



Oral mucosa lesions in hypereosinophilic syndrome - an update.

Marius A. Ionescu, Hideyuki Murata, Anne Janin

► To cite this version:

Marius A. Ionescu, Hideyuki Murata, Anne Janin. Oral mucosa lesions in hypereosinophilic syndrome - an update.: Hypereosinophilic syndrome and oral ulcers. Oral Diseases, 2008, 14 (2), pp.115-22. 10.1111/j.1601-0825.2007.01393.x . inserm-00151217

HAL Id: inserm-00151217

<https://inserm.hal.science/inserm-00151217>

Submitted on 23 May 2014

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Oral Diseases / Review**Oral mucosa lesions in hypereosinophilic syndrome: an update**

Running title: Hypereosinophilic syndrome and oral ulcers

Keywords: hypereosinophilic syndrome, oral ulcers, myeloproliferative and lymphocytic variants, imatinib mesylate

Marius A. IONESCU, MD, PhD^{1,2}, Hideyuki MURATA, MD, PhD^{1,2}, Anne JANIN, MD, PhD^{1,2,3}

1 Inserm, U728, Paris, F-75010, France

2 Université Paris 7, U728, Paris, F-75010, France

3 AP-HP, Hôpital Saint-Louis, Service de Pathologie, Paris, F-75010, France

Word count: Abstract: 196 words; Text 2460 words

Corresponding author:

Anne JANIN, MD, PhD

Service de Pathologie and Inserm U728, Université Paris VII,

Hôpital Saint Louis, 1 Avenue Claude Vellefaux, 75475, Paris Cedex 10, France.

Phone : + 33 1 42 49 99 33

Fax : + 33 1 42 49 49 22

E-mail: anne_janin@yahoo.com

Date of submission: January, 19, 2007

Date of revision: March, 10, 2007

Date of acceptance: 24 March 2007

Abstract

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 fifteen 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). Imatinib's target is a novel kinase resulting from a 800kb deletion on chromosome 4. Recently, the resulting FIP1L1-PDGFR α 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.

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; Roufosse et al., 2000; Simon et al., 1999).

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

Diagnostic criteria for Hypereosinophilic syndrome

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

- a. blood eosinophilia (>1500 eosinophils / μ L) for more than 6 months;
- b. exclusion of reactive eosinophilia caused by parasitic infections, allergies, eosinophilia associated with neoplasia;
- c. 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 interleukine-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; Roufosse et al., 2000; Simon et al., 1999). 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 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-PDGFR α) fusion gene), and of resistance to this drug (Thr 674Ile mutation) (Cools et al., 2003; Gleich et al., 2002; 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 I), the field of “idiopathic” HES is now greatly reduced (Ballanger et al., 2006; Gleich and Leiferman, 2005).

Clinical variants and outcome

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

The myeloproliferative HES variant (M-HES) is more often associated with mucosal ulcerations. It predominates 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 from endomyocardial lesions, peripheral thromboembolism related to an increased number of blood eosinophils may occur (Alter and Maisch, 2006; Mabilat-Pragnon et al., 1997).

Clinical and pathological features of oral lesions in Hypereosinophilic syndrome

HES is a rare disorder with an estimated incidence rate of 0.5 to 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-PDGFR α), characteristic of patients with M-HES (Hofmann et al., 2006; Leiferman and Gleich, 2004).

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

HES mucosal lesions can be ulcerations, erosions or aphthous lesions localized on the lips, gingival, tongue, palatine or jugal mucosa (Fig 1a). They are characterized by discrete, round or oval ulcers, sometimes confluent, located on nonkeratinized, unattached mucosa such as buccal

and labial mucosa, sulci, lateral and ventral tongue, soft palate, and 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; Scully, 1992b). 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, 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 (Fig 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 inflammatory infiltrate. Antibodies directed against eosinophilic cationic proteins (eosinophil peroxidase - EPO, major basic protein - MBP, eosinophil cationic protein - ECP, eosinophil-derived neurotoxin - EDN) can be used on histological sections in order to identify eosinophils and the extracellular granules resulting from eosinophil degranulation (Fig 1c).

