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HOT TOPIC

Oral mucosa lesions in hypereosinophilic syndrome – an update

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Hypereosinophilic syndrome (HES) is a rare disorder characterized by persistent and marked eosinophilia. Some HES forms have a poor prognosis, either because of end-organ damage (particularly endomyocardial fibrosis), or because of associated myeloid leukemia or malignant T-cell lymphoma. Oral mucosa ulcerations can be early clinical signs in severe forms. They are discrete, round or oval, sometimes confluent ulcers or erosions, located on non-keratinized, unattached oral mucosa. In the last 15 years a better understanding of eosinophil biology has led to a new clinical classification of HES. The lymphocytic form is characterized by T-lymphocyte clonality, IL-5 production, and a possible progression to T-cell lymphoma. Oral lesions are more frequently associated with the myeloproliferative form, characterized by an increased risk of developing myeloid malignancies and a good response to a recent anti-tyrosine kinase therapy (imatinib mesylate). The target of imatinib is a novel kinase resulting from an 800-kb deletion on chromosome 4. Recently, the resulting FIP1L1-PDGFRα fusion gene was characterized as a marker of response to imatinib. Exclusion of other erosive ulcerative oral disease and early recognition of HES in patients with oral ulcerations, and precise characterization of the lymphocytic or myeloproliferative form are therefore important to rapidly initiate an effective therapy.
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Introduction

Hypereosinophilic syndrome (HES) is a disorder characterized by persistent and marked eosinophilia complicated with end-organ damage (Hardy and Anderson, 1968). Some HES forms have a poor prognosis, either because of an eosinophilic myocarditis followed by endomyocardial fibrosis, or because of an associated myeloid leukemia or malignant T cell lymphoma (Cogan *et al*, 1994; Simon *et al*, 1999; Roufosse *et al*, 2000).

Oral mucosa ulcerations, when present, have been reported to be associated with severe forms of HES, and can be a presenting feature (Leiferman *et al*, 1982; Aractingi *et al*, 1996; Billon *et al*, 1997; Barouky *et al*, 2003). Their precise characterization is important for early diagnosis and treatment, more especially as recent therapeutic advances have changed the prognosis of HES-associated myeloid proliferations.

Diagnostic criteria for HES

For the first time in 1968 Hardy and Anderson proposed the concept of HES. Diagnostic criteria of idiopathic HES were proposed in 1975 (Chusid *et al*, 1975):

1 blood eosinophilia (>1500 eosinophils μl^{-1}) for more than 6 months;
2 exclusion of reactive eosinophilia caused by parasitic infections, allergies, and eosinophilia associated with neoplasia;
3 evidence of end-organ damage related to hypereosinophilia.

A National Institute of Health (NIH) conference in 1982 defined the clinical spectrum for idiopathic HES (Fauci *et al*, 1982). It was not before 1994 that clonal proliferation of type 2 helper (Th2) T cells was reported in HES. The production of interleukin-5 (IL-5), a major mediator for eosinophil activation and survival, by the clonal T lymphocytes was further described, validating the concept of lymphocytic HES (L-HES) variant (Cogan *et al*, 1994; Simon *et al*, 1999; Roufosse *et al*, 2000). In 2001, the dramatic response of certain forms of HES to a new drug, imatinib mesylate, a tyrosine kinase inhibitor efficient in chronic myeloid leukemia (CML) (Druker *et al*, 2001) led to a better characterization of a myeloid variant of HES (M-HES). A cytogenetic

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mutational deletion on chromosome 4 is constantly found in this M-HES variant, this deletion being specifically linked to tyrosine kinase activity. Further cytogenetic studies led to the recognition of markers of response to imatinib [FIP1-like-1-platelet-derived growth factor receptor-α (FIP1L1-PDGFRA) fusion gene], and of resistance to this drug (Thr 674Ile mutation) (Gleich *et al*, 2002; Cools *et al*, 2003; Griffin *et al*, 2003; Pardanani *et al*, 2003; Wilkins *et al*, 2005). As a result of the characterization of the lymphocytic (L-HES) and myeloproliferative (M-HES) variants of HES (summarized in Table 1), the field of 'idiopathic' HES is now greatly reduced (Gleich and Leiferman, 2005; Ballanger *et al*, 2006).

