FIP1L1–PDGFRA positive chronic eosinophilic leukaemia and associated central nervous system involvement

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ABSTRACT
Interstitial deletion involving chromosome 4q12 generates the novel tyrosine kinase fusion protein encoded by FIP1L1–PDGFRA, which is present in many patients previously labelled as having hypereosinophilic syndrome, initially reported in 2003. Reports in recent literature document excellent clinical and molecular response to the tyrosine kinase inhibitor imatinib (Glivec). This report describes the case of a 58-year-old lady, diagnosed with FIP1L1–PDGFRA positive hypereosinophilic disorder, who subsequently developed symptoms related to an intracranial lesion. Biopsy and molecular genetic studies confirmed a diffuse infiltrative lesion, with evidence of FIP1L1–PDGFRA gene fusion. Initiation of imatinib treatment led to impressive clinical and radiological response.

CASE REPORT
A 58-year-old Caucasian lady was referred as an outpatient to the haematology department of our hospital with marked neutropenia and eosinophilia (haemoglobin 13.5 g/dl, white blood cell (WBC) count 79.1×10^9/L, neutrophils 53.8×10^9/L, eosinophils 11.9×10^9/L, platelets 156×10^9/L). She had a background diagnosis of rheumatoid arthritis, previously treated with methotrexate and meloxicam. There was no evidence of hepatosplenomegaly, lymphadenopathy or active infection. Peripheral blood microscopy revealed neutrophilia and marked eosinophilia. Bone marrow aspirate was markedly hypercellular with moderate eosinophilic infiltrate, minimal mast cells and no evidence of dysplasia. Trephine biopsy yielded a specimen that was maximally hypercellular with expanded granulopoiesis and marked fibrosis, consistent with chronic myeloproliferative disorder, and in keeping with chronic eosinophilic leukaemia. Bone marrow cytogenetic analysis revealed a clone with a 47, XX, +8 karyotype (ie, having trisomy 8). Fluorescence in situ hybridisation (FISH) was carried out using the FIP1L1–CHIC–PDGFRA probe set (QBogene, Cambridge, UK). This identified cryptic interstitial deletion leading to FIP1L1–PDGFRA fusion in 81% of nuclei (fig 1A). The fusion was confirmed by reverse transcription (RT)-PCR with direct sequencing of the PCR product (fig 1B).

Although imatinib was initially considered, the patient’s WBC normalised spontaneously within 1 month, and she was managed conservatively, according to her preference. Subsequently she developed progression of her arthritis, requiring treatment with prednisolone 5 mg daily and hydroxychloroquine 400 mg daily. Two weeks later, she self-presented with double vision and mild headache. Systemic examination showed no sign of infection or inflammation. She was found to have an isolated right sixth cranial nerve palsy. Full blood count (FBC) revealed an increase in WBC to 32.2×10^9/L with eosinophilia of 6.3×10^9/L. Inflammatory markers including erythrocyte sedimentation rate and C-reactive protein were normal. Auto-antibody screening, including antibody to extractable nuclear antigen, antinuclear antibody, antineutrophil cytoplasmic antibody and acetylcholine receptor antibodies, were negative. Hepatitis screen and borrelia serology were also negative.

MRI of the patient’s head revealed abnormal soft tissue partly surrounding the clivus and extending posteriorly into the prepontine cistern, laterally...
The patient was reviewed in the haematology outpatient clinic 1 month later, having made a full recovery from her recent bone marrow (fig 1C).

Within 3 months after starting imatinib, the patient’s diplopia had improved dramatically, with reduction of her squint from 30–35 dioptres to 10–12 dioptres.

Three months later she was reviewed at our Regional Neurosciences Centre. She had no observable squint when looking forwards but persistent diplopia on rightward gaze. FBC including eosinophil count was normal. She underwent a repeat MRI scan, which showed complete resolution of the intracranial infiltrative lesion (fig 2C, D).

At last haematological review (12 months after initial diagnosis), the patient’s FBC was normal with eosinophil count of $0.07 \times 10^9/l$, maintained by imatinib 100 mg on alternate days. Recent FISH analysis of peripheral blood revealed no evidence of FIP1L1–PDGFRA fusion or trisomy 8 in all 100 nuclei analysed. Interestingly the patient’s diplopia persists. She remains under close haematological and neurological surveillance.

