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SHORT COMMUNICATION

PDGFRalpha/FIP1L1-positive chronic eosinophilic leukemia presenting with retro-orbital localization: efficacy of imatinib treatment

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Abstract
Introduction The fusion protein between the platelet-derived growth factor receptor alpha (PDGFRalpha, P) gene and the Fip1-like1 (FIP1L1, F) may be identified in 14 to 60% of HES and it indicates a clonal hypereosinophilic syndrome called F/P-positive CEL. We herein report a case of F/P-positive CEL with retro-orbital localization, who was successfully treated with imatinib.
Case report A 53-year-old male presented an absolute eosinophil count of 25,000/mm^3, anemia (Hb 10.2 g/dl) and a moderate increase in the platelet count (571,000/mm^3). A clinical examination revealed left exophthalm, associated with diffuse hypoesthesia and diplopia. A CT scan of orbits showed a lesion located in the lachrymal fossa of the left orbit with intra- and extra-conical extension. Molecular analysis excluded the presence of bcr/abl transcript while a F/P fusion tyrosine kinase signal was documented. Imatinib mesylate (IM) was started and, after 7 days of treatment eosinophil count significantly declined along with a dramatic reduction of the left exophthalm. IM dosage was increased up to 300 mg/day. The drug was well tolerated with an initial modest haematological toxicity. The left exophthalm, as well as hypoesthesia and diplopia, disappeared after IM therapy. MRI showed a clear reduction of the intra- and extra-conical growth process. BM molecular signal of the F/P fusion gene resulted undetectable after 4 weeks of treatment.
Conclusion In our case, the diagnosis of FIPIL1-PDGFRA-positive CEL and IM therapy has allowed the patient to experience an excellent clinical therapeutic result, avoiding surgical treatment of the retro-orbital mass

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Introduction

Eosinophilia is an uncommon hematological condition with interesting clinical presentations which falls into one of three broad categories: (1) idiopathic hypereosinophilic syndrome (HES), (2) reactive eosinophilia in response to benign and malignant illnesses, and (3) eosinophilia as part of a clonal myeloid disorder [1]. HES is currently defined as an unexplained severe peripheral blood eosinophilia (>1,500/mm^3) sustained for more than 6 months and accompanied by end-organ damage, resulting from direct organ infiltration by eosinophils [2]. Although the etiology remains unclear, a subset of patients with HES has been shown to have an interstitial deletion in chromosome 4q12, undetectable by conventional cytogenetic analysis, which results in the generation of a fusion protein between the platelet-derived growth factor receptor alpha (PDGFRα) gene and a previously uncharacterized gene, Fip1-like1 (FIP1L1) [3, 4]. The fusion gene product (F/P), which acts as a constitutively active tyrosine kinase, has been identified in 14 to 60% of the patients [3, 5, 6] and has been indicated as a cause of clonal hypereosinophilic syndrome called F/P-positive chronic eosinophilic leukemia (CEL), according to World Health Organization (WHO) disease classification criteria. Those patients with F/P-positive CEL appear to have a more severe disease phenotype involving

extensive end-organ pathology [7–10]. Although F/P-positive CEL is, by definition, a neoplastic disorder, the susceptibility to imatinib mesylate (IM) inhibition of the F/P tyrosine kinase represents, on the other hand, a chance of cure for this group of patients [3, 11–13].

We herein report a case of F/P-positive CEL with retro-orbital localization, who was successfully treated with IM.

