy.

KEY WORDS: hypereosinophilic syndrome, T-cell lymphomas, myeloproliferative disorders

INTRODUCTION

Hypereosinophilia is commonly associated with atopy, parasitosis, drug hypersensitivity, and malignancies. When there is no underlying disease but multiple organ involvement by eosinophilic infiltrates, the diagnosis of hypereosinophilic syndrome (HES) is proposed (1). HES is a rare disorder with an estimated incidence rate of 0.5 to 1.0 cases *per* 100,000 inhabitants *per* year (2) and is characterized by persistent eosinophilia associated with end-organ damage (3). HES prognosis can be poor because of eosinophilic myocarditis and fibrosis, or because of associated malignant diseases such as myeloid leukemia or T-cell lymphoma (4-6).

THE HYPEREOSINOPHILIC SYNDROME: THE EVOLUTION OF THE CONCEPT

Hypereosinophilia with no evident etiology was initially proposed as a syndrome by Hardy and Anderson in 1968 (3). In 1975, Chusid *et al*.

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(7) established diagnostic criteria for "idiopathic HES": 1) peripheral eosinophilia (>1500 eosinophils/mm^3) for more than six months; 2) absence of reactive eosinophilia, caused by parasites, allergies, neoplasia; and 3) evidence of end-organ damage related to hypereosinophilia. The clinical spectrum for idiopathic HES was proposed at the National Institute of Health Conference in 1982 (8). In 1994, clonal proliferation of T-cell type helper 2 (Th2) was reported in one case of HES (4).

The lymphocytic variant of HES (L-HES) was later defined and related to an increased interleukin-5 (IL-5) expression by clonal T-cells and activated eosinophils. IL-5 is one of the key mediators for eosinophilic activation and survival (4-6). Based on these findings, L-HES targeted therapies have been recently developed, using anti-IL-5 monoclonal antibodies (mepolizumab, alemtuzumab) associated with systemic steroids (9).

The myeloid variant of HES (M-HES) was described in the last decade, based on HES and chronic myeloid leukemia (CML) cases that responded successfully to tyrosine-kinase inhibitors (imatinib mesylate) (10). In M-HES and CML cases, interstitial deletions on chromosome 4q12 were found, with fusion of the FIP1-like 1 and platelet-derived growth factor receptor alpha genes, and a fusion product encoding a protein with constitutive tyrosine kinase activity (11). Markers of response to imatinib (FIP1L1-PDGFR-αfusion gene) were then identified (Thr 674Ile mutation) (12-16). New generations of tyrosine-kinase inhibitors have now been developed (nilotinib, PKC412).

With characterization of the two HES variants (L-HES and M-HES), "idiopathic HES" is now a temporary diagnosis necessitating further investigations (11,17,18).

CLINICAL FEATURES AND LABORATORY FINDINGS IN HES VARIANTS

Cutaneous and mucosal signs occur in 27% to 64% of HES cases (19-22), in both L-HES and M-HES variants.

Lymphocytic HES variant (L-HES)

This variant of HES is characterized by pruritus, nonspecific erythematous papules and plaques, urticaria-like lesions, erythroderma, and angioedema. Endomyocardial fibrosis is rarely reported; pulmonary and digestive involvement due to eosinophilic infiltrates can be found. In this variant, clonal CD3- CD4+ T cells of phenotype express IL-4, IL-5 and IL-13 cytokines (Th2 profile). Progression to T cell lymphomas has been reported (18,23,24). This form is equally distributed in females and males.

Myeloproliferative HES variant (M-HES)

M-HES shows male predominance with 4-9:1 ratio (25) and is characterized by hepatosplenomegaly; mucosal ulcerations can occur (26). Blood tests show persistent eosinophilia, increased levels of serum tryptase, vitamin B12 and leukocyte alkaline phosphatase, anemia and/or thrombocytopenia, and circulating leukocyte precursors (27). The prognosis of the M-HES variant is poor, with severe cardiac complications, resistance to steroid therapy, and an increased risk of developing myeloid malignancies. Patients with M-HES can develop blast crisis revealing acute eosinophilic or myeloid leukemia. They can also develop granulocytic sarcoma (28). Mucosal lesions such as ulcerations, erosions or aphthous lesions may occur in M-HES and are considered as one of the clinical markers of M-HES with characteristic genetic mutation (2,29). The mucosal lesions can be discrete, round or oval ulcers, located on oral, labial, conjunctival and/or genital mucosa. Oral ulcerations in HES must be differentiated from ulcerations of other causes, mainly aphthae (primarily aphthosis in AIDS), Behçet's disease, local traumas, malignant neoplasms, drug- or irradiation-induced ulcerations, cyclic neutropenia, FAPA (fever, aphthous stomatitis, pharyngitis, adenitis), gluten-sensitive enteropathy, and hematinic deficiencies (iron, zinc, folate, vitamin B) (30). A major complication of severe HES, whatever the variant, is endomyocardial necrosis (often asymptomatic) or endomyocardial thrombosis. This is followed by endomyocardial fibrosis, leading to severe cardiac failure (31). Atrioventricular valves can be involved in the late stage of endomyocardial fibrosis, leading to congestive heart failure. Peripheral thromboembolism may also occur, independently of endomyocardial lesions, due to an increased number of blood eosinophils (32,33).