**DISCUSSION**

Over the last decade there have been significant advances in our understanding of the molecular pathophysiology of eosinophilic disorders. This has enabled an increasing proportion of patients to have diagnoses of “idiopathic hypereosinophilic syndrome” replaced by genetically defined diagnoses of eosinophilic diseases with recurrent molecular abnormalities. The FIP1L1–PDGFRA fusion gene is a recurrent molecular lesion in eosinophilia-associated myeloproliferative disorders, predicting a favourable response to imatinib. A recent study evaluated 11 patients with FIP1L1–PDGFRA expression, and 9 of the 11 patients achieved a molecular remission (with assay sensitivities of 1 in $10^{4–5}$) after imatinib therapy.

Neurological complications occur frequently in the eosinophil disorders. However, there are only scanty case reports of direct neurological involvement in the clonal eosinophilic disorders. Cools et al reported a 39-year-old man with cranial nerve palsies and paraspinal masses, with a FIP1L1–PDGFRA fusion gene and complete haematological remission after imatinib therapy. Interestingly, cytogenetic analysis in this patient also revealed trisomy 8 (similar to our patient), despite the fact that the vast majority of cases show normal karyotype. Malagola et al reported a 47-year-old male with FIP1L1–PDGFRA positive disease presenting with a temporal/parietal mass lesion, who subsequently achieved haematological, radiological and molecular remission after imatinib treatment. Frichkhoen et al obtained a similar result in a 35-year-old male with chronic eosinophilic leukaemia and clinically significant CNS involvement.

We believe we report a first case with simultaneous molecular evidence of FIP1L1–PDGFRA fusion in bone marrow and tissue from a CNS deposit of the neoplastic haemopoietic cells, with excellent clinical and haematological response to imatinib. CNS involvement in this patient seems likely to have arisen by direct extension from involved bone marrow of the adjacent clivus. We highlight this important case to increase awareness of central nervous system involvement as a potential complication of clonal eosinophilic disorders. The good response to imatinib in our patient illustrated by almost complete resolution of her neurological lesion, is additive to previously well documented haematological and molecular responses achieved with the use of this agent. Interestingly, previous reports have shown that cerebrospinal fluid imatinib concentrations were <1% of simultaneous plasma concentrations in the mouse model (attaining one-third of the concentrations required to achieve 50% inhibition of cellular BCR-ABL1-related tyrosine phosphorylation), suggesting limited CNS penetration of the drug.

**Figure 1**

(A) Fluorescence in situ hybridisation using the Obiogene FIP1L1–PDGFRA probe set. Metaphase from presentation bone marrow showing FIP1L1–PDGFRA gene fusion resulting from cryptic interstitial deletion in 4q12 (normal chromosome 4, red–green “fusion” signal; deleted chromosome 4, green signal). (B) Reverse transcription-PCR analysis of presentation bone marrow. The positive (++, control shows two bands due to alternate splicing.) Abbreviated nucleotide sequence showing the molecular junction of exon 13 of the FIP1L1 sequence (green bold) and exon 13 of the PDGFRA sequence (green italics). The intervening sequence (white), representing an Alu repeat sequence, has 100% homology to a region of intron 13 of FIP1L1, with no homology present in intron 12 of PDGFRA. However, this sequence also shows 100% homology with many other regions of the human genome so it cannot be stated with certainty that this sequence is derived from the FIP1L1 gene. Genbank sequences: FIP1L1, NM_030917; PDGFRA, NM_006206. (C) Interphase nuclei released from paraffin-embedded brain tumour showing the abnormal “fusion + green” signal pattern.
limited penetration of imatinib into the cerebrospinal fluid of non-human primates after oral and intravenous administration has also been shown in a paper by Neville et al. However in this case, as in the case reported by Malagola et al., the infiltrative mass was extra-axial in location.

An atypical feature in our case is the apparent spontaneous resolution of her peripheral eosinophilia within 1 month of bone marrow diagnosis. In the absence of initial end-organ complications, with normalisation of her blood counts and the preference of the patient, we decided not to treat prophylactically with imatinib. However, pre-emptive imatinib therapy in this case may have prevented later neurological complications. Further research and reporting of additional cases with molecular and clinical correlations, will improve understanding of the clinical implications of the FIP1L1–PDGFRA oncogenic mutation.

Competing interests: None.

Patient consent: Informed consent has been obtained for the publication of the details in this report.

REFERENCES


Take-home messages

- It is important to screen for the FIP1L1–PDGFRA fusion gene in all cases of primary hypereosinophilia.
- The majority of patients with FIP1L1–PDGFRA positive hypereosinophilic disease will achieve a molecular response when treated with low dose imatinib.
- The ultimate goal of imatinib therapy in FIP1L1–PDGFRA positive hypereosinophilic disease must be a molecular, rather than merely haematological response.
- Neurological complications occur frequently in the eosinophil disorders.
- Extramedullary manifestations of FIP1L1–PDGFRA positive disease may respond to imatinib, as demonstrated in this case.