Case report

In February 2006, a 53-year-old male with a recent history of a successful surgical treatment of duodenal ulcer and peritonitis, presented an absolute eosinophil count of 25,000/mm^3, anemia (Hb 10.2 g/dl) and a moderate increase of the platelet count (571,000/mm^3). Clinical examination revealed left exophthalm, associated with diffuse hypoesthesia and diplopia. A CT scan of orbits showed a lesion located in the lachrymal fossa of the left orbit with intra and extra-conical extension. The superior and the lateral rectus compressed the optic nerve that diverted in the middle, while the globus pushed down causing a slight exophthalmus. The MRI scan of the orbits confirmed the presence of a significant lesion in the left side with precise edges. The lesion had an intermediate signal in T1 and an isohypointense signal in T″-STIR (Fig. 1a). The mass did not show a clear cleavage with lachrymal gland and with superior rectus. Instead the medial rectus remarkably bent down. Finally the globe appeared pushed forward and slightly towards the interior. The optic nerve appeared to be shifted internally. Additional laboratory studies excluded parasitic, allergic, or other known causes of eosinophilia. Moreover, echocardiography as well as ultrasonography of the liver and a total body CT scan were normal, excluding any organ involvement. Bone marrow histology showed myeloid hyperplasia with a significant increase in the eosinophilic lineage. Cytogenetics and reverse transcription polymerase chain reaction (RT-PCR) did not detect the presence of t(9;22)(q34;q11) or of its fusion transcript bcr/abl. Finally, molecular analysis of the patient's bone marrow showed a signal for the F/P fusion tyrosine kinase evaluated by RT-PCR (Fig. 2). The final diagnosis was, therefore, F/P-positive CEL.

Therapeutic strategy

We decided to avoid the neurosurgical excision of the retro-orbital mass and to start a specific therapy with IM using an escalating dose from 100 mg/die to 400 mg/die according to a protocol for HES. After 7 days of treatment eosinophil count significantly declined (560/mm^3) along with a dramatic reduction of the left exophthalm after 14 days of imatinib.

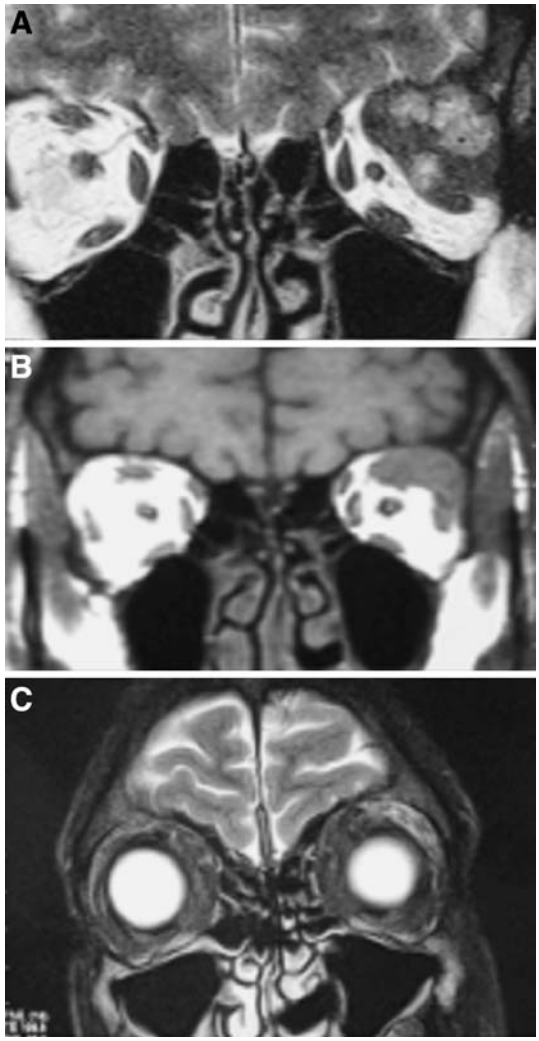

Fig. 1 MRI scans. **a** At the level of the left orbit, in the superior external sector with in intra and extra conical distribution, it is possible to observe a significant lesion with precise edges. **b** In the left, a partial volumetric reduction of the in intra and extra conical growth process which involves the superior and the side straight muscles after 5 weeks of Imatinib treatment. **c** Clear reduction of the in intra and extra conical growth process after 9 weeks of Imatinib treatment

After 5 weeks of IM treatment, a partial volumetric reduction of the intra and extra conical growth process which involves the superior and the side straight muscles was documented (Fig. 1b). IM dosage was increased up to 200 mg/day from the 4th week to 300 mg/day in the 5th week. The drug was well tolerated with grade I anemia (Hb 10.9 g/dl). Notably, the left exophthalm, as well as hypoesthesia and diplopia, disappeared after the 4th week of IM therapy. After 9 weeks of IM treatment, an additional MRI showed a further clear reduction of the intra and extra conical growth process (Fig. 1c). Finally, the bone marrow molecular signal of the fusion gene product F/P was undetectable after 3 months of imatinib treatment (Fig. 2). The patient still maintains the response after a follow-up of more than 1 year.

