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Successful Long-Term Control of the Syndrome of Episodic Angioedema With Eosinophilia (Gleich Syndrome) With Low-Dose Imatinib Mesylate and Prednisone

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Abstract

The syndrome of episodic angioedema with eosinophilia, first reported over 40 years ago, is a hypereosinophilic disorder that, uniquely, is not associated with end-organ pathology. However, patients develop a constellation of symptoms that include angioedema, urticaria, fatigue, and fever. Episodes are accompanied by massive hypereosinophilia and weight gain. Type II serum cytokine levels (IL-5, IL-13, IL-9, and IL-10) show cyclic variations peaking at or just prior to the peak of eosinophilia and an abnormal Th2 cell phenotype has been reported. Attacks may occur with predictable regularity and have been described in both adults and children. Glucocorticoid therapy reliably reverses symptoms with accompanying diuresis, defervesce, and normalization of the eosinophil count. In this report, a patient who had the syndrome of episodic angioedema with eosinophilia exceeding 20 years is reported. He has had no end-organ damage to date. Testing for the $CHIC_2$ deletion, a surrogate for the FIP1L1-PDGFRA fusion, was negative. Use of imatinib mesylate, initially as a steroid-sparing agent, and subsequently as a maintenance medication, plus low-dose prednisone has provided long-term control of hypereosinophilia and all clinical manifestations.

Keywords

hypereosinophilia, hypereosinophilic syndromes, episodic angioedema with eosinophilia syndrome, Gleich syndrome, imatinib mesylate

Introduction

Episodic angioedema with eosinophilia (Gleich) syndrome is a hypereosinophilic (HE) disorder first described in 1976 by Cooper and Patterson and shortly thereafter in 1980 by Marti et al.[1,2] Subsequently other accounts followed including international reports.[3]

Initially termed the MEEF syndrome (hypergammaglobulinemia M, Eosinophilia, Edema, Fatigue),[2] it has subsequently been labeled Gleich syndrome after Gleich et al reported the largest series to that date in 1984.[4] This disorder occurs both in adults and in children among whom the clinical course mirrors that of adults.[5,6]

Striking hypereosinophilia, angioedema, urticaria, fatigue, and fever occur during attacks. Weight gain may be substantial.[1,4] Attacks can occur with near-predictable regularity.[4,5] During attacks, 24-hour urine output may be <250 mL.[7]

Symptoms can regress spontaneously[1,3] but respond rapidly to oral glucocorticoid therapy with weight loss, defervescence, and diuresis.[1,4] Elevated levels of polyclonal immunoglobulin (Ig) M are common but are not always present.[8]

An increased percentage of activated T cells staining for both CD3 and HLA-DR precedes by 10 days maximal eosinophilia.[9] Subsequently, immunophenotypic analysis of peripheral blood has shown an abnormal Th2-cell phenotypic population, CD2(+), CD3(−), CD4(+), CD7(+), CD8(−), CD56(−), CD25(+), and CD95(+).[10] Aberrant CD3(−) CD4(+) lymphocyte populations have been described in a series of 4 reported cases 3 of whom had clonal (TCR γ)

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lymphocyte populations by polymerase chain reaction, and parallel cycling of neutrophils and lymphocytes but not of monocytes, platelets, or hemoglobin was found.[11]

The pathogenesis of this disorder remains unknown. Increased serum levels of IL-5 have been reported during attacks of angioedema.[6,12] These levels return to normal with resolution of symptoms or after prednisone administration.[6,12] Type II serum cytokine levels (IL-5, IL-13, IL-9, and IL-10) show cyclic variations peaking prior to the peak of eosinophilia; however, levels of GM-CSF, G-CSF, IFN-γ, MIP-1-β, TNF-α, IL-1-β, and IL-6 do not appear to be related to the onset of symptoms or the absolute eosinophil level.[11] Eosinophilia during attacks of swelling can be extreme with total eosinophil counts as high as 95×10^9/L reported.[4]

Not unexpectedly, serum levels of eosinophil major basic protein, eosinophil cationic protein, and eosinophil-derived neurotoxin are increased[7,12] and involved skin has stained positively for the presence of extracellular major basic protein.[4] Remarkably, with a single exception to date, despite the significant eosinophilia in these patients, and the presence of circulating anti-endothelial antibodies, end-organ damage to tissues such as the heart and nervous system, which commonly are targeted and damaged in HE syndrome (HES), is not reported in this disorder. Successful pregnancy has been described in one woman treated intermittently with 3-week burst-and-taper courses of prednisone.[13] The baby did not manifest features of this disorder.

