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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.

In 2003, Cools *et al*[1] described a novel tyrosine kinase, generated from the fusion of the FIP1-like 1 (*FIP1L1*) gene to the platelet-derived growth factor receptor α (*PDGFRA*) gene, resulting from a cryptic interstitial deletion of chromosome 4q12. The *FIP1L1–PDGFRA* fusion gene was identified in 9 (56%) of 16 patients deemed to have hypereosinophilic syndrome with a significant male preponderance. The protein encoded by the *FIP1L1–PDGFRA* fusion transforms haemtopoietic cells and its kinase activity is inhibited by imatinib (Glivec; Novartis, Horsham, UK) at a cellular 50% inhibitory concentration 100-fold lower than that effective for *BCR-ABL1*.[1] Treatment with low-dose imatinib (100 mg/day) produced complete and durable responses in all eight *FIP1L1–PDGFRA* positive cases reviewed by Pardanani *et al*.[2] Since the seminal paper in 2003,[1] there have been numerous excellent reviews and case series providing further understanding of this novel oncogenic mutation and its implications for patient management.[3–5] We now report the case of a patient diagnosed with a *FIP1L1–PDGFRA* positive clonal eosinophilic disorder, presenting with bone marrow infiltration, who subsequently developed central nervous system (CNS) involvement by the same process, associated with probable bone marrow involvement of the clivus. This intracranial infiltration resolved shortly after introduction of imatinib therapy. Eosinophilic disorders have been reported to have neurological sequelae such as neuropathy, encephalopathy and cerebral venous sinus thrombosis.[6 7 9 10] We believe this presentation validated by parallel documentation of the *FIP1L1–PDGFRA* mutation in bone marrow tissue and CNS tissue is unique in current literature.

CASE REPORT

A 58-year-old Caucasian lady was referred as an outpatient to the haematology department of our hospital with marked neutrophilia 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 136×10^9/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 (QBiogene, Cambridge , UK). This identified cryptic interstitial deletion leading to *FIPL1–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

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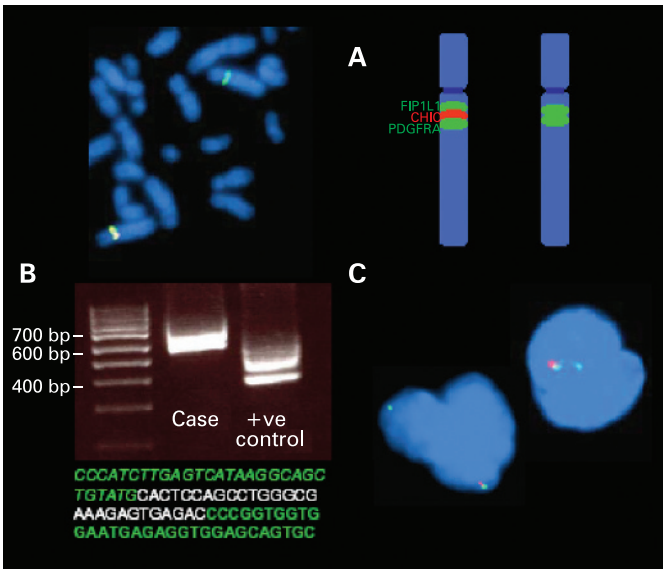

Figure 1 (A) Fluorescence in situ hybridisation using the Qbiogene *FIP1L1*-CHIC-*PDGFRA* probe set. Metaphase from presentation bone marrow showing *FIP1L1–PDGFRA* gene fusion resulting from cryptic interstitial deletion in 4q12 (normal chromosome 4, red–green "fusion" signal; deleted chromosome 4, green signal). (B) Reverse transcription-PCR analysis of presentation bone marrow. (The positive (+ve) 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; *PDGFRα*, NM_006206. (C) Interphase nuclei released from paraffin-embedded brain tumour showing the abnormal "fusion + green" signal pattern.

into the left cavernous sinus and Meckel's cave (fig 2A, B). The epicentre of the lesion was in the left side of the sphenoid sinus. The signal within the clivus bone was abnormally low, indicating infiltration of the marrow. The infiltrative lesion showed a moderate degree of enhancement. Lumbar puncture was unremarkable with normal cell count and absent oligoclonal bands. The patient commenced carbamazepine (100 mg/day) for headache, and continued prednisolone (5 mg/day).