Electron microscopic examination (Fig 1 d) 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 (Daneshpouy et al., 2002b; Janin et al., 1996). Eosinophil activation can also lead to full cell lysis, with ultrastructural features associating 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 characteristic sharp and dense crystal shape (Janin et al., 1992). These Charcot-Leyden crystals are particularly resistant. They can be found in the tissue two to three weeks after the 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

1 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 predominates in mucosa, and eosinophil activation is observed in oral and bronchial mucosa of asthmatic patients (Gosset et al., 1995; Tsicopoulos et al., 2000), in digestive tract of patients with eosinophilic gastroenteritis (Desreumaux et al., 1996) in both 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 as flare-ups (Daneshpouy et al., 2002a; Tillie-Leblond et al., 1998; Vandezande et al., 1999) or early recurrences (Desreumaux et al., 1992; Dubucquoi et al., 1995) of inflammatory diseases, microvascular lesions and necrosis (Launay et al., 2000; Leiferman, 1991). Release of cationic proteins (ECP and MBP) can also lead to lipid membrane disruption and target cell death (Weller, 1994). In Hypereosinophilic syndromes, activated eosinophils are observed in early oral ulcerations (Aractingi et al., 1996; Leiferman et al., 1982) as in late endomyocardial fibrosis (Janin, 2005).

2 Mechanisms of eosinophil chemotactism and activation

Eosinophils are derived from myeloid progenitors (granulocyte/erythrocyte/macrophage/megakaryocyte-colony forming unit; GEMM-CFU) in 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 blood stream and rapidly migrate towards their target tissues (Mishra et al., 1999; Rothenberg and Hogan, 2006; Wardlaw, 1999). In physiological conditions, tissue eosinophils survival is short (24-48h) (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; Lorentz et al., 1999; Phillips et al., 2003; Till et al., 1997). T-helper lymphocytes with a cytokine profile type Th2

express of IL-5, IL-4 and IL-13. 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 (Gotlib et al., 2004; Keung et al., 2002). 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., 1996; Desreumaux et al., 1992; Desreumaux et al., 1993; Dubucquoi et al., 1994).

Hypereosinophilic syndrome 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 has not yet been diagnosed. Topic or systemic steroids efficiently decrease eosinophilic activation and tissue recruitment by apoptosis induction (Gleich and Leiferman, 2005; Roufosse et al., 2003).

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). Imatinib's target is a novel kinase resulting from a 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 (Coutant et al., 1993; Varon et al., 1986; Weller and Bubley, 1994), interferon alpha (Butterfield, 2005; Weller and Bubley, 1994). 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 (Amano et al., 2005; Huntgeburth et al., 2005; Wallen et al., 1991; Weller and Bubley, 1994). IFN-alpha can be associated to *L-HES treatment* (Schandene et al., 1996; Schandene et al., 2000; Yoon et al., 2000). Other treatments are cyclosporin A (Nadarajah et al., 1997; Zabel and Schlaak, 1991). 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) (Jabbour et al., 2005; Ueno et al., 1997). 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 (Garrett et al., 2004; Plotz et al., 2003; 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. Since oral mucosa ulcerations are more often associated to 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.

Figure Legends

Hypereosinophilic Syndrome and oral mucosa lesions clinical and microscopic features

Figure 1a: clinical aspect of mucosal erosions

1b: 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 μ m

1c: indirect immunohistochemical staining with an antibody directed against Eosinophil Peroxidase (EPO) revealed by alkaline phosphatase labelled secondary antibody: the specific staining is found in the cytoplasm of intact eosinophils (arrowheads) as well as in cytoplasmic component of altered eosinophils (arrow). Scale bar: 50 μ m

1d: 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).