Clinical variants and outcome

A new clinical classification of HES has emerged from recent clinical and biological progress (Gleich and Leiferman, 2005; Gotlib, 2005).

The myeloproliferative HES variant (M-HES) is more often associated with mucosal ulcerations. It is predominant in males and is characterized by hepatomegaly and splenomegaly. Blood tests show a persistent hypereosinophilia, an increased level of serum tryptase and vitamin B12, an altered leukocyte alkaline phosphatase score, chromosomal abnormalities, anemia and/or thrombocytopenia, and circulating leukocyte precursors (Klion *et al*, 2003). 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 a blast crisis revealing an acute eosinophilic or myeloid leukemia. They can also develop a granulocytic sarcoma (Roufosse *et al*, 2003).

The lymphocytic HES variant (L-HES) is equally distributed in females and males. Mucosal lesions are less frequent than in M-HES. Skin manifestations are pruritus, erythematous, urticaria-like, papules and plaques, erythroderma, and angioedema. Patients rarely develop endomyocardial fibrosis. The lungs and the digestive tract can be involved. Clonal T cells, of $CD3^-$ $CD4^+$ phenotype, express Th2 cytokines as IL-4, IL-5, and IL-13. These clonal T-cells are often detected in patients progressing to T cell lymphomas (Ravoet *et al*, 2005).

Mucosal ulcerations are often associated with severe forms of HES with systemic involvement. A major complication of severe HES, whatever the form, is endomyocardial fibrosis. It is the late stage of cardiac involvement, after early necrotic stage (rarely symptomatic), or thrombotic stage (intracavitary thrombi developing along the damaged endocardium) (Desreumaux *et al*, 1993). In the late fibrotic stage with endomyocardial fibrosis, cardiac damage involves atrioventricular valves and induces congestive heart failure. Independently of endomyocardial lesions, peripheral thromboembolism related to an increased number of blood eosinophils may occur (Mabilat-Pragnon *et al*, 1997; Alter and Maisch, 2006).

Clinical and pathological features of oral lesions in HES

Hypereosinophilic syndrome is a rare disorder with an estimated incidence rate of 0.5–1.0 cases per 100 000 per year. In a recent study, emphasis was placed on mucosal ulcerations, considering this variant presentation of HES as commonly associated with the genetic change resulting in a gain-of-function gene (FIP1L1-PDGFRA), characteristic of patients with M-HES (Leiferman and Gleich, 2004; Hofmann *et al*, 2006).

Cutaneous and mucosal signs occur in 27 to 64% of HES cases (Kazmierowski *et al*, 1978; Leiferman *et al*, 1982; Aractingi *et al*, 1996; Barouky *et al*, 2003).

In HES mucosal lesions can be ulcerations, erosions, or aphthous lesions localized on the lips, gingival, tongue, palatine, or jugal mucosa (Figure 1a). They are characterized by discrete, round, or oval ulcers,

Table 1 Clinical and pathological features of the different forms of HES (modified from Gleich and Leiferman, 2005)

HES variants	*Myeloid (M-HES)*	*Lymphocytic (L-HES)*	*Unclassified*
Features (clinical and pathological)	Males	Males/females	Episodic angioedema with eosinophilia
	Mucosal ulcers	Pruritus	Necrotizing eosinophilic vasculitis
	Eosinophilic endomyocarditis	Erythematous papules erythroderma	
	Splenomegaly	Urticaria-like plaques	
	Possible progression to myeloproliferative disorders	Possible progression to T cell lymphomas	Immunological disorders
	Blood eosinophilia (>1500 eosinophils μl^{-1}) >6 months	Blood eosinophilia (>1500 eosinophils μl^{-1})	Blood eosinophilia
	Raised vitamin B12 and tryptase serum levels	>6 months	(>1500 eosinophils μl^{-1})
	Bone marrow: CD25+ atypical mast cells	Th2 profile clonal T-lymphocyte secretion (interleukin-5 expression)phenotype $CD3^-$ $CD4^+$	>6 months
	FIP1L1-PDGFRA gene		
Treatment	Imatinib-mesylate therapy good response	Cortisone	Cortisone
		Anti-IL-5 (mepolizumab)	IFN
		Cyclosporin	Hydroxyurea

