

CASE REPORT

A case of hypereosinophilic syndrome presenting with chronic cough successfully treated with imatinib

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ABSTRACT

Chronic cough is caused by a wide variety of disease conditions, including asthma, rhino-sinusitis and gastro-oesophageal reflux. We describe the case of a 42-year-old man with hypereosinophilic syndrome presenting with chronic dry cough. The cough did not respond to inhaled corticosteroid or leucotriene receptor antagonists. Hepatosplenomegaly was noted and the patient became anaemic and thrombocytopenic. He was refractory to treatment with hydroxyurea and interferon- α . Administration of imatinib resulted in complete resolution of eosinophilia and cough, without the use of anti-asthma drugs. Analysis of RNA from this patient demonstrated expression of the Fip1-like 1/platelet-derived growth factor receptor- α (*FIP1L1-PDGFR α*) fusion gene. The myeloproliferative variant of hypereosinophilic syndrome may cause chronic intractable cough, and a trial of imatinib treatment may be warranted.

Key words: airway inflammation, *FIP1L1-PDGFR α* fusion gene, hypereosinophilic syndrome, imatinib, myeloproliferative variant.

INTRODUCTION

The hypereosinophilic syndrome (HES) comprises a heterogeneous group of haematological disorders characterized by unexplained sustained eosinophilia ($> 1.5 \times 10^9/L$ for more than 6 months), associated with signs and symptoms of organ involvement.^{1,2}

It was recently reported that approximately 50% of cases of HES were caused by a cryptic deletion on chromosome 4q12, resulting in expression of the Fip1-like 1/platelet-derived growth factor receptor- α (*FIP1L1-PDGFR α*) fusion gene and aberrant tyrosine kinase activity.³⁻⁶ *FIP1L1-PDGFR α* is a constitutively activated tyrosine kinase that provides proliferative

and survival signals, and is inhibited by the small molecule kinase inhibitor, imatinib.^{3,6} *FIP1L1-PDGFR α* -positive patients show dramatic responses to imatinib therapy, and most demonstrate complete haematological and molecular remission. Several studies have indicated that at least two subgroups of HES patients can be distinguished: those with the lymphocytic variant of HES⁷ and those with the myeloproliferative variant of HES.^{3,5,8-10} Patients who cannot be classified into either of these two subgroups are considered to have idiopathic HES.

We report the unique case of a patient with the myeloproliferative variant of HES, manifesting as a chronic cough, who was successfully treated with the tyrosine kinase inhibitor, imatinib.

CASE REPORT

A 42-year-old man presented with a chronic dry cough mimicking cough variant asthma and was admitted to Kochi Medical School Hospital in August, 2000. Chest auscultation showed the absence of rhonchi throughout his clinical course. A CXR was normal. The WCC was $11.5 \times 10^9/L$ with 31% eosinophils. Serum IgE was 65.7 IU/mL. Pulmonary function testing revealed a VC of 4.17 L (106.1% of predicted), FEV₁ 2.93 L and FEV₁% 71.8. DL_{CO} was normal. Sputum cytology showed numerous eosinophils, suggesting the possibility of asthma. Bronchial mucosal biopsy demonstrated mild to moderate submucosal infiltration of eosinophils, with moderate thickening of the basement membrane, minimal subepithelial fibrosis and rare epithelial shedding (Fig. 1). Goblet cell hyperplasia was also noted.

The patient was treated with inhaled corticosteroid and a leucotriene receptor antagonist. Occasional concomitant use of oral corticosteroid (20–30 mg of prednisolone daily) was necessary. His dry cough diminished in frequency following these treatments, but did not disappear completely. One year later, the WCC increased gradually and reached $31.3 \times 10^9/L$ with 32% eosinophils. At a second admission for further evaluation, hepatosplenomegaly was noted, with anaemia (haemoglobin 98 g/L) and