References

- Alter P and Maisch B. (2006). Endomyocardial fibrosis in Churg-Strauss syndrome assessed by cardiac magnetic resonance imaging. *Int J Cardiol* 108: 112-113.
- Amano A, Sakai N, Higashi N, Yoshizawa Y and Kawana S. (2005). A case of hypereosinophilic syndrome. *J Dermatol* 32: 286-289.
- Aractingi S, Janin A, Zini JM, Gauthier MS, Chauvenet L, Tobelem G, Prin L, Chosidow O and Frances C. (1996). Specific mucosal erosions in hypereosinophilic syndrome. Evidence for eosinophil protein deposition. *Arch Dermatol* 132: 535-541.
- Bain BJ. (2000). Hypereosinophilia. *Curr Opin Hematol* 7: 21-25.
- Ballanger F, Barbarot S and Hamidou M. (2006). Syndromes hyperéosinophiliques primitifs : actualités. *Ann Dermatol* 133: 1487-1494
- Barouky R, Bencharif L, Badet F, Salles G, Vital Durand D and Rousset H. (2003). Mucosal ulcerations revealing primitive hypereosinophilic syndrome. *Eur J Dermatol* 13: 207-208.
- Billon C, Gautier C, Villaret E, Ducos MH, Martin JC and Geniaux M. (1997). [Isolated mucosal ulcers disclosing idiopathic hypereosinophilic syndrome]. *Ann Dermatol Venereol* 124: 248-250.
- Broide DH, Paine MM and Firestein GS. (1992). Eosinophils express interleukin 5 and granulocyte macrophage-colony-stimulating factor mRNA at sites of allergic inflammation in asthmatics. *J Clin Invest* 90: 1414-1424.
- Butterfield JH. (2005). Interferon treatment for hypereosinophilic syndromes and systemic mastocytosis. *Acta Haematol* 114: 26-40.
- Chusid MJ, Dale DC, West BC and Wolff SM. (1975). The hypereosinophilic syndrome: analysis of fourteen cases with review of the literature. *Medicine (Baltimore)* 54: 1-27.
- Clutterbuck EJ and Sanderson CJ. (1990). Regulation of human eosinophil precursor production by cytokines: a comparison of recombinant human interleukin-1 (rhIL-1), rhIL-3, rhIL-5, rhIL-6, and rh granulocyte-macrophage colony-stimulating factor. *Blood* 75: 1774-1779.

Cogan E, Schandene L, Crusiaux A, Cochaux P, Velu T and Goldman M. (1994). Brief report: clonal proliferation of type 2 helper T cells in a man with the hypereosinophilic syndrome. *N Engl J Med* 330: 535-538.

Collins PD, Marleau S, Griffiths-Johnson DA, Jose PJ and Williams TJ. (1995). Cooperation between interleukin-5 and the chemokine eotaxin to induce eosinophil accumulation in vivo. *J Exp Med* 182: 1169-1174.

Colombel JF, Janin A and Torpier G. (1990). Activated eosinophils in coeliac disease. *Gut* 31: 583-584.

Cools J, DeAngelo DJ, Gotlib J, Stover EH, Legare RD, Cortes J, Kutok J, Clark J, Galinsky I, Griffin JD et al. (2003). A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med* 348: 1201-1214.

Coutant G, Bletry O, Prin L, Hauteville D, de Puyfontaine O, Abgrall JF and Godeau P. (1993). [Treatment of hypereosinophilic syndromes of myeloproliferative expression with the combination of hydroxyurea and interferon alpha. Apropos of 7 cases]. *Ann Med Interne (Paris)* 144: 243-250.

Daneshpouy M, Facon T, Jouet JP and Janin A. (2002a). Acute flare-up of conjunctival graft-versus-host disease with eosinophil infiltration in a patient with chronic graft-versus-host disease. *Leuk Lymphoma* 43: 445-446.

Daneshpouy M, Socie G, Lemann M, Rivet J, Gluckman E and Janin A. (2002b). Activated eosinophils in upper gastrointestinal tract of patients with graft-versus-host disease. *Blood* 99: 3033-3040.

Del Prete G, Tiri A, Maggi E, De Carli M, Macchia D, Parronchi P, Rossi ME, Pietrogrande MC, Ricci M and Romagnani S. (1989). Defective in vitro production of gamma-interferon and tumor necrosis factor-alpha by circulating T cells from patients with the hyper-immunoglobulin E syndrome. *J Clin Invest* 84: 1830-1835.

Desreumaux P, Bloget F, Seguy D, Capron M, Cortot A, Colombel JF and Janin A. (1996). Interleukin 3, granulocyte-macrophage colony-stimulating factor, and interleukin 5 in eosinophilic gastroenteritis. *Gastroenterology* 110: 768-774.