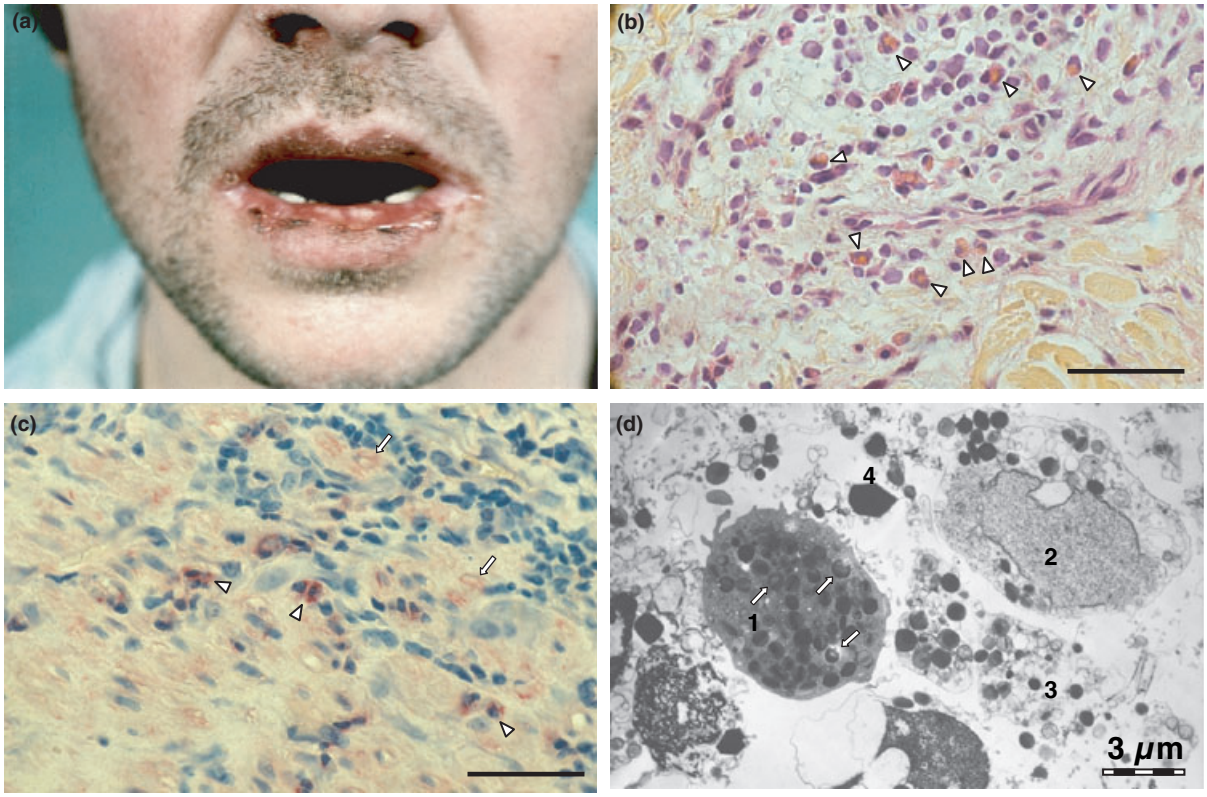

Figure 1 Hypereosinophilic Syndrome and oral mucosa lesions clinical and microscopic features (**a**) Clinical aspect of mucosal erosions. (**b**) Histological aspect of the inflammatory infiltrate in the biopsy of a mucosal erosion: large number of eosinophils with binucleated nucleus and eosinophilic cytoplasm (arrowheads). Scale bar: 50 μm. (**c**) Indirect immunohistochemical staining with an antibody directed against eosinophil peroxidase (EPO) revealed by alkaline phosphatase-labeled secondary antibody: the specific staining is found in the cytoplasm of intact eosinophils (arrowheads) as well as in the cytoplasmic component of altered eosinophils (arrow). Scale bar: 50 μm. (**d**) Ultrastructural aspect of the infiltrate, associating activated eosinophils with cytoplasmic granule with inverted density of the central cores (1, arrows), degranulating eosinophil with lytic nucleus (2), free extracellular cytoplasmic granules (3), and Charcot-Leyden crystal with characteristic crystal shape (4)

