

CASE REPORTS

Pediatric hypereosinophilia: *FIP1L1-PDGFR*A myeloproliferative disease in a 14-year-old male

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ABSTRACT

Hypereosinophilic myeloproliferative disease is a rare entity in the pediatric population. We report the fifth known pediatric case of *FIP1L1-PDGFR*A hypereosinophilia. This fusion drives hypereosinophilia, and often neutrophilia, with the propensity for T-cell or myeloid transformation. The exquisite sensitivity of the *FIP1L1-PDGFR*A fusion to the tyrosine kinase inhibitor Imatinib, abrogates the short-term life threatening complications of hyper-eosinophilia. The issues arising from long-term treatment with Imatinib, including optimal dosing, length of treatment, and bone marrow transplantation, are explored in the accompanying discussion. These issues are particularly relevant in pediatric patients facing life-long therapy.

Key Words: Hypereosinophilia, *FIP1L1-PDGFR*A, Pediatric hematology/Oncology, Imatinib

1. INTRODUCTION

The hypereosinophilic syndromes, first described by Chusid *et al.* in 1970s,^[1] comprise a heterogeneous group of non-hematologic (secondary or reactive) and hematologic (primary or clonal) diseases. The diagnosis is united by a persistently elevated eosinophil count of greater than 1,500/mm³, and resultant end-organ damage from eosinophilic tissue infiltration. Hypereosinophilia contributes to significant morbidity and mortality, with frequently reported causes of death from progressive cardiac disease, thromboembolic phenomena, neurologic dysfunction, and infection.^[2]

Treatment for secondary eosinophilia focuses upon treating the underlying disease process; in contrast, treatment of primary/clonal hypereosinophilia historically has been limited to corticosteroids and cytotoxic agents, *e.g.* hydroxyurea, with profoundly disappointing high mortality and morbidity rates.^[1] The discovery of the fusion protein *FIP1L1-PDGFR*A revolutionized treatment and outcome for patients,

as the presence of the *FIP1L1-PDGFR*A fusion correlates to an exquisite sensitivity to the tyrosine kinase inhibitor (TKI) Imatinib.^[3] Whilst well described in adults, pediatric hypereosinophilia is rare, with only four cases of *FIP1L1-PDGFR*A fusion in children reported.^[4-7] We report the fifth known case of pediatric *FIP1L1-PDGFR*A hypereosinophilia; the fourth with documented morphological and molecular remission to Imatinib.

2. CASE PRESENTATION

Our patient was a 14-year-old male of Sri-Lankan origin, who presented with a 2-week history of loss of weight, shortness of breath on exertion, and frequent cough. Examination revealed hepato-splenomegaly and bilateral inguinal lymphadenopathy, with no identified focal neurology. A 1.5 cm lump was noted on his posterior occiput that was firm to palpate, non-tender and non-mobile. Ophthalmological examination was normal.

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Initial white cell count was $200 \times 10^9/L$, with a predominance of eosinophils (40%, $39.88 \times 10^9/L$). A chest X-ray demonstrated bilateral peri-bronchial thickening and pulmonary infiltrates. Echocardiogram showed no evidence of pulmonary hypertension and good biventricular function with a normal fractional shortening. Lumbar Puncture was normal.

Bone marrow aspirate and trephine revealed a markedly hypercellular medullary space with immature and mature myeloid cells including neutrophils and eosinophils (see Figure 1). The immunophenotypic features were consistent with an excess of eosinophils and precursors with a modest myeloblast excess (6%) and evidence of monocytoid differentiation by flow cytometry.