Desreumaux P, Delaporte E, Colombel JF, Capron M, Cortot A and Janin A. (1998). Similar IL-5, IL-3, and GM-CSF syntheses by eosinophils in the jejunal mucosa of patients with celiac disease and dermatitis herpetiformis. *Clin Immunol Immunopathol* 88: 14-21.

Desreumaux P, Janin A, Colombel JF, Prin L, Plumas J, Emilie D, Torpier G, Capron A and Capron M. (1992). Interleukin 5 messenger RNA expression by eosinophils in the intestinal mucosa of patients with coeliac disease. *J Exp Med* 175: 293-296.

Desreumaux P, Janin A, Delaporte E, Dubucquoi S, Piette F, Cortot A, Capron M and Colombel JF. (1995). Parallel interleukin 5 synthesis by eosinophils in duodenal and skin lesions of a patient with dermatitis herpetiformis. *Gut* 37: 132-135.

Desreumaux P, Janin A, Dubucquoi S, Copin MC, Torpier G, Capron A, Capron M and Prin L. (1993). Synthesis of interleukin-5 by activated eosinophils in patients with eosinophilic heart diseases. *Blood* 82: 1553-1560.

Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, Lydon NB, Kantarjian H, Capdeville R, Ohno-Jones S et al. (2001). Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med* 344: 1031-1037.

Dubucquoi S, Janin A, Desreumaux P, Rigot JM, Copin MC, Francois M, Torpier G, Capron M and Gosselin B. (1994). Evidence for eosinophil activation in eosinophilic cystitis. *Eur Urol* 25: 254-258.

Dubucquoi S, Janin A, Klein O, Desreumaux P, Quandalle P, Cortot A, Capron M and Colombel JF. (1995). Activated eosinophils and interleukin 5 expression in early recurrence of Crohn's disease. *Gut* 37: 242-246.

Fauci AS, Harley JB, Roberts WC, Ferrans VJ, Gralnick HR and Bjornson BH. (1982). NIH conference. The idiopathic hypereosinophilic syndrome. Clinical, pathophysiologic, and therapeutic considerations. *Ann Intern Med* 97: 78-92.

Fukushima T, Kuriyama K, Ito H, Miyazaki Y, Arimura K, Hata T, Saitoh M and Tomonaga M. (1995). Successful bone marrow transplantation for idiopathic hypereosinophilic syndrome. *Br J Haematol* 90: 213-215.

Garrett JK, Jameson SC, Thomson B, Collins MH, Wagoner LE, Freese DK, Beck LA, Boyce JA, Filipovich AH, Villanueva JM et al. (2004). Anti-interleukin-5 (mepolizumab) therapy for hypereosinophilic syndromes. *J Allergy Clin Immunol* 113: 115-119.

Genton C, Wang Y, Izui S, Malissen B, Delsol G, Fournie GJ, Malissen M and Acha-Orbea H. (2006). The Th2 lymphoproliferation developing in LatY136F mutant mice triggers polyclonal B cell activation and systemic autoimmunity. *J Immunol* 177: 2285-2293.

Gleich GJ and Leiferman KM. (2005). The hypereosinophilic syndromes: still more heterogeneity. *Curr Opin Immunol* 17: 679-684.

Gleich GJ, Leiferman KM, Pardananani A, Tefferi A and Butterfield JH. (2002). Treatment of hypereosinophilic syndrome with imatinib mesilate. *Lancet* 359: 1577-1578.

Gosset P, Tillie-Leblond I, Janin A, Marquette CH, Copin MC, Wallaert B and Tonnel AB. (1995). Expression of E-selectin, ICAM-1 and VCAM-1 on bronchial biopsies from allergic and non-allergic asthmatic patients. *Int Arch Allergy Immunol* 106: 69-77.

Gotlib J. (2005). Molecular classification and pathogenesis of eosinophilic disorders: 2005 update. *Acta Haematol* 114: 7-25.

Gotlib J, Cools J, Malone JM, 3rd, Schrier SL, Gilliland DG and Coutre SE. (2004). The FIP1L1-PDGFRalpha fusion tyrosine kinase in hypereosinophilic syndrome and chronic eosinophilic leukemia: implications for diagnosis, classification, and management. *Blood* 103: 2879-2891.