sometimes confluent, located on non-keratinized, unattached mucosa such as buccal and labial mucosa, sulci, lateral and ventral tongue, soft palate, and the oropharynx. Lesions are painful and may interfere with eating, speaking, or swallowing. These oral lesions may be associated with similar genital mucosa or conjunctival lesions.

Oral ulcerations from HES must be differentiated from ulcerations of other causes, mainly local traumas, malignant neoplasms, drug or irradiation-induced ulcerations. More numerous are the causes of oral ulcerations associated with systemic diseases – microbial diseases, bullous skin diseases, inflammatory bowel diseases, and necrotic vasculitis (Scully, 1992a,b).

Ulcerated lesions from HES must also be differentiated from aphthae, either simple aphtosis, or recurrent aphthous stomatitis, recurrent oral and genital aphthae, and Behçet's disease. They are less difficult to differentiate from secondary complex aphtosis within HIV, cyclic neutropenia, FAPA (fever, aphthous stomatitis, pharyngitis, adenitis), gluten-sensitive enteropathy, and hematinic deficiencies (iron, zinc, folate, vitamin B) (Letsinger *et al*, 2005).

On hematoxylin–eosin stain, mucosal lesions contain, under an ulcerated epithelium, a polymorphous infiltrate composed of lymphocytes, plasma cells, and macrophages, with some characteristic eosinophils, with bilobated nucleus and eosinophilic cytoplasm (Figure 1b). A specific May-Grünwald–Giemsa stain is required to precisely assess the number of eosinophils and their distribution. Moreover, activated eosinophils often degranulate, with specific granules scattered in the intercellular space within the inflammatory infiltrate. Antibodies directed against eosinophilic cationic proteins [eosinophil peroxidase, major basic protein (MBP), eosinophil cationic protein (ECP), and eosinophil-derived neurotoxin] can be used on histologic sections in order to identify eosinophils and the extracellular granules resulting from eosinophil degranulation (Figure 1c).

Electron microscopic examination (Figure 1d) can be used to identify eosinophils, and their state of degranulation. When intact, they are characterized by cytoplasmic granules with a dense matrix and a crystallized central core. When observed at different stages of degranulation, they have an inverted density of the central cores of the cytoplasmic granules and a partially dissociated cytoplasm (Janin *et al*, 1996; Daneshpouy *et al*, 2002b). Eosinophil activation can also lead to full cell lysis, with ultrastructural features associated with

a necrotic nucleus, a disintegrated cytoplasm, and surrounding extracellular free granules (Colombel *et al*, 1990; Janin *et al*, 1994). The ultimate stage of eosinophil lysis results in the constitution of Charcot-Leyden crystals, with the characteristic sharp and dense crystal shape (Janin *et al*, 1992). These Charcot-Leyden crystals are particularly resistant. They can be found in the tissue 2–3 weeks after eosinophil lysis (Janin *et al*, 1993). They can also be detected in the blood and body fluids as broncho-alveolar lavage or urine (Dubucquoi *et al*, 1994).

HES pathogenetic mechanisms

Eosinophil activation and induction of tissue damage

The release of cationic proteins through eosinophil degranulation and/or lysis can induce tissue damage, as demonstrated *in vitro* on helminthes and epithelial cells (Jong *et al*, 1981). In human pathology, eosinophil infiltration is predominant in the mucosa, and eosinophil activation is observed in the oral and bronchial mucosa of asthmatic patients (Gosset *et al*, 1995; Tsicopoulos *et al*, 2000), in the digestive tract of patients with eosinophilic gastroenteritis (Desreumaux *et al*, 1996), and in both the skin and duodenal mucosa of patients with dermatitis herpetiformis (Desreumaux *et al*, 1995). The biological signs of eosinophilic activation in the blood are hypodense eosinophils. In the tissues, the pathological signs of eosinophil activation is characterized by the release of cationic proteins, the presence of hypodense granules on ultrastructural examination, and the synthesis of IL-5.