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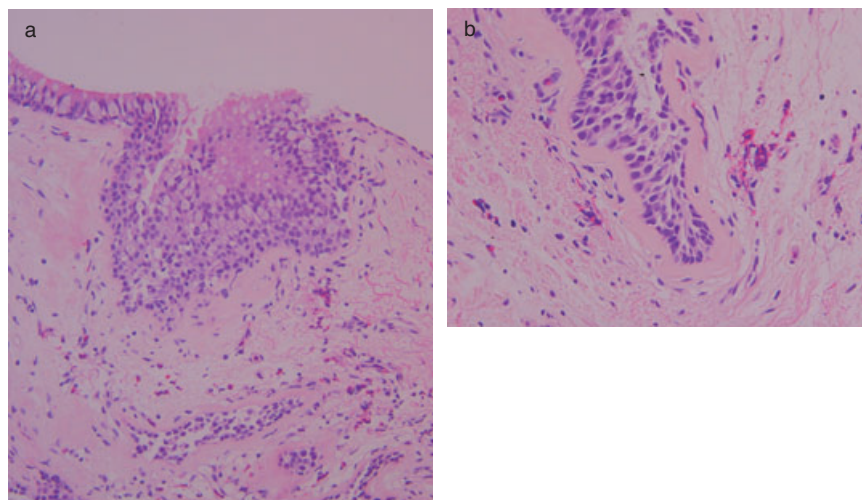


Figure 1 (a) Light microscopy of bronchial biopsy demonstrating moderate submucosal infiltration of eosinophils. There was minimal subepithelial fibrosis with rare epithelial shedding. Goblet cell hyperplasia was also noted (original magnification: $\times 200$, HE stain). (b) High magnification view of the bronchial biopsy revealed moderate thickening of the basement membrane associated with submucosal infiltration of eosinophils (original magnification: $\times 400$, HE stain).

FIP1L1-PDGFR α fusion gene

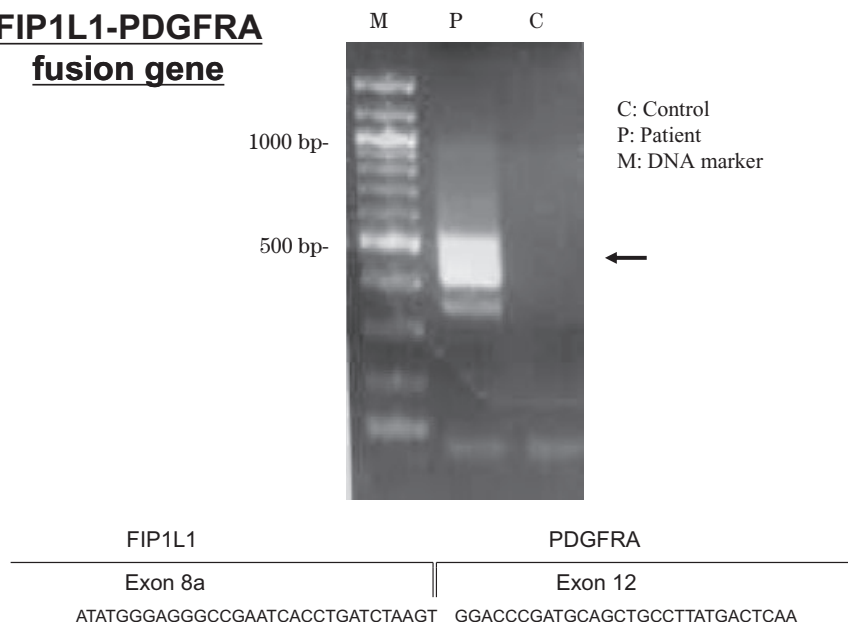


Figure 2 Upper panel shows the result of RT-PCR, indicating the expression of fusion gene *FIP1L1-PDGFR α* RNA (arrow). C, P and M indicate a control sample, a patient sample and DNA size marker, respectively. Lower panel shows the DNA sequence of the amplified product for one in-frame splice variant expressed in the patient.

thrombocytopenia ($58 \times 10^9/L$). Bone marrow aspiration revealed moderate eosinophilia. Cytogenetic analysis of bone marrow aspirates showed a normal karyotype (46, XY). Serum vitamin B12 increased to 7569 pg/mL. Therefore, a diagnosis of idiopathic HES was made. Administration of hydroxyurea was commenced in June, 2001 and the eosinophilia was initially controlled but recurred later. Administration of interferon- α was successful for several months.