Granel B, Serratrice J, Swiader L, Horshowski N, Blaise D, Vey N, Metras D, Habib G, Disdier P and Weiller PJ. (2000). Lymphomatoid papulosis associated with both severe hypereosinophilic syndrome and CD30 positive large T-cell lymphoma. *Cancer* 89: 2138-2143.

Griffin JH, Leung J, Bruner RJ, Caligiuri MA and Briesewitz R. (2003). Discovery of a fusion kinase in EOL-1 cells and idiopathic hypereosinophilic syndrome. *Proc Natl Acad Sci U S A* 100: 7830-7835.

Hardy WR and Anderson RE. (1968). The hypereosinophilic syndromes. *Ann Intern Med* 68: 1220-1229.

Hofmann SC, Technau K, Muller AM, Lubbert M and Bruckner-Tuderman L. (2007). Bullous pemphigoid associated with hypereosinophilic syndrome: Simultaneous response to imatinib. *J Am Acad Dermatol*. 56 Suppl, pp S68-S72.

Huntgeburth M, Lindner M, Fries JW and Hoppe UC. (2005). Hypereosinophilic syndrome associated with acute necrotizing myocarditis and cardiomyopathy. *Z Kardiol* 94: 761-766.

Ionescu MA, Rivet J, Daneshpouy M, Briere J, Morel P and Janin A. (2005). In situ eosinophil activation in 26 primary cutaneous T-cell lymphomas with blood eosinophilia. *J Am Acad Dermatol* 52: 32-39.

Jabbour E, Verstovsek S, Giles F, Gandhi V, Cortes J, O'Brien S, Plunkett W, Garcia-Manero G, Jackson CE, Kantarjian H et al. (2005). 2-Chlorodeoxyadenosine and cytarabine combination therapy for idiopathic hypereosinophilic syndrome. *Cancer* 104: 541-546.

Janin A. (2005). Eosinophilic myocarditis and fibrosis. *Hum Pathol* 36: 592-593; 593.

Janin A, Copin MC, Dubos JP, Rouland V, Delaporte E and Blanchet-Bardon C. (1996). Familial peeling skin syndrome with eosinophilia: clinical, histologic, and ultrastructural study of three cases. *Arch Pathol Lab Med* 120: 662-665.

Janin A, Socie G, Devergie A, Aractingi S, Esperou H, Verola O and Gluckman E. (1994). Fasciitis in chronic graft-versus-host disease. A clinicopathologic study of 14 cases. *Ann Intern Med* 120: 993-998.

Janin A, Torpier G, Capron M, Courtin P and Gosselin B. (1992). Immunopathological study of eosinophils in eosinophilic granuloma of bone: evidence for release of three cationic proteins and subsequent uptake in macrophages. *Virchows Arch A Pathol Anat Histopathol* 421: 255-261.

Janin A, Torpier G, Courtin P, Capron M, Prin L, Tonnel AB, Hatron PY and Gosselin B. (1993). Segregation of eosinophil proteins in alveolar macrophage compartments in chronic eosinophilic pneumonia. *Thorax* 48: 57-62.

Jong EC, Mahmoud AA and Klebanoff SJ. (1981). Peroxidase-mediated toxicity to schistosomula of *Schistosoma mansoni*. *J Immunol* 126: 468-471.

Kazmierowski JA, Chusid MJ, Parrillo JE, Fauci AS and Wolff SM. (1978). Dermatologic manifestations of the hypereosinophilic syndrome. *Arch Dermatol* 114: 531-535.

Keung YK, Beaty M, Steward W, Jackle B and Pettnati M. (2002). Chronic myelocytic leukemia with eosinophilia, t(9;12)(q34;p13), and ETV6-ABL gene rearrangement: case report and review of the literature. *Cancer Genet Cytogenet* 138: 139-142.

Kiehl P, Falkenberg K, Vogelbruch M and Kapp A. (2001). Tissue eosinophilia in acute and chronic atopic dermatitis: a morphometric approach using quantitative image analysis of immunostaining. *Br J Dermatol* 145: 720-729.

Kitano K, Ichikawa N, Shimodaira S, Ito T, Ishida F and Kiyosawa K. (1997). Eosinophilia associated with clonal T-cell proliferation. *Leuk Lymphoma* 27: 335-342.