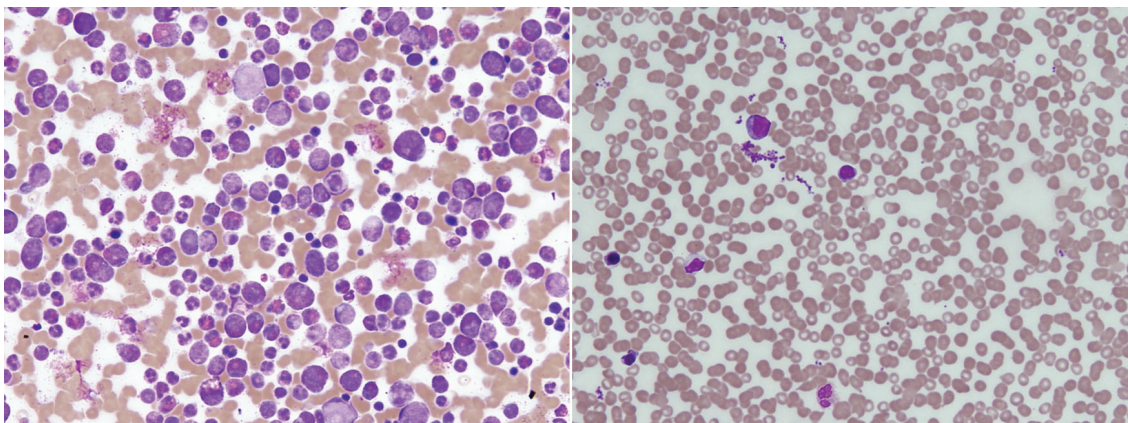


Figure 1. Bone marrow aspirate (BMA) smears at diagnosis and after 1 month of treatment with Imatinib. Initial BMA at diagnosis demonstrates marked eosinophilia with all stages of eosinophilic differentiation. Subsequent BMA at Day 29 of treatment demonstrates no eosinophilia or excess of blasts, with no morphological evidence of disease. Picture credit to David Hughes.

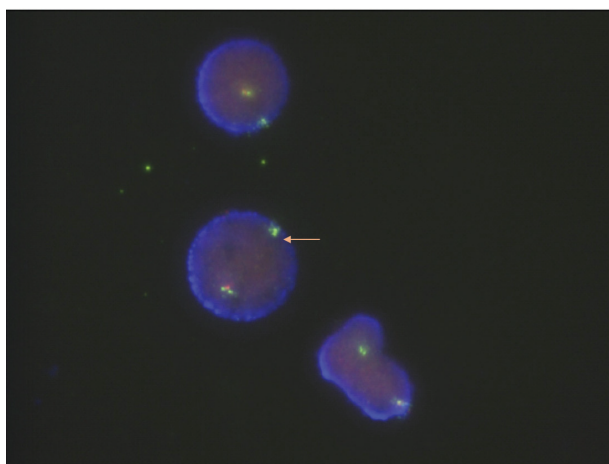


Figure 2. Fluorescence in situ hybridisation (FISH) analysis. Triple-color FISH probes hybridizing to the region between the FIP1L1 and PDGFRA genes, incorporating the CHIC2 (cysteine-rich hydrophobic domain 2) gene. Interstitial deletion of CHIC2 (in red) occurs when the FIP1L1-PDGFR fusion is present (arrow). Picture credit to Meghan Wall.

The patient commenced steroid and hydroxyurea whilst awaiting completion of molecular studies, but the peripheral blood eosinophilia and leucocytosis continued to rise. Fluorescent in-situ hybridisation (see Figure 2) revealed a FIP1L1-PDGFR fusion, and the patient was commenced on Imatinib at a dose of 100 mg daily. His response to Imatinib

was brisk, with normalisation of his peripheral eosinophil count within 48 hours of commencing the TKI (see Figure 3). After a week of treatment with Imatinib, the patient had no further respiratory symptoms and the lump on his posterior occiput was no longer palpable.