Eosinophil counts may return to normal between attacks or may remain moderately elevated.[4,11] Bone marrow findings have not shown features of myeloproliferative disorders and tests for the *FIP1L1/PDGFRα* fusion have uniformly been negative.[11,14]

Case Report

A 40-year-old man was initially seen in the year 2000 for a 15-year history of hypereosinophilia with associated episodic symptoms. Prednisone 8 to 10 mg/day generally controlled the eosinophilia; however, recurrent eosinophil surges occurred requiring up to 60 mg/day of prednisone to control. At these times, he had experienced flu-like symptoms, swelling, a 10 to 15 pound weight gain, fatigue, lethargy, and tightness in the arms, legs, and trunk. At the time of his initial appointment while not taking prednisone, his white blood cell count was 22.6×10^9/L with 68% eosinophils, and the physical examination showed a punctate, macular rash, which blanched with pressure on the lower chest upper abdomen and back. Edema was present in the forearms, trunk, and lower extremities. He was lost to follow-up for 2 years but returned in 2002.

At that time, the IL-5 level was normal, and in order to reduce his long-term need for prednisone, a trial of imatinib mesylate 100 mg/day was begun. Over the next several months, the dose of imatinib was increased to 300 mg/day and the dose of prednisone was titrated to maintain an eosinophil count $<1 \times 10^9$/L and subsequently $<0.5 \times 10^9$/L. Because of intermittent flares of symptoms and eosinophilia interferon alpha 2b (IFN), 3 million units by subcutaneous injection 3 times per week was added to his treatment. Although his eosinophil counts improved, he became intolerant of IFN and it was discontinued. For the remainder of 2002, he did well with eosinophil counts generally $<0.5 \times 10^9$/L, while the dose of imatinib was reduced to 200 and then 100 mg/day while continuing prednisone 5 mg/day.

Over the next several years, direct face to face contact with the patient was limited; however, his clinical symptoms and laboratory reports obtained showed that the eosinophilia remained controlled on a program of imatinib and prednisone. Attempts to taper the prednisone below 3 mg/day were met with flaring of symptoms.

For the past 11 years, more regular contact with the patient was established. He reported only rare attacks of swelling. During this time, several adjustments to his medication program were attempted. These resulted in some oscillation in the eosinophil counts, which generally remained between 0.2 and 0.5×10^9/L. Attempts to change imatinib to an every-other-day schedule were initially unsuccessful as were attempts to lower the prednisone dose to <2.5 mg/day.

For the past 5 years, he has remained free of attacks while on a program of imatinib plus prednisone 2.5 mg/day. A taper of the imatinib dose from 100 mg/day to 100 mg every-other-day for 18+ months and subsequently to 50 mg every-other-day has been successful to date.

A summary of laboratory studies is presented in Table 1.

Discussion

Nearly 100 disorders are associated with eosinophilia. In some of these disorders, the increase is modest; however, in others, "hyper" eosinophilia, $\geq 1.5 \times 10^9$ eosinophils/L, is found. In recent years, efforts have continued to classify hypereosinophilic disorders into a usable framework based on improved understanding of the mechanisms driving the eosinophilic process.[15,16] The initial recognition by Hardy and Anderson of "hypereosinophilic syndromes," rather than a single "hypereosinophilic syndrome," was a valuable observation as hypereosinophilic states are heterogeneous.[17] The criteria of Chusid et al codified 3 benchmarks for diagnosing hypereosinophilic syndrome(s) (HES): (1) eosinophilia of $\geq 1.5 \times 10^9$ eosinophils/L for >6 months, (2) lack of evidence for secondary causes for the eosinophilia such as parasitic infestations or allergic diatheses, and (3) signs and symptoms of end-organ dysfunction otherwise not explained except by the hypereosinophilia.[18] For decades, these criteria have served as a guide for patient evaluation; however, the realization that sustained hypereosinophilia can rapidly cause irreversible organ damage has made it increasingly rare that hypereosinophilia will go untreated for 6 months. A recent modified paradigm for diagnosing HES includes the

Table 1. Patient Test Results.