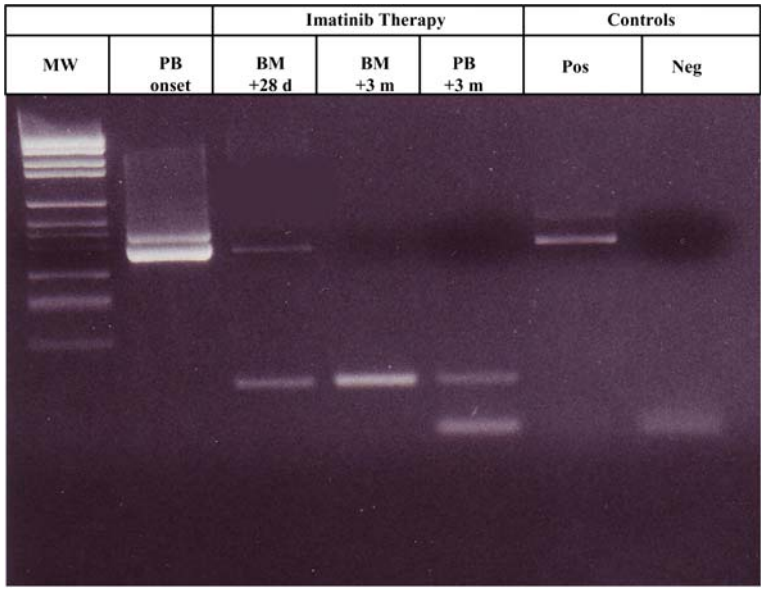

Fig. 2 Reverse transcriptase-polymerase chain reaction (RT-PCR) analysis of the PDGFRα/FIP1L1 fusion protein isolated from bone marrow (BM) and/or peripheral blood (PB) of the patient with HES at diagnosis (PB onset), after 28 days (BM ± 28 days) and 3 months of Imatinib therapy (BM ± 3 months; and PB ± 3 months)

Discussion

CEL is a neoplastic condition whose most important hematological abnormality is represented by persistent hypereosinophilia. We have reported a case of CEL associated with a retro-orbital localizaton. This patient fulfilled the diagnostic criteria for CEL established by the WHO criteria. In fact, the patient showed persistent hypereosinophilia $\geq 1.5 \times 10^9$/L with an increased number of eosinophils in the bone marrow. Furthermore, causes of benign reactive eosinophilia such as drug reactions, allergy, parasitic diseases, pulmonary disease, and collagen vascular diseases were ruled out by the clinical picture and history. Finally, malignant causes of reactive eosinophilia were excluded through CT imaging, while clonal myeloid disorders commonly associated with hypereosinophilia, such as chronic myeloid leukaemia, were also excluded since the search of both philadelphia chromosome and bcr-abl transcript resulted negative. Recently, cytogenetic evidence for a clonal myeloproliferative disorder has been provided in a significant proportion of HES patients through the description of an interstitial deletion on chromosome 4q12, resulting in fusion of FIP1L1 and PDGFRa genes. The fusion gene is in-frame and encodes a F/P protein with constitutive tyrosine kinase activity, which is highly susceptible to the tyrosine kinase inhibitor, IM. FIP1L1-PDGFR-α positive CEL cases with unusual extramedullary localizations were described [14, 15]. In particular, Malagola et al. [14] and Frickhofen et al [15] obtained similar therapeutic results in a patient with a soft tissue and skeletal involvement and in a 33-year-old man with CEL and clinically significant CNS involvement. In our case, it is essential to remind that the demonstration of the presence of the F/P transcript supported (1) the diagnosis of FIPIL1-PDGFRA-positive CEL; (2) the prediction of response to IM and, (3) the demonstration of a molecular complete response after IM treatment. Moreover, the patient experienced an excellent clinical therapeutic result which notably avoided surgical treatment of the retro-orbital mass.

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