A Case Report with Gleich Syndrome (Episodic Angioedema with Eosinophilia) Accompanied by C1 Inhibitor Function Deficiency and MEFV Gene Mutation

Fatma Merve Tepetam1*, Ismet Bulut1, Cihan Orcen1, Toluy Ozgumus2 and Alperen Mengi3

1Department of Immunology and Allergy, University of Health Sciences Süreyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Istanbul, Turkey
2Department of Hematology, Marmara University Medical Faculty Hospital, Istanbul, Turkey
3Department of Rheumatology, University of Health Sciences Umraniye Training and Research Hospital, Istanbul, Turkey

*Corresponding Author: Fatma Merve Tepetam, Department of Immunology and Allergy, University of Health Sciences Süreyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Istanbul, Turkey.

Abstract

Hypereosinophilic syndrome (HES) is characterized by persistant eosinophilia. One of the rare forms of HES is undefined forms, including nonepisodic/epsodic angioedema with eosinophilia. Episodic angioedema with eosinophilia (EAE) known as Gleich Syndrome is characterized by recurrent episodes of fever, angioedema, arthralgia and elevated serum IgM. On the other hand Hereditary angioedema (HAE) and Acquired angioedema (AAE) present with angioedema attacks without urticaria due to C1-INH function or C1-INH level and/or C1 q deficiency. Familial Mediterranean fever (FMF) is a autosomal recessive genetic disease characterized by recurrent fever, abdominal pain, and serositis.

We report a case with EAE characterized by recurrent episodes of angioedema, eosinophilia, fever, weight gain and elevated serum IgM. To our best knowledge this is the first case report on patient with EAE in whom lower C1 INH function level and FMF releated gene mutation was detected. It may be assumed that these conditions may overlap or associated with each other.

Keywords: Gleich Syndrome; Episodic Angioedema; Eosinophilia; C1 Inhibitor; MEFV Gene

Introduction

Hypereosinophilic syndrome (HES) is a rare disorder characterized by persistant eosinophilia and multible organ damage. It is difficult to diagnose the disease because, other causes of eosinophilia such as allergy, infectious, autoimmune, immunodeficiency and malignant related disorders, must be ruled out. After the exclusion if an absolute eosinophil count is more than 1500 cells/L at least two occasions for 1 month and/or tissue eosinophilia is detected HES can be confirmed [1]. Frequently encountered forms of HES are lymphocytic variant, releated with overproduction of interleukin-5 (IL-5) and myeloproliferative variant releated with clonal proliferation in hematopoietic stem cells mostly due to FIP1L1-PDGFRA fusion gene defect. One of the rare forms of HES is undefined forms including nonepisodic/epsodic angioedema with eosinophilia [2,3].

On the other hand Hereditary angioedema (HAE) and Acquired angioedema (AAE) present with angioedema attacks without urticaria due to C1-INH function or C1-INH and/or C1 q deficiency. The rare form AEE presents without family history and associated with autoimmunity and lymphoproliferative disorders range from monoclonal gammopathies to lymphomas [4]. It is already known that eosinophilia can be observed in lymphoproliferative conditions too.

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Familial Mediterranean Fever (FMF) is a autosomal recessive genetic disease commonly seen in the races around Mediterranean Sea (Turks, Sephardic Jews, Armenians, and Arabians) characterized by recurrent fever, abdominal pain, and serositis attacks. To our best knowledge there is only one case reported FMF with hypereosinophilia [5].

Episodic angioedema with eosinophilia (EAE) known as Gleich Syndrome was first reported in 1984 and is characterized by recurrent episodes of urticaria, fever, angioedema, arthralgia, weight gain, dramatic eosinophilia, elevated serum IgM, increased body weight, and a benign clinical course without organ damage [6]. It seems to be associated with cyclic alterations in serum interleukin (IL)-5 or GM-CSF levels [7-9]. The other form is non-episodic angioedema with eosinophilia (NEAE), which was limited to a single attack defined in 1998 by Chikama, et al [10]. Herein, the case a patient with EAE, who has low C1 INH function level and FMF related gen mutation is described.