Eosinophil activation is also associated with acute symptoms such as flare-ups (Tillie-Leblond *et al*, 1998; Vandezande *et al*, 1999; Daneshpouy *et al*, 2002a) or early recurrences (Desreumaux *et al*, 1992; Dubucquoi *et al*, 1995) of inflammatory diseases, microvascular lesions, and necrosis (Leiferman, 1991; Launay *et al*, 2000). Release of cationic proteins (ECP and MBP) can also lead to lipid membrane disruption and target cell death (Weller, 1994). In HES, activated eosinophils are observed in early oral ulcerations (Leiferman *et al*, 1982; Aractingi *et al*, 1996) as in late endomyocardial fibrosis (Janin, 2005).

Mechanisms of eosinophil chemotactism and activation

Eosinophils are derived from myeloid progenitors (granulocyte/erythrocyte/macrophage/megakaryocyte-colony forming unit; GEMM-CFU) in the bone marrow, through the action of three hematopoietic cytokines – granulocyte/macrophage-colony stimulating factor (GM-CSF), interleukin (IL)-3, and IL-5 (Sanderson, 1992). Mature eosinophils are released into the bloodstream and rapidly migrate toward their target tissues (Mishra *et al*, 1999; Wardlaw, 1999; Rothenberg and Hogan, 2006). In physiological conditions, tissue eosinophil survival is short (24–48 h) (Leiferman, 1991; Moqbel *et al*, 1994; Rothenberg, 1998). In pathological conditions IL-5 prolongs tissue eosinophil survival (Collins *et al*, 1995; Matthews *et al*, 1998). The main chemotactic mediators are eotaxin-1, eotaxin-2, eotaxin-3, and IL-5. IL-5 is also a major mediator for eosinophil activation and *in situ* survival (Clutterbuck and Sanderson, 1990; Rothenberg *et al*, 1997; Zimmermann *et al*, 2003). IL-5 can be produced by different cells – lymphocytes, mastocytes, basophils, and eosinophils themselves (Broide *et al*, 1992; Till *et al*, 1997; Lorentz *et al*, 1999; Phillips *et al*, 2003). T-helper lymphocytes with a cytokine profile type Th2 express IL-5, IL-4, and IL-13. The Th2-type of response is linked to hypereosinophilia, high serum IgE levels and polyclonal hypergammaglobulinemia (due to polyclonal B-cell activation) (Del Prete *et al*, 1989; Genton *et al*, 2006). Th2 T cells are found in atopic dermatitis, a common chronic dermatitis associated with eosinophilia (Kiehl *et al*, 2001). Clonal Th2 T cells are found in T-cell lymphomas, a major complication of the lymphocytic variant of HES (Kitano *et al*, 1997).

In pathological conditions, eosinophilic recruitment, proliferation, and activation can be initially induced by an acquired abnormal genetic change of myeloid line (Keung *et al*, 2002; Gotlib *et al*, 2004). This takes place in the context of an increased hematopoiesis, and is more frequently found in the M-HES variant, associated with myeloproliferative disorders.

Eosinophil recruitment and activation can also be induced by an overproduction of IL-5, IL-3, and GM-CSF (Desreumaux *et al*, 1998; Pazdrak *et al*, 1998). This is observed mainly in the L-HES variant, as in hypereosinophilia associated with Hodgkin's disease, T-cell lymphomas or solid tumors (Bain, 2000; Ionescu *et al*, 2005). Moreover, autocrine production of IL-5 by the eosinophil can contribute to chronic eosinophil infiltration (Desreumaux *et al*, 1992, 1993, 1996; Dubucquoi *et al*, 1994).