Klion AD, Noel P, Akin C, Law MA, Gilliland DG, Cools J, Metcalfe DD and Nutman TB. (2003). Elevated serum tryptase levels identify a subset of patients with a myeloproliferative variant of idiopathic hypereosinophilic syndrome associated with tissue fibrosis, poor prognosis, and imatinib responsiveness. *Blood* 101: 4660-4666.

Launay D, Delaporte E, Gillot JM, Janin A and Hachulla E. (2000). An unusual cause of vascular purpura: recurrent cutaneous eosinophilic necrotizing vasculitis. *Acta Derm Venereol* 80: 394-395.

Leiferman KM. (1991). A current perspective on the role of eosinophils in dermatologic diseases. *J Am Acad Dermatol* 24: 1101-1112.

Leiferman KM and Gleich GJ. (2004). Hypereosinophilic syndrome: case presentation and update. *J Allergy Clin Immunol* 113: 50-58.

Leiferman KM, O'Duffy JD, Perry HO, Greipp PR, Giuliani ER and Gleich GJ. (1982). Recurrent incapacitating mucosal ulcerations. A prodrome of the hypereosinophilic syndrome. *Jama* 247: 1018-1020.

Letsinger JA, McCarty MA and Jorizzo JL. (2005). Complex aphthosis: a large case series with evaluation algorithm and therapeutic ladder from topicals to thalidomide. *J Am Acad Dermatol* 52: 500-508.

Lorentz A, Schwengberg S, Mierke C, Manns MP and Bischoff SC. (1999). Human intestinal mast cells produce IL-5 in vitro upon IgE receptor cross-linking and in vivo in the course of intestinal inflammatory disease. *Eur J Immunol* 29: 1496-1503.

Mabilat-Pragnon C, Janin A, Michel L, Thomaidis A, Legrand Y, Soria C and Lu H. (1997). Urokinase localization and activity in isolated eosinophils. *Thromb Res* 88: 373-379.

Matthews AN, Friend DS, Zimmermann N, Sarafi MN, Luster AD, Pearlman E, Wert SE and Rothenberg ME. (1998). Eotaxin is required for the baseline level of tissue eosinophils. *Proc Natl Acad Sci U S A* 95: 6273-6278.

Mishra A, Hogan SP, Lee JJ, Foster PS and Rothenberg ME. (1999). Fundamental signals that regulate eosinophil homing to the gastrointestinal tract. *J Clin Invest* 103: 1719-1727.

Moqbel R, Levi-Schaffer F and Kay AB. (1994). Cytokine generation by eosinophils. *J Allergy Clin Immunol* 94: 1183-1188.

Nadarajah S, Krafchik B, Roifman C and Horgan-Bell C. (1997). Treatment of hypereosinophilic syndrome in a child using cyclosporine: implication for a primary T-cell abnormality. *Pediatrics* 99: 630-633.

Pardanani A, Reeder T, Porrata LF, Li CY, Tazelaar HD, Baxter EJ, Witzig TE, Cross NC and Tefferi A. (2003). Imatinib therapy for hypereosinophilic syndrome and other eosinophilic disorders. *Blood* 101: 3391-3397.

Pazdrak K, Olszewska-Pazdrak B, Stafford S, Garofalo RP and Alam R. (1998). Lyn, Jak2, and Raf-1 kinases are critical for the antiapoptotic effect of interleukin 5, whereas only Raf-1 kinase is essential for eosinophil activation and degranulation. *J Exp Med* 188: 421-429.

Phillips C, Coward WR, Pritchard DI and Hewitt CR. (2003). Basophils express a type 2 cytokine profile on exposure to proteases from helminths and house dust mites. *J Leukoc Biol* 73: 165-171.

Pitini V, Teti D, Arrigo C and Righi M. (2004). Alemtuzumab therapy for refractory idiopathic hypereosinophilic syndrome with abnormal T cells: a case report. *Br J Haematol* 127: 477.

Plotz SG, Simon HU, Darsow U, Simon D, Vassina E, Yousefi S, Hein R, Smith T, Behrendt H and

Ring J. (2003). Use of an anti-interleukin-5 antibody in the hypereosinophilic syndrome with eosinophilic dermatitis. *N Engl J Med* 349: 2334-2339.