Case

Our case is 58-year-old man presenting with a 2-years history of recurrent cyclical attacks with peripheral oedema in upper and lower extremities, weight gain (10 - 13 kg) and chest tightness. Other complaints of the patient were fever, arthralgia and itchy skin rash. After detection of peripheric blood hypereosinophilia (White blood cells: 19100/mm$^3$; eosinophils 8800/mm$^3$, 46.2%) he was evaluated in Hematology Department. Renal, liver function (except for a increased level of lactate dehydrogenase (448 U/ml; normal value, 0-248) tests, vitamin B12 and folic acid levels were normal. For excluding infectious disease HBsAg, anti HBs, anti HCV and parasite investigation in feces were carried out and in th evaluation for autoimmune disease ANA, RF, pANCA and cANCA were also negative. While erythrocyte sedimentation rate was within normal limits (6 mm/h; normal value, 5 - 20) C-reactive protein was high (33.5 mg/dl; normal value, 0 - 5). A bone marrow aspirate revealed hypercellularity with increased eosinophils (Cellularity: 70 - 80%). Analyses for FIP1L1/CHIC2/PDGFRA, PDGFRB and t(9;22) (q34;q11.2) were negative by fluorescent in situ hybridization. Mediterranean fever gene (MEFV) analysis showed heterozygous for mutation in exon 2 (R202Q) with PCR method. In addition, flow cytometric analysis of leukemia/lymphoma phenotypes showed no evidence of leukemia, or lymphoproliferative disorder. Because eosinophilia was maintained in his follow-up evaluations, he was admitted to our immunology and allergy department. When the patient was asked about drug allergy history and other allergic diseases, there was nothing remarkable. We completed the missing tests including immunoglobulins (IgG, IgA, IgM, IgE), prick test, spirometric measurements, CT of lung and abdomen, Echocardiography by consulting cardiologist, C3, C4, C1q, C1 inhibitor level and function. Tests with abnormal results were as follows: IgG (2054 mg/dl; normal value, 700 - 1600), IgM (295 mg/dl; normal value, 40-230) and C1 inhibitor function (first 60%, second 58% normal value 70-130) levels. While the patient has no family history of HAO, 1 daughter and 1 son of the patient have the same MEFV gene analysis with the symptoms of fever and abdominal pain attacks and are on colchicine therapy. Our patient has also started to receive colchicine therapy due to new onset abdominal pain. We diagnosed the patient with EAE and administered treatment with methylprednisolone at the dose of 40 mg, the dose was lowered depending on clinical improvement (no episode of angioedema) and the reduction in eosinophil levels. Currently, (in the third month of treatment ) the patient receives drug at the dose of 4 mg, the final eosinophil level is 400/mm$^3$ and so we decided to taper the treatment before withdrawal.

Discussion

We report a case with EAE characterized by recurrent episodes of angioedema, leukocytosis, eosinophilia, weight gain, elevated serum IgM, without organ damage. Unlike other published cases, we detected deficiency of C1 inhibitor function level and mutation in exon 2 (R202Q) in the MEFV gene analysis. In many published cases or case series, C1 inhibitor level and function was not evaluated or remarked as could not be measured; only in few studies C4 level was studied and some of them detected lower levels [6,11,12]. To date only one case report was published on FMF accompanied hypereosinophilia, which was reported from Turkey. Unlike this case, our patient had angioedema and did not have Hereditary elliptocytosis [5]. Interestingly our patients' clinical findings of fever, slight arthralgia were the common findings of EAE. Another report was published also from Turkey, which was the first; with coexistence of HAE (Type 1: C1 inhibitor level deficiency) and FMF with the same gene R202Q but homozygote mutation [13].

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Conclusion

In conclusion, it may be hypothesized that these conditions (EAE, HAE and FMF) may overlap or be associated with each other; further studies are required for the elucidation of accompanying common pathological pathways.

Conflicts of Interest

The authors whose names listed immediately below declare that they have NO affiliations with or involvement in any organization or entity with any financial interest.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent

Written informed consent was obtained from the patient for publication of this case report.

Bibliography