Test	Patient result	Reference range
IL-5, pg/mL (baseline)	<7.8	<7.8
FISH for $CHIC_2$ anomalies with probes for 4q12	Negative	Negative
B_{12}, pmol/L	180	132.8-674.5
Folate, nmol/L	23.34	≥9.06
Alkaline phosphatase	69 U/L	45-115 U/L
AST	28 U/L	8-48 U/L
Hepatitis screen	Negative	Negative
Peak eosinophil count × 10^9/L	15.6	0.03-0.48
HgB, g/L	141	135-155
Platelet count × 10^9/L	223	150-450
BUN, µmol/L	0.175	0.0824-0.247
Creatinine, µmol/L	0.014	0.0076-0.0139
EKG	Sinus bradycardia	
Peripheral blood flow cytometric immunophenotyping	No monoclonal B-cell population identified	Negative
IgM, µmol/L	2.083	0.3811-2.95
IgG, µmol/L	10.02	7.9-16.4
IgA, µmol/L	1.67	0.63-3.67
C4, µmol/L	0.23	0.14-0.41

Abbreviations: FISH, fluorescence in situ hybridization; AST, aspartate aminotransferase; HgB, hemoglobin; BUN, blood urea nitrogen; EKG, electrocardiogram; Ig, immunoglobulin.

following: (1) the finding of blood eosinophilia that exceeds 1.5×10^9 eosinophils/L on at least 2 occasions or evidence of prominent tissue eosinophilia associated with symptoms and marked blood eosinophilia and (2) exclusion of secondary causes of the eosinophilia.[19]

A recent consensus document on eosinophilic disorders provides an excellent workable outline for classifying hypereosinophilic conditions.[20] Additionally it makes the valuable distinction between hypereosinophilia(s)(HE) and HES. HE, the presence of $\geq 1.5 \times 10^9$ eosinophils/L, but without evident end-organ damage, can be subdivided into the following categories: (1) Hereditary/Familial HE (HE_{FA}); (2) Primary or Neoplastic HE (HE_N); (3) Secondary or Reactive HE (HE_R); and (4) HE of undetermined significance (HE_{US}). Once organ damage from hypereosinophilia and treatable secondary causes for it have been excluded, it is possible to simply follow HE patients closely, monitoring the eosinophil counts and observing for any sign of end-organ symptoms before treatment may be necessary.

HES are distinguished from HE by the presence of organ damage that otherwise cannot be ascribed to another pathophysiologic process. HES are commonly subclassified into the following: (1) Neoplastic HES (HES_N) in which eosinophils are frequently clonal, that is, myeloid neoplasms, with platelet-derived growth factor receptor (or other) gene abnormalities. The most common of these is the FIP1L1-PDGFRA fusion, which is associated with nearly uniform beneficial clinical response to imitinab.[21] (2) Secondary or Reactive HES (HES_R), including lymphocyte-variant (L-HES), a subclass in which abnormal clones of T cells secrete large amounts of IL-5 resulting in hypereosinophilia. The broad group of HES_R also encompasses various infectious diseases such as parasitic infestations, allergic disorders, chronic inflammatory, and autoimmune disorders.[22] (3) Overlap HES in which there is a single organ system dysfunction accompanied by hypereosinophilia, for example, eosinophilic gastroenteritis. (4) Associated HES in which eosinophilia $\geq 1.5 \times 10^9$/L is found in a distinct diagnosis in which a subset of affected patients have eosinophilia. This includes disorders such as hyper-IgE syndrome and primary immunodeficiency syndromes.[22]

Secondary causes of hypereosinophilia as well as the presence of the FIP1L1-PDGFRA fusion must be excluded before arriving at a final diagnosis of (5) idiopathic HES. Patients with idiopathic HES do have associated organ damage; however, no causation for the hypereosinophilia can be determined.