PATHOLOGY

Being present in blood (>1500/mm^3), eosinophils can also be localized in the skin or mucosa, inducing similar histopathologic changes in both variants. On hematoxylin-eosin stain, skin biopsies from HES untreated lesions such as plaques or papules show a cellular infiltrate composed of lymphocytes, macrophages and eosinophils that are characterized by bilobate nuclei and eosinophilic

cytoplasm. May-Grünwald-Giemsa stain provides precise assessment of eosinophil count and tissue distribution. Activated eosinophils are often degranulated, with eosinophil granules scattered in the intercellular space within the inflammatory infiltrate. On immunohistochemistry, antibodies directed against eosinophil cationic proteins (eosinophil peroxidase (EPO), major basic protein (MBP), eosinophil cationic protein (ECP) and eosinophil-derived neurotoxin (EDN)) can be used on histologic sections in order to identify eosinophils or their extracellular granules as the result of cellular degranulation. Electron microscopy (EM*)* allows for precise identification of eosinophils and their degranulation. Intact, non-activated eosinophils are characterized by cytoplasmic granules with a dense matrix and crystallized central core. When eosinophils are activated, they undergo degranulation and have an inverted density of the central cores of the cytoplasmic granules associated with a partially dissociated cytoplasm (34,35). Eosinophil activation can also lead to full cell lysis, with ultrastructural features associating a necrotic nucleus, a disintegrated cytoplasm, and surrounding extracellular free granules (36,37). The ultimate stage of eosinophil lysis results in the constitution of Charcot-Leyden crystals, with a characteristic sharp and dense crystal shape on EM (38). These Charcot-Leyden crystals are resistant markers of eosinophil lysis and can be found within the tissue two to three weeks after eosinophil lysis (39). They can also be detected in the blood and body fluids such as bronchoalveolar lavage or urine (40).

PATHOPHYSIOLOGY

The activation of polynuclear eosinophilic cells is made first by the release of cationic proteins, through eosinophil degranulation and/or lysis that induce tissue damage (41). Eosinophil infiltrates can be found in the skin and mucosa lesions of HES patients (42,43), in digestive tract of patients with eosinophilic gastroenteritis (44), and in both the skin and duodenal mucosa of patients with dermatitis herpetiformis (45). Hypodense eosinophils are among basic signs of blood eosinophil activation. Tissue eosinophil infiltrates show signs of cellular activation, i.e. the release of cationic proteins, the presence of hypodense granules on ultrastructural examination, and eosinophilic synthesis of IL-5.

Eosinophil activation is also associated with acute symptoms such as flare-ups (46-48) or early recurrences (49,50) of inflammatory diseases, microvascular lesions and necrosis (51,52). The release of cationic proteins (ECP and MBP) can also lead to lipid membrane disruption and target cell death (53). In hypereosinophilic syndromes, activated eosinophils are observed in early oral ulcerations (20,21) as well as in late endomyocardial fibrosis (54).

Eosinophil trafficking to tissues and activation are also increased in HES. Eosinophils are derived from bone marrow myeloid progenitors (granulocyte-erythrocyte-megakaryocyte-macrophage colony-forming units, GEMM-CFU) through the action of granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin (IL)-3 and IL-5 (55). Eosinophils are then released into the blood stream and migrate within 24-48 hours towards their target tissues (56-58). In physiological conditions, tissue eosinophils survival is short (one or two days) (52,59,60). IL-5 expressed by T cells or/and by eosinophils increases the survival of eosinophils (61,62).