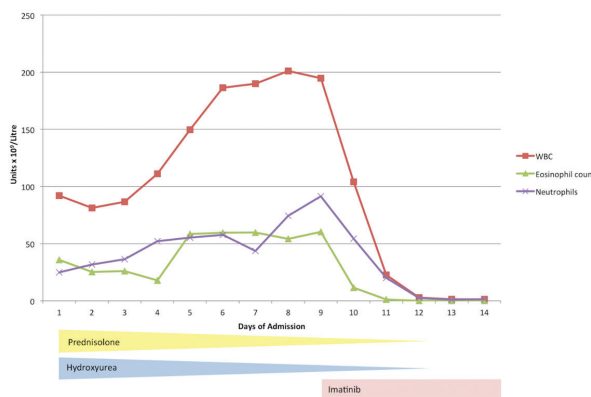


Figure 3. Timeline of treatment and hematological markers. Dramatic improvement of white cell count, eosinophilia and neutrophilia after commencement of Imatinib. Abbreviations: WBC – white blood cell count.

Evidence of response to Imatinib was demonstrated clearly by Bone Marrow Aspirate (BMA) analysis, and Minimal Residual Disease (MRD) analysis – FIP1L1-PDGFRa identi-

fied by Polymerase Chain Reaction (sensitivity down to 10^{-4}). A BMA performed at Day 29 of treatment already demonstrated impressive response to Imatinib, with no eosinophils or blast cells identified (see Figure 1), and MRD identified by Polymerase Chain Reaction of 1×10^{-3} . His 6-month marrow showed MRD further reduced to 1×10^{-4} , and by 9 months of treatment, MRD was not detectable. His parents were keen to discuss the merits of a bone marrow transplant as a potentially curative option for his condition.

3. DISCUSSION

The exquisite sensitivity to the TKI Imatinib appears to abrogate the immediate complications of hypereosinophilia in children (see Table 1), as it does in adults. However, this case report highlights several outstanding issues relating to treatment, particularly relevant to pediatric and young adult patients.

Table 1. Clinical characteristics of pediatric patients with clonal hypereosinophilia and molecular abnormalities of PDGFRA, PDGFRB or FGFR1

Reference	Age	Sex	History at presentation	Clonal cytogenetic abnormality	Eosinophil count at diagnosis	Treatment	Outcome
Wang <i>et al.</i> , 2015 (current case)	14 years	M	3 months loss of weight, bone pain, headaches, dizziness	FIP1L1-PDGFR fusion	$60 \times 10^9/L$	Steroids Hydroxyurea Imatinib 100 mg daily	Recovery
Rives <i>et al.</i> , 2005 [6]	7 years	M	Pruritus and malaise. No HSM	FIP1L1-PDGFR fusion	$6.1 \times 10^9/L$	Steroids	Recovery, Imatinib planned if relapse
Rapanotti <i>et al.</i> , 2010 [7]	16 years	M	Restrictive cardiomyopathy, lymphadenopathy. HSM present	FIP1L1-PDGFR fusion	$5.3 \times 10^9/L$	Imatinib 400 mg daily	Recovery
Rathe <i>et al.</i> , 2010 [8]	2 year	F	3 days malaise, fatigue, loss of appetite. No HSM	FIP1L1-PDGFR fusion	$22.5 \times 10^9/L$	Imatinib 300 mg/m ² daily	Recovery
Farruggia <i>et al.</i> , 2013 [9]	14 years	M	2 months weight loss, pallor. Left shoulder pain HSM present	FIP1L1-PDGFR fusion	$49 \times 10^9/L$	Imatinib 200 mg daily	Recovery
Li <i>et al.</i> , 2010 [10]	8 years	M	Cough, pallor and ulcers. HSM present	TPM3-PDGFRB fusion	N.A. Bone Marrow 45.5% eosinophils	Hydroxyurea Interferon Imatinib 200 mg/m ² daily	Recovery
Abraham <i>et al.</i> , 2012 [11]	3 months	M	Nodular lesions, HSM	TPM3-PDGFRB fusion	$5.6 \times 10^9/L$	Hydroxyurea, Imatinib, 340 mg/m ² daily	Recovery
	4 years	M	Failure to thrive, respiratory infections, HSM	FISH positive for 5q33 rearrangement involving PDGFRB	$3.9 \times 10^9/L$	Imatinib, 340 mg/m ² daily	Recovery
Wilkinson <i>et al.</i> , 2003 [51]	11 months	F	Malaise, poor feeding. HSM	PDGFRB-PDE4DIP fusion	WCC $43.9 \times 10^9/L$ with "marked eosinophilia"	Etoposide, Cytarabine, Interferon, Imatinib	Recovery

Note. N.A., not available; HSM, Hepatosplenomegaly; WCC, white cell count; Bold and italicised font indicates treatment that achieved clinical remission.