Because abnormal T-cell clones producing IL-5 have been reported in the episodic angioedema with eosinophilia (Gleich's) syndrome, this disorder has been considered by some authors to be a subtype of L-HES,[23] but as there has been only a single report of end-organ damage reported in this disorder and no reported eosinophil clonality, Gleich's syndrome is classified by others as a subtype of HE.[20]

The syndrome of episodic angioedema with hypereosinophilia has responded favorably to several therapeutic options that can allow corticosteroid reduction or discontinuation including intravenous Ig,[8] rituximab,[14] and mepolizumab.[24] A related condition has been reported in Asian patients. These reports are noteworthy for (1) non-recurrence of

clinical symptoms; (2) a near uniformly female population; (3) improvement/resolution of symptoms without corticosteroid need; and (4) a normal serum IgM level. Whether this represents a separate syndrome or a variant of the original condition cannot be stated with certainty at this point.[25]

Imatinib use has been reported with mixed results in Gleich's syndrome. A prior report documented the successful use of imatinib in this syndrome for 2 years at a daily oral dose of 100 mg in one patient with resulting eosinophil counts $<0.5 \times 10^9$/L.[26] For both this patient and the patient described in the current report, the doses of imatinib necessary for control of eosinophilia approximate those used successfully to treat HE patients having the *FIP1L1/PDGFRα* fusion.[27] In another report, episodic angioedema and eosinophilia proved resistant to imatinib (and cyclosporine), but remained responsive to corticosteroids.[28]

A significant aspect to this patient's case is the beneficial clinical response to imatinib mesylate in the absence of the FIP1L1-PDGFRA fusion. The reason imatinib can be effective in controlling eosinophilia in this disorder is not without precedent. In a case of HES reported in which the *FIP1L1-PDGFRα* fusion was absent, a similar combination of imatinib 100 mg/day plus low-dose prednisone was also successful at controlling the eosinophil count after an initial short-term, high-dose burst of imatinib was given and then tapered.[29] It is noteworthy that even in the initial report of this mutation in HES, 4 of 9 patients having a clinical response to imatinib lacked the FIP1L1-PDGFRA fusion.[30] HES patients with this gene fusion respond to small doses of imatinib mesylate, and after clinical and molecular remission has been achieved may be able to discontinue imatinib for an extended period of time.[21]

One possible explanation for the clinical response witnessed in the present case is the presence of heretofore undiscovered non-kinase targets responsive to imatinib, which promote eosinophilopoiesis or eosinophil survival. Alternatively, other imatinib-susceptible kinases, perhaps of low kinase activity, acting together could provide eosinophilopoietic activity. Supporting these hypotheses, it has been reported in a recent review that of the over 500 kinases of the human kinome, only a fraction are tested in available kinase panels. Nonetheless, kinase panel-based investigations have now discovered multiple novel targets (kinase as well as non-kinase) for imatinib, nilotinib, and dasatinib.[31]

Another example of varied imatinib responsiveness is found in patients with systemic mastocytosis. In this heterogeneous disorder of mast cell proliferation, the majority of patients have an activating mutation in c-*KIT* a tyrosine kinase that is the receptor for stem cell factor. This mutation causes autophosphorylation activity of the kinase without the need for stem cell factor binding and results in unchecked proliferation of mutated mast cells. Numerous mutations in c-*KIT* have been reported; however, a mutation (Asp816Val) affecting the enzyme's phosphotransferase domain is present in most patients and is associated with resistance to imatinib.[32] Mutations affecting other sites in the c-KIT receptor remain susceptible to imatinib where it can be used with good clinical effect.[33]

Conclusion

Successful treatment for a rare hypereosinophilic disorder, Gleich's syndrome, is reported. This therapy initially employed a higher dose of imatinib as a steroid-sparing agent, and subsequently used a tapered, now every-other-day, imatinib dose and low-dose prednisone. Our experience suggests that imatinib mesylate can be successfully employed to treat some non-*FIP1L1-PDGFRα* fusion associated hypereosinophilic conditions and that its effectiveness does not diminish with prolonged use.

Declaration of Conflicting Interests

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Ethics Approval

This report was deemed "not research" (as found under Federal (US) Policy for the Protection of Human Subjects, 45 CFR 46.102) by the Mayo Clinic Institutional Review Board.

Informed Consent

Written informed consent was obtained from the patient for his anonymized information to be published in this article.

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