In L-HES, the main role is played by IL-5 and eotaxin-1, eotaxin-2 and eotaxin-3. IL-5 is the main factor for the activation and *in situ* survival of tissue eosinophils (63-65). IL-5 can be produced by lymphocytes, mastocytes, basophils and eosinophils (66-70). T-helper lymphocytes with a cytokine profile type Th2 express IL-5, IL-4 and IL-13. This type of response is linked to hypereosinophilia, high serum IgE levels and polyclonal hypergammaglobulinemia, mainly found in L-HES (71,72). Th2 T cells are found in atopic dermatitis, commonly associated with eosinophilia (73). Clonal Th2 T cells are also found in T-cell lymphomas, often as a complication of L-HES (74). Eosinophil recruitment and activation can be induced by an overproduction of IL-5, IL-3 and GM-CSF (75,76). This is observed mainly in the L-HES variant associated with Hodgkin's disease, T-cell lymphomas or solid tumors (70,77). Eosinophil autocrine expression of IL-5 involves chronic eosinophil infiltration (31,40,44,49).

In M-HES, the eosinophilic recruitment, proliferation, and activation can be induced by an acquired chromosome change within myeloid cells (78,79), followed by an increased hematopoiesis and subsequently associated with myeloproliferative disorders. M-HES characteristic genetic changes are deletions on chromosome 4q12 and induction of FIP1L1-PDGFR-αfusion gene and platelet-derived growth factor receptor alpha genes, with the consequent fusion product encoding a protein that has constitutive tyrosine kinase activity. The marker of anti-tyrosine-kinase therapy response is the presence of FIP1L1-PDGFR-αfusion gene, while the

marker of resistance to this type of therapy is the mutation of Thr 674Ile gene (12-16).

TREATMENT

Steroids are first line therapy for HES. Topic or systemic corticotherapy decreases dramatically the eosinophilic activation and tissue recruitment by inducing eosinophilic apoptosis (18,28).

Treatment of L-HES

In the lymphocytic variant, steroids are first line therapy. Interferon alpha (IFN-α) and cyclosporin A can be co-administered. If signs of malignant transformation are diagnosed, the treatment lines specific for T-cell lymphoma are proposed, with chemotherapy (cyclophosphamide, hydroxydoxorubicin, oncovin, prednisone, i.e. CHOP-like regimen), with or without monoclonal antibodies, fludarabine, 2-chlorodeoxyadenosine (2-CdA). In resistant or recurrent cases, intensive high dose chemotherapy followed by hematopoietic stem cell transplantation can be used. Specific L-HES therapy is based on anti-IL-5 monoclonal antibodies mepolizumab and alemtuzumab (80,81). In a double blind clinical trial in 85 patients with L-HES (FIP1L1–PDGFRA negative), mepolizumab significantly decreased the clinical activity of HES and was corticosteroid-sparing (9).

Targeted treatment for M-HES

Imatinib mesylate is a tyrosine kinase inhibitor initially introduced for the treatment of chronic myeloid leukemias, and remains the first line treatment in M-HES, leading to dramatic improvement (13). Imatinib target is a kinase resulting from a 800 kb deletion on chromosome 4 cDNA derived from the fusion gene encoded novel protein composed of the kinase domain of platelet-derived growth factor receptor-alpha (PDGFRA) linked to the FIP1 gene. This genetic rearrangement was found in the eosinophilic cell line EOL-1 (peripheral blood, leukemia, acute myeloid, DSMZ ACC 386), and was also detected in blood cells from patients with HES (14). In an animal model (Ba/F3 mouse, peripheral blood, pro B cell, DSMZ ACC 300), cells expressing FIP1L1–PDGFRA were 100-times more sensitive to imatinib than cells expressing BCR-ABL (13). In chronic eosinophilic leukemia (n=23) and hypereosinophilic syndrome (n=13), imatinib mesylate provided complete molecular remission in 87% of cases at 12 months (82).

Other drugs used in the treatment of M-HES are hydroxyurea and IFN-α. If signs of malignant transformation are found, chemotherapy or hematopoietic stem cell transplantation must be proposed.

CONCLUSIONS

The field of “idiopathic hypereosinophilic syndromes” has been consistently reduced, due to better understanding of the eosinophil biology. Hypereosinophilic syndrome therapy has been dramatically changed by anti-tyrosine kinase derivatives (imatinib) indicated in myeloproliferative forms of HES. The fusion gene FIP1L1-PDGFRA associated with the kinase target of imatinib has been recognized as a biological marker in patients that may benefit from this targeted therapy. In the L-HES variant (FIP1L1-PDGFRA negative patients), anti-IL-5 therapy (mepolizumab, alemtuzumab) has been proved to be active and corticosteroid-sparing. The early identification of the two HES variants is therefore crucial for the rapid introduction of early and appropriately adjusted therapy.

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