

LETTER TO THE EDITOR

Dramatic resolution of respiratory symptoms with imatinib mesylate in patients with chronic myeloid leukemia presenting with lower airway symptoms resembling asthma

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Recent observations show that imatinib mesylate induces early normalization of leukotriene C4 synthase expression in patients with chronic myeloid leukemia (CML) [1]. There is a strong association between increased leukotriene C4 levels and exercise-induced asthma [2,3]. Normalization of leukotriene C4 levels with imatinib mesylate treatment can lead to resolution of asthma-like symptoms. We describe two cases supporting this who presented with lower airway symptoms resembling asthma and CML in whom treatment with imatinib mesylate led to complete resolution of lower airway symptoms.

Case 1. A 40-year-old male presented to the respiratory department with a 1-year history of exercise-induced breathlessness and cough. These symptoms were also precipitated by changes in atmospheric temperature. He was diagnosed with exercise-induced asthma (EIA), and the treatment was initiated with inhalers and oral corticosteroids. There was a minimal response to the treatment. Subsequently his symptoms deteriorated. He experienced weight loss and developed night sweats. Based on these symptoms and his blood count results, he was referred to the hematology department for investigation. Clinical examination revealed normal cardiovascular and respiratory findings. The spleen was palpable 15 cm below the costal margin. There was no palpable lymphadenopathy. Full blood count results were as follows: Hb 8.6 g/dL, WBC $309 \times 10^9/L$ and platelets $435 \times 10^9/L$. The blood

film showed leucocytosis mostly neutrophilia with a left shift predominantly showing increased myelocytes, distinctive basophilia, and myeloblast typical of CML. A diagnosis of CML in chronic phase was confirmed by cytogenetics which showed t(9;22) (q34;q11). He was commenced on imatinib mesylate 400 mg daily. Within five days his respiratory symptoms and the night sweats resolved. He achieved a hematological remission within 5 months of starting treatment, and a complete cytogenetic response at 12 months. At the time of writing, he remained in complete cytogenetic remission but has not achieved molecular remission.

Case 2. A 34-year-old male presented to his general practitioner complaining of cough. He was treated with salbutamol inhalers, two courses of antibiotics and two courses of prednisolone, as his symptoms resembled asthma. He did not respond to this treatment and his symptoms persisted. Seven months after initial presentation a full blood count revealed Hb 8.7 g/dL, WBC $366 \times 10^9/L$ and platelets $521 \times 10^9/L$. On examination he had massive splenomegaly. The blood film showed leucocytosis mostly neutrophilia with a left shift predominantly showing increased myelocytes, distinctive basophilia, and myeloblast typical of CML. A diagnosis of CML in chronic phase was confirmed following bone marrow examination with cytogenetic analysis showing the Philadelphia chromosome. He was treated initially with hydroxycarbamide. His WBC fell

rapidly, the spleen decreased in size, and his respiratory symptoms improved. After 10 days of hydroxycarbamide therapy he was commenced on imatinib mesylate 400 mg daily. His respiratory symptoms then resolved completely. After 6 months of imatinib mesylate therapy, the Philadelphia chromosome was detected in 85% of his marrow cells. The dose of imatinib mesylate was increased to 500 mg daily as this was the dose that was tolerated by the patient at that time. He achieved a complete cytogenetic remission after 12 months of therapy. He had a subsequent cytogenetic relapse which did not respond to an increased dose of imatinib mesylate of 800 mg/day but has responded to dasatinib 100 mg/day and he has now had a molecular response.

These two cases show that CML can present with lower airway symptoms resembling asthma. To our knowledge, this observation has not been reported previously. Studies in patients with EIA show increased leukotriene C4 synthesis as a consequence of increased expression of the 5-lipoxygenase gene (ALOX-5) and increased expression of the ALOX-5-activating protein gene [2,3]. Imatinib mesylate therapy normalizes aberrant neutrophil leukotriene C4 synthase expression in CML hemopoietic cells [1], thereby reducing or eliminating lower airway

symptoms. Experimental studies in cockroach allergen asthma mouse models have shown attenuated airway responses with imatinib mesylate [4]. Further, CML is associated with pulmonary leucostasis. CML directed therapy may reduce pulmonary leucostasis and may alleviate respiratory symptoms [5]. This supports our observation of resolution of lower airway symptoms in our patients following initiation of imatinib mesylate therapy.

References

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