Like Chronic Myeloid Leukaemia (CML), *FIP1L1-PDGFR* hypereosinophilia patients face challenges regarding total length of required therapy. A group from the Mayo Clinic [8] recently reported upon 741 adult patients with hypereosinophilia, of which 3% (21) were *FIP1L1-PDGFR* positive. 14 of the 21 patients treated with Imatinib all achieved a complete response. Of these 14, 4 patients attempted to discontinue therapy but all relapsed. [11] Several other studies have also reported small numbers of patients who relapsed following Imatinib discontinuation. [12, 13] These findings suggest that the use of TKI does not completely eradicate the clone, and that the use of TKI should be life-long.

Given that pediatric patients may require Imatinib long-term, the issue of possible Imatinib resistance becomes more relevant. To date, there are no reported pediatric cases of Imatinib resistance in patients with *FIP1L1-PDGFR*. Imatinib resistance in adult patients with FIP1L1-PDGFR positive disease is low, occurring most frequently in patients developing blast crisis. A 2005 case report of a 67-year-old male patient with *FIP1L1-PDGFR* positive hypereosinophilia reported that Imatinib resistance occurred 6 months into treatment, and cor-

related with blast crisis. The T6741 mutation present showed a change of nucleotide 2417 of PDGFRA from cytosine to thymine, [14] and has been described in three other reported cases of advanced disease, including blast crisis. [15-17] Therefore, although few reported cases of resistance exist, what is clear is that in the face of resistance, disease factors (*i.e.* blast crisis) contribute to poor therapeutic options.

The optimal dose of Imatinib that maintains remission is unclear. Helbig *et al.* [18] reported upon 6 patients positive for *FIP1L1-PDGFR* initially treated with Imatinib 100-400 mg daily, until they achieved complete haematological remission (CHR). Subsequently they were dose decreased, till most were maintained on a single weekly dose of Imatinib of 100 mg-200 mg weekly. A similar dose reduction method was also adopted by the French Eosinophil Network series, who achieved complete molecular response in 95% of patients at a starting daily dose of 165 mg, then tapered Imatinib to a maintenance dose of 58 mg daily. [19] The limited studies to date suggest that in certain circumstances Imatinib can be dose reduced, provided MRD can be easily monitored.

There are very few case reports in the literature that analyse the efficacy of bone marrow transplant in eradicating the *FIPIL1-PDGFR* transcript. Halaburda *et al.*^[20] report a 29-year-old patient who was transplanted for hypereosinophilia, in whom the *FIPIL1-PDGFR* transcript was retrospectively shown to be positive in the sample at diagnosis. The patient received a matched sibling donor transplant using a myeloablative regime, and three years post-transplant remains well, in a molecular remission for the *FIPIL1-PDGFR* fusion transcript.

This case highlights the importance of ongoing molecular target research in this new area of target therapy. The exquisite sensitivity to the TKI Imatinib appears to abrogate the immediate complications of hypereosinophilia in children. Though

the incidence of Imatinib resistance in this disease is low in adults, it appears the use of Imatinib needs to be life-long; as yet, the long-term prognosis of these children is uncertain. Given the scant case reports for bone marrow transplant in *FIPIL1-PDGFR* hypereosinophilic disease, it would appear that in pediatric or young adult patients, matched sibling transplants are only to be explored in cases that are refractory to Imatinib. Parents requesting transplantation should have individual cases presented to hospital Ethics committees, as this request would stand outside of current recommendations for this condition.

CONFLICTS OF INTEREST DISCLOSURE

The authors have declared no conflicts of interest.

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