Trans-sphenoidal biopsy of the intracranial lesion was performed. Histological examination of the biopsy specimen showed neoplastic tissue containing mixed cells including abundant eosinophil precursors and maturing granulopoietic cells. There were no features to suggest the presence of acute leukaemia, lymphoma or solid metastatic tumour.

Interphase nuclei released from formalin-fixed paraffin-wax-embedded brain tumour tissue were tested with the FISH probe described above. *FIPL1–PDGFRA* fusion was apparent in 87% of nuclei, with an abnormal signal pattern identical to that seen in bone marrow (fig 1C).

The patient was reviewed in the haematology outpatient clinic 1 month later, having made a full recovery from her recent surgery. WBC had risen further to 60.5×10^9/l and a decision was made to initiate definitive therapy with imatinib (100 mg/day). A week later, WBC decreased to 2.4×10^9/l and imatinib was reduced to 100 mg on alternate days, with normalisation of her blood parameters.

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 0.07×10^9/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.[8] 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 $10^{3–5}$) after imatinib therapy.[5]

Neurological complications occur frequently in the eosinophil disorders.[6 7 9] 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.[1] 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.[10] Frickhofen *et al* obtained a similar result in a 33-year-old male with chronic eosinophilic leukaemia and clinically significant CNS involvement.[11]

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.[1 2 5 9] 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.[12] The

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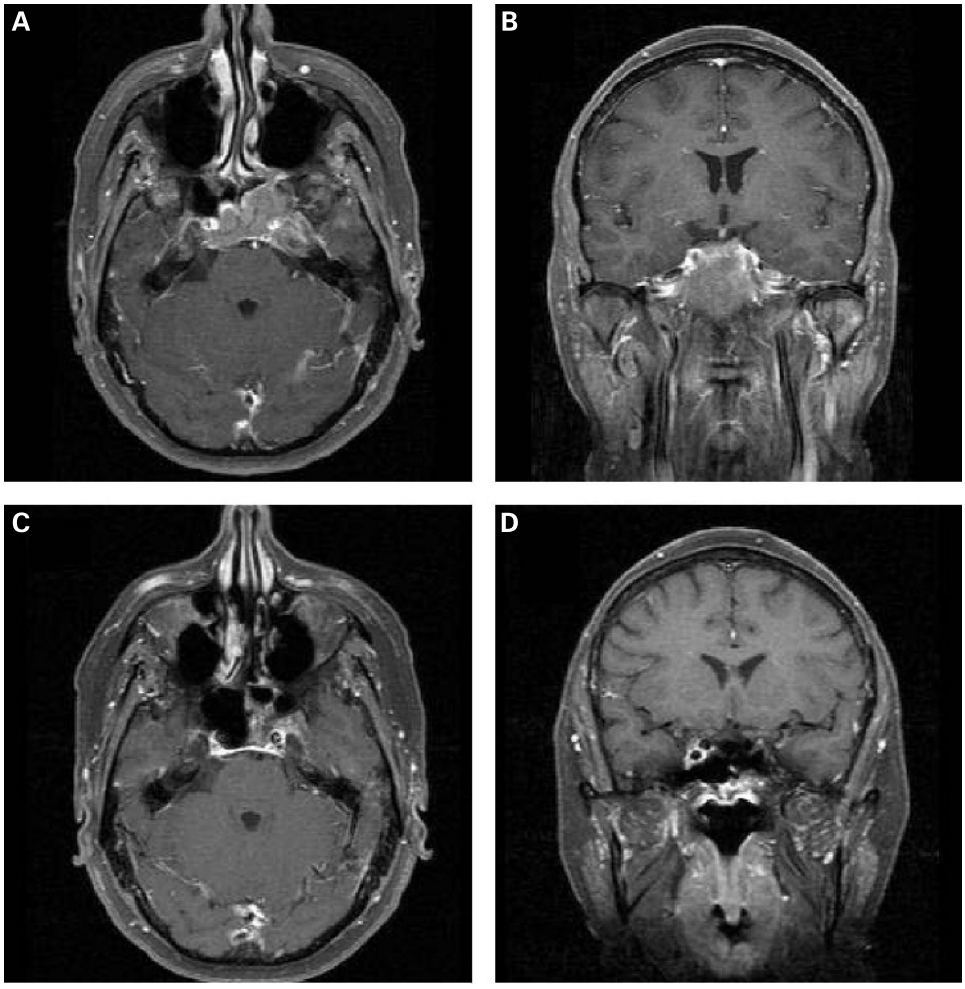