Ravoet M, Sibille C, Roufosse F, Duvillier H, Sotiriou C, Schandene L, Martiat P, Goldman M and Willard-Gallo KE. (2005). 6q- is an early and persistent chromosomal aberration in CD3-CD4+ T-cell clones associated with the lymphocytic variant of hypereosinophilic syndrome. *Haematologica* 90: 753-765.

Rothenberg ME. (1998). Eosinophilia. *N Engl J Med* 338: 1592-1600.

Rothenberg ME and Hogan SP. (2006). The eosinophil. *Annu Rev Immunol* 24: 147-174.

Rothenberg ME, MacLean JA, Pearlman E, Luster AD and Leder P. (1997). Targeted disruption of the chemokine eotaxin partially reduces antigen-induced tissue eosinophilia. *J Exp Med* 185: 785-790.

Roufosse F, Cogan E and Goldman M. (2003). The hypereosinophilic syndrome revisited. *Annu Rev Med* 54: 169-184.

Roufosse F, Schandene L, Sibille C, Willard-Gallo K, Kennes B, Efira A, Goldman M and Cogan E. (2000). Clonal Th2 lymphocytes in patients with the idiopathic hypereosinophilic syndrome. *Br J Haematol* 109: 540-548.

Sanderson CJ. (1992). Interleukin-5, eosinophils, and disease. *Blood* 79: 3101-3109.

Schandene L, Del Prete GF, Cogan E, Stordeur P, Crusiaux A, Kennes B, Romagnani S and Goldman M. (1996). Recombinant interferon-alpha selectively inhibits the production of interleukin-5 by human CD4+ T cells. *J Clin Invest* 97: 309-315.

Schandene L, Roufosse F, de Lavareille A, Stordeur P, Efira A, Kennes B, Cogan E and Goldman M. (2000). Interferon alpha prevents spontaneous apoptosis of clonal Th2 cells associated with chronic hypereosinophilia. *Blood* 96: 4285-4292.

Scully C (1992a). The Oral Cavity. In: Champion RH, Burton J, Ebling FJG, eds. *Rook/Wilkinson/Ebling's Textbook of Dermatology*, 5th Edition. vol. IV, pp. 2709. Oxford, Blackwell Science.

- Scully C (1992b). The Oral Cavity. In: Champion RH ,Burton J, Ebling FJG, eds. *Rook/Wilkinson/Ebling's Textbook of Dermatology*, 5th Edition. vol. IV, pp. 2698. Oxford, Blackwell Science.
- Sefcick A, Sowter D, DasGupta E, Russell NH and Byrne JL. (2004). Alemtuzumab therapy for refractory idiopathic hypereosinophilic syndrome. *Br J Haematol* 124: 558-559.
- Simon D, Braathen LR and Simon HU. (2005). Anti-interleukin-5 antibody therapy in eosinophilic diseases. *Pathobiology* 72: 287-292.
- Simon HU, Plotz SG, Dummer R and Blaser K. (1999). Abnormal clones of T cells producing interleukin-5 in idiopathic eosinophilia. *N Engl J Med* 341: 1112-1120.
- Sutton SA, Assa'ad AH and Rothenberg ME. (2005). Anti-IL-5 and hypereosinophilic syndromes. *Clin Immunol* 115: 51-60.
- Tanaka Y, Kurata M, Togami K, Fujita H, Watanabe N, Matsushita A, Maeda A, Nagai K, Sada A, Matsui T et al. (2006). Chronic eosinophilic leukemia with the FIP1L1-PDGFRalpha fusion gene in a patient with a history of combination chemotherapy. *Int J Hematol* 83: 152-155.
- Tauchi T and Ohyashiki K. (2006). The second generation of BCR-ABL tyrosine kinase inhibitors. *Int J Hematol* 83: 294-300.
- Till S, Dickason R, Huston D, Humbert M, Robinson D, Larche M, Durham S, Kay AB and Corrigan C. (1997). IL-5 secretion by allergen-stimulated CD4+ T cells in primary culture: relationship to expression of allergic disease. *J Allergy Clin Immunol* 99: 563-569.
- Tillie-Leblond I, Gosset P, Janin A, Salez F, Prin L and Tonnel AB. (1998). Increased interleukin-6 production during the acute phase of the syndrome of episodic angioedema and hypereosinophilia. *Clin Exp Allergy* 28: 491-496.
- Tsicopoulos A, Janin A, Akoum H, Lamblin C, Vorng H, Hamid Q, Tonnel AB and Wallaert B. (2000). Cytokine profile in minor salivary glands from patients with bronchial asthma. *J Allergy Clin Immunol* 106: 687-696.
- Ueno NT, Anagnostopoulos A, Rondon G, Champlin RE, Mikhailova N, Pankratova OS,

