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Hematology Quiz – Case 30

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2012, 29(3):379–380

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A 37-year-old man referred to the outpatient department because of prominent eosinophilia along with persistent non productive cough and recurrent sinusitis. The symptoms started 6 months ago, with concomitant discovery of an absolute eosinophil count of 2.97×10^9/L that remained at that level throughout this period. His past medical history was insignificant. He was treated with antihistamines, corticosteroid-based bronchodilators, oral corticosteroids and several courses of antibiotics, without any improvement.

On physical examination the patient appeared in no acute distress and without any remarkable signs. His full blood count was as follows: WBC=9.46×10^9/L (neutrophils=42%, lymphocytes=18%, monocytes=5%, eosinophils=35%), Hb=14.6 g/dL, Ht=44%, PLT=235×10^9/L. Eosinophils were mature in appearance, although many of them were hypogranulated with nuclear hypersegmentation (fig. 1). Biochemistry profile, –protein electrophoresis, serum immunoglobulin levels (including IgE), ANAs, ESR, CRP, serum vitamin B_{12} were all normal. Stool cultures for ova and parasites were also negative. Serum tryptase levels (a surrogate marker for PDGFRα rearrangement) were normal whereas chest and abdomen computed tomography were not indicative for the presence of malignancy or collagen vascular disease. The bone marrow aspirate showed numerous eosinophilic myelocytes and eosinophils without an increase in blasts, and the immunophenotypic studies did not suggest the presence of any aberrant T-cell population (figures 2, 3). The bone marrow cytogenetic analysis normal. Finally, extensive evaluation of cardiorespiratory status did not reveal end organ damage. At that point, a diagnostic test was performed.

Comment

Eosinophilia is relatively common in the tropical regions of the world, with the main cause being tissue-invasive helminthic infections. Apart from myeloproliferative disorders, the main causes of secondary eosinophilia in the Western world are allergic or vasculitic conditions, helminthic disease, drugs, and nonmyeloid malignancies.

Hypereosinophilic syndrome (HES) comprises a heterogeneous group of disorders. Diagnostic criteria (a) Persistent eosinophilia of

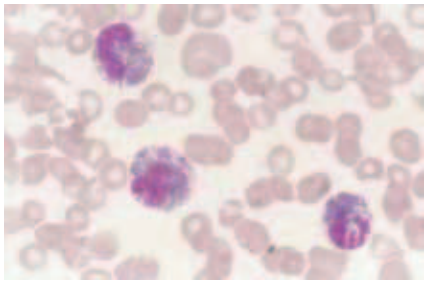

Figure 1

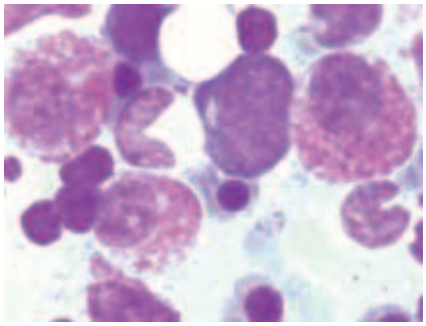

Figure 2

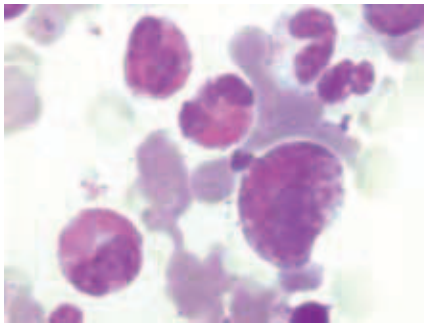

Figure 3

1.5×10⁹/L for more than 6 months; (b) lack of evidence for parasitic, allergic or other known causes of eosinophilia; (c) signs and symptoms of organ involvement. According to the World Health Organisation (WHO) classification all myeloproliferative variants of HES are clonal disorders (leukemias). The absence of a specific genetic abnormality defines chronic eosinophilic leukemia not otherwise specified (CEL-NOS) while in the presence of a genetic lesion the condition described under the term myeloid/lymphoid neoplasm with eosinophilia and mutations involving platelet-derived growth factor receptor (PDGFR) α/β or fibroblast growth factor receptor 1.

HES presents with protean clinical manifestations that vary from non-specific features such as malaise, weight loss or excessive sweating to organ-specific symptoms, involving lung, heart, nervous system and skin. The FIP1L1-PDGFRα fusion oncoprotein represents the first described gain-of-function protein, that results from a cryptic interstitial deletion between genes rather than a reciprocal translocation. It exerts an aberrant kinase activity with a pivotal role in transforming hematopoietic cells.

The cornerstone of diagnosis was the positive PCR test for the presence of FIP1L1-PDGFRa rearrangement. Our case illustrates also that normal serum tryptase levels does not rule out this form of HES. Though, serum tryptase positivity is a good surrogate marker for FIP1L1-PDGFRα gene indicating that mast cells are also affected.

The mainstay of treatment in the presence of FIP1L1-PDGFRα translocation is imatinib mesylate. The kinase activity of FIP1L1-PDGFRα is inhibited by imatinib at a cellular 50% inhibitory concentration (IC50) 100-fold lower than bcr-abl. Therefore, adequate evidence supports the use of low dose imatinib mesylate (100 mg/day) for achievement of hematologic and molecular remission in FIP1L1-PDGFRα-positive clonal eosinophilia. In responding patients, restoration of normal eosinophil count usually occurs within 3 weeks. The use of lower imatinib doses (e.g., 100 mg/week) is questionable, as it might be associated with clinically occult and overt relapse. Treatment with imatinib mesylate has been associated with heart failure in some cases and cardiac troponin is mandatory to monitor therapy. In rare cases of imatinib resistance, interferon alfa or second generation tyrosine kinase inhibitors are reasonable alternatives.

The patient was started on imatinib mesylate at the dose of 100 mg/day with concomitant oral methylprednisolone (0.8 mg/kg/day) during the initial two weeks of imatinib therapy. After 7 days of imatinib treatment, the eosinophil count dropped to 0.2×10⁹ with resolution of symptoms. Sperm banking was undertaken before treatment, because the effect of imatinib on fertility has not been clarified yet.

References

1. TEFFERI A, GOTLIB J, PARDANANI A. Hypereosinophilic syndrome and clonal eosinophilia: Point-of-care diagnostic algorithm and treatment update. *Mayo Clin Proc* 2010, 85:158–164
2. GOTLIB J, COOLS J, MALONE JM 3rd, SCHRIER SL, GILLILAND DG, COUTRÉ SE. The FIP1L1-PDGFRα fusion tyrosine kinase in hypereosinophilic syndrome and chronic eosinophilic leukemia: Implications for diagnosis, classification, and management. *Blood* 2004, 103:2879–2891
3. BACCARANI M, CILLONI D, RONDONI M, OTTAVIANI E, MESSA F, MERANTE S ET AL. The efficacy of imatinib mesylate in patients with FIP1L1-PDGFRα positive hypereosinophilic syndrome. Results of a multicenter prospective study. *Haematologica* 2007, 92:1173–1179
4. TEFFERI A, VARDIMAN JW. Classification and diagnosis of myeloproliferative neoplasms: The 2008 World Health Organization and point of care diagnostic algorithms. *Leukemia* 2008, 22:14–22
5. MELETIS J. *Atlas of hematology.* 3rd ed. Nireas Publ Inc, Athens, 2009:410–412

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