Figure 2 MRI (fat suppression sequences) at presentation and after treatment with imatinib for 3 months. (A, B) Axial and coronal MRI images prior to biopsy. (C, D) Axial and coronal MRI images after imatinib therapy.

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*.[13] However in this case, as in the case reported by Malagola *et al*,[10] 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.

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.

Competing interests: None.

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

REFERENCES

1. **Cools J,** DeAngelo D J, Gotlib J, *et al*. A tyrosine kinase created by fusion of the *PDGFRA* and *FIP1L1* genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med* Mar 27 2003;**348**:1201–14.
2. **Pardanani A,** Brockman SR, Paternoster SF, *et al*. *FIP1L1–PDGFRA* fusion: prevalence and clinicopathologic correlates in 89 consecutive patients with moderate to severe eosinophilia. *Blood* 2004;**104**:3038–45.
3. **Gotlib J,** Cools J, Malone III JM, *et al*. The FIP1L1–PDGFR alpha fusion tyrosine kinase in hypereosinophilic syndrome and chronic eosinophilic leukemia: implications for diagnosis, classification, and management. *Blood* 2004;**103**:2879–91.
4. **Tefferi A,** Patnaik M, Pardanani A. Eosinophilia: secondary, clonal and idiopathic. *Br J Haematol* 2006;**133**:468–92.
5. **Jovanovic J V,** Score J, Waghorn K, *et al*. Low-dose imatinib mesylate leads to rapid induction of major molecular responses and achievement of complete molecular remission in *FIP1L1–PDGFRA* positive chronic eosinophilic leukaemia. *Blood* 2007;**109**:4635–40.
6. **Kwon SU,** Kim JC, Kim JS. Sequential magnetic resonance imaging findings in hypereosinophilia-induced encephalopathy. *J Neurol* 2001;**248**:279–84.
7. **Sakuta R,** Tomika Y, Ohashi M, *et al*. Idiopathic hypereosinophilic syndrome complicated by central sinovenous thrombosis. *Brain Dev* 2007;**29**:182–4.

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8. **Gotlib J,** Cross NC, Gilliland DG. Eosinophilic disorders: molecular pathogenesis, new classification and modern therapy. *Best Pract Res Clin Haematol* 2006;**16**:535–69.
9. **Moore PM,** Hartley JB, Fauci AS. Neurologic dysfunction in the idiopathic hypereosinophilic syndrome. *Ann Intern Med* 1985;**102**:109–14.
10. **Malagola M,** Martinelli G, Rondoni M, *et al*. Soft tissue and skeletal involvement in FIP1L1-PDGFR-α positive chronic eosinophilic leukemia: imatinib mesylate may induce complete molecular and imaging remission. *Haematologica* 2004;**89**:e85–6.
11. **Frickhofen N,** Märker-Hermann E, Reiter A, *et al*. Complete molecular remission of chronic eosinophilic leukemia complicated by CNS disease after targeted therapy with imatinib. *Ann Hematol* 2004;**83**:477–80.
12. **Druker B J,** Tamura S, Buchdunger E, *et al*. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. *Nat Med* 1996;**2**:561–6.
13. **Neville K,** Parise R, Thompson P, *et al*. Plasma and cerebrospinal fluid pharmacokinetics of imatinib after administration to nonhuman primates. *Clinl Cancer Res* 2004;**10**:2525–9.

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