Zoubarovskaya LS, Semenova EV, Afanasyev BV, O'Brien S et al. (2002). Successful non-myeloablative allogeneic transplantation for treatment of idiopathic hypereosinophilic syndrome. *Br J Haematol* 119: 131-134.

Ueno NT, Zhao S, Robertson LE, Consoli U and Andreeff M. (1997). 2-Chlorodeoxyadenosine therapy for idiopathic hypereosinophilic syndrome. *Leukemia* 11: 1386-1390.

Vandezande LM, Wallaert B, Desreumaux P, Tsicopoulos A, Lamblin C, Tonnel AB and Janin A. (1999). Interleukin-5 immunoreactivity and mRNA expression in gut mucosa from patients with food allergy. *Clin Exp Allergy* 29: 652-659.

Varon D, Wetzler M and Berrebi A. (1986). Hypereosinophilic syndrome associated with polycythemia vera. *Arch Intern Med* 146: 1440-1441.

Wallen N, Kita H, Weiler D and Gleich GJ. (1991). Glucocorticoids inhibit cytokine-mediated eosinophil survival. *J Immunol* 147: 3490-3495.

Wardlaw AJ. (1999). Molecular basis for selective eosinophil trafficking in asthma: A multistep paradigm. *J Allergy Clin Immunol* 104: 917-926.

Weller PF. (1994). Eosinophils: structure and functions. *Curr Opin Immunol* 6: 85-90.

Weller PF and Bubley GJ. (1994). The idiopathic hypereosinophilic syndrome. *Blood* 83: 2759-2779.

Wilkins HJ, Crane MM, Copeland K and Williams WV. (2005). Hypereosinophilic syndrome: an update. *Am J Hematol* 80: 148-157.

Yoon TY, Ahn GB and Chang SH. (2000). Complete remission of hypereosinophilic syndrome after interferon-alpha therapy: report of a case and literature review. *J Dermatol* 27: 110-115.

Zabel P and Schlaak M. (1991). Cyclosporin for hypereosinophilic syndrome. *Ann Hematol* 62: 230-231.

Zimmermann N, Hershey GK, Foster PS and Rothenberg ME. (2003). Chemokines in asthma: cooperative interaction between chemokines and IL-13. *J Allergy Clin Immunol* 111: 227-242;

quiz 243.

Table I: 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)	<p>Males</p> <p>Mucosal ulcers</p> <p>Eosinophilic endomyocarditis</p> <p>Splenomegaly</p> <p>Possible progression to myeloproliferative disorders</p>	<p>Males/Females</p> <p>Pruritus</p> <p>Erythematous papules erythroderma</p> <p>Urticaria-like plaques</p> <p>Possible progression to T cell lymphomas</p>	<p>Episodic angioedema with eosinophilia</p> <p>Necrotizing eosinophilic vasculitis</p> <p>Immunological disorders</p>
	<p>Blood eosinophilia (>1500 eosinophils /μL) > 6 months</p> <p>Raised vitamin B12 and tryptase serum levels</p> <p>Bone marrow: CD25+ atypical mast cells</p> <p>FIP1L1-PDGFRA gene</p>	<p>Blood eosinophilia (>1500 eosinophils /μL) > 6 months</p> <p>Th2 profile clonal T-lymphocyte secretion (Interleukin-5 expression)phenotype CD3⁻ CD4⁺</p>	<p>Blood eosinophilia (>1500 eosinophils /μL) > 6 months</p>
Treatment	Imatinib-mesylate therapy good response	Cortisone Anti-IL-5 (mepolizumab) Cyclosporin	Cortisone IFN Hydroxyurea