HES treatment

A new therapy is now proposed for different variants of HES, based on clinical and biological data. Corticotherapy is a first line therapy. It is an efficient therapy, particularly for mucosal ulcerations, when HES is not yet diagnosed. Topic or systemic steroids efficiently decrease eosinophilic activation and tissue recruitment by apoptosis induction (Roufosse *et al*, 2003; Gleich and Leiferman, 2005).

M-HES-targeted treatment

Imatinib mesylate is a tyrosine kinase inhibitor (initially introduced for the treatment of CML), and it is the first choice treatment in M-HES, leading to a dramatic improvement (Gleich *et al*, 2002). The target of imatinib is a novel kinase resulting from an 800-kb deletion on chromosome 4. cDNA derived from the fusion gene encoded a novel protein composed of the kinase domain of PDGFR-α linked to a previously uncharacterized gene resembling FIP1. This genetic rearrangement, initially found in the eosinophilic cell line EOL-1 [human acute myeloid (eosinophilic) leukemia, DSMZ ACC 386], was also detected in blood cells from patients with HES (Griffin *et al*, 2003). A recent study of 16 HES patients showed that nine responded to imatinib, including all five with the FIP1L1–PDGFRA fusion gene.

Furthermore, Ba/F3 (murine pro B cell, DSMZ ACC 300) cells expressing FIP1L1–PDGFRA were over 100 times more sensitive to imatinib than cells expressing *breakpoint cluster region- Abelson* (*BCR-ABL*) (Cools *et al*, 2003).

The second generation of BCR–ABL tyrosine kinase inhibitors is used in imatinib-resistant HES (Tauchi and Ohyashiki, 2006). Other drugs used in M-HES treatment are hydroxyurea (Varon *et al*, 1986; Coutant *et al*, 1993; Weller and Bubley, 1994) and α-interferon (IFN-α) (Weller and Bubley, 1994; Butterfield, 2005). If signs of malignant transformation are found, chemotherapy (Tanaka *et al*, 2006) or hematopoietic stem cell transplantation (HSCT) must be initiated (Fukushima *et al*, 1995).

L-HES treatment

In the lymphocytic variant, steroids are very efficient and are the treatment of choice (Wallen *et al*, 1991; Weller and Bubley, 1994; Amano *et al*, 2005; Huntgeburth *et al*, 2005). IFN-α can also be associated to L-HES treatment (Schandene *et al*, 1996, 2000; Yoon *et al*, 2000). Other treatments are cyclosporin A (Zabel and Schlaak, 1991; Nadarajah *et al*, 1997). If signs of malignant transformation are diagnosed, the treatment lines specific for T-cell lymphoma are proposed, with chemotherapy (cyclophosphamide, hydroxydoxorubicin, oncovin, prednisone; CHOP-like regimen) (Granel *et al*, 2000), associated or not with monoclonal antibodies (Pitini *et al*, 2004; Sefcick *et al*, 2004), fludarabine, 2-chlorodeoxyadenosine (2-CdA) (Ueno *et al*, 1997; Jabbour *et al*, 2005). In resistant or recurrent cases, intensive high-dose chemotherapy followed by HSCT can be used (Ueno *et al*, 2002). Recently, a specific targeted therapy based on an anti-IL-5 monoclonal antibody mepolizumab (Plotz *et al*, 2003; Garrett *et al*, 2004; Simon *et al*, 2005; Sutton *et al*, 2005; Wilkins *et al*, 2005) has been proposed.

Conclusion

The field of 'idiopathic hypereosinophilic syndromes' has been consistently reduced due to the better understanding of eosinophil biology. The therapeutic indications have also been completely changed by the efficiency of imatinib on the myeloproliferative forms of HES. The characterization of a fusion gene associated with the kinase target of imatinib offers to the physicians a biological marker to recognize patients who could benefit from this targeted therapy. As oral mucosa ulcerations are more often associated with M-HES, and can be a presenting sign, oral physicians play a key role in the early recognition of M-HES, a necessary step for an efficient therapy.

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