On the patient's fourth admission in May, 2003, he developed high fever and generalized arthralgia. The WCC was $8.3 \times 10^9/L$ with 34% eosinophils and 10% leucocyte precursors, with a platelet count of $50 \times 10^9/L$ and a haemoglobin concentration of 60 g/L. The serum LDH level was elevated at 492 IU/L. Administration of imatinib mesylate (100 mg a day) was commenced and resulted in the prompt and complete resolution of eosinophilia. In the subse-

quent 2 months, leucocyte, erythrocyte and platelet counts returned to normal. In addition, the long-lasting cough subsided completely. Testing for the *FIP1L1-PDGFR α* fusion gene by nested RT-PCR, as described by Cools *et al.*,⁶ was positive (Fig. 2). Sequencing of the *FIP1L1-PDGFR α* fusion gene revealed a breakpoint involving exon 8 of the *FIP1L1* gene and exon 12 of the *PDGFR α* gene (Fig. 2). The diagnosis of myeloproliferative variant of HES was thus established. The patient has been well for approximately 3 years on a continuing daily dose of imatinib mesylate (100 mg/day).

DISCUSSION

HES is defined as sustained hypereosinophilia of $> 1.5 \times 10^9/L$ for more than 6 months, with organ

involvement. Tissue eosinophilic infiltration frequently involves the heart, lung, skin and nervous system. Thus, HES is a heterogeneous disorder with clinically variable manifestations. Until recently, the diagnosis was only made after exclusion of other causes of eosinophilia such as infections, inflammation and neoplastic disease.^{1,2}

Recent reports document the efficacy of low-dose imatinib mesylate (100 mg/day) in 65% of HES patients.^{3,5} The discovery of the novel *FIP1L1-PDGFR* fusion gene, which is a gain-of-function gene on chromosome 4q12, elucidated the theoretical background to the effectiveness of imatinib mesylate in HES patients.^{3,6,10} Consequently, the detection of *FIP1L1-PDGFR* fusion gene is useful for distinguishing patients with the myeloproliferative variant of HES from those with idiopathic HES.

In the present case, the patient initially complained of chronic cough, and subsequently suffered from evolving hypereosinophilia and hepatosplenomegaly associated with anaemia and thrombocytopenia. He was finally diagnosed as having the myeloproliferative variant of HES, based on the presence of the *FIP1L1-PDGFR* fusion gene. The patient's long-sustained eosinophilia resolved immediately after the commencement of imatinib treatment. At the same time, the long-lasting and distressing cough disappeared.

Chronic cough is a symptom of many disease conditions, including asthma, rhino-sinusitis and gastro-oesophageal reflux.¹¹ In this patient, cough variant asthma was initially suspected, because of the presence of numerous eosinophils in sputum and mild to moderate infiltration of eosinophils in the bronchial submucosa, as well as the lack of typical wheeze on chest auscultation. Endobronchial biopsy showed thickening of basement of membrane with minimal subepithelial fibrosis and rare epithelial shedding, as assessed by light microscopy. Prior to the onset of hepatosplenomegaly, it was assumed that these findings indicated airway inflammation associated with cough variant asthma, rather than HES.

During the preparation of this manuscript, the first report describing persistent cough caused by HES was published.¹² In that patient, testing for the *FIP1L1-PDGFR* fusion gene was positive and the persistent cough was completely suppressed after imatinib treatment, as observed in the present patient. In the previous case, endobronchial biopsy showed goblet

cell hyperplasia and eosinophilic stromal inflammation.¹² Taken together, these findings suggest that submucosal infiltration of eosinophils, thickening of basement membrane and goblet cell hyperplasia may be key features of airway inflammation in HES, leading to chronic dry cough.

In conclusion, HES may be accompanied by chronic cough. Because this involves expression of the *FIP1L1-PDGFR* fusion gene, resulting in aberrant tyrosine kinase activity, it can be successfully treated with the tyrosine kinase inhibitor, imatinib.

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