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Persistent cough as the sole manifestation of chronic eosinophilic leukemia (CEL) expressing FIP1L1-PDGFRA fusion gene

Długotrwały kaszel jako jedyny objaw przewlekłej białaczki eozynofilowej z ekspresją genu FIP1L1-PDGFRA

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S u m m a r y

We report on a male patient with persistent, non-productive cough. He has been receiving several oral and inhaled agents including steroids for the last 10 years. Two years before his current admission to Hematological Unit, an increased white blood cell (WBC) count with hypereosinophilia was documented with no further investigation. On admission his eosinophil count was 9.4 x 10^9/L with eosinophilic infiltration in marrow of 61%. The presence of FIP1L1-PDGFRA (F/P) fusion transcript was detected on molecular study and tyrosine kinase inhibitor-imatinib was initiated at a dose of 100mg daily. His eosinophil count dropped to 0.8 x 10^9/L with symptoms resolution merely 7 days after imatinib commencement. The repeated molecular study performed one month later did not detect the presence of F/P fusion. Currently, patient is free of any symptoms with normal eosinophil count while still on imatinib at 100 mg weekly.

Key words: chronic eosinophilic leukemia, imatinib, cough, FIP1L1-PDGFRA

S t r e s z c z e n i e

Prezentujemy pacjenta z długotrwałym, nieproduktywnym kaszlem. Leczony od 10 lat z zastosowaniem różnych leków doustnych i wziewnych, w tym kortykosteroidów. Dwa lata przed skierowaniem na Oddział Hematologii, zwrócono uwagę na hiperleukocytozę z hipereozynofilią, ale nie podjęto dalszych badań. Przy przyjęciu liczba komórek kwasochłonnych wynosiła 9,4 x 10^9/L z 61% naciekiem kwasochłonnym w szpiku. Obecność onkogenu FIP1L1-PDGFRA (F/P) wykazano w badaniu molekularnym i rozpoczęto leczenie z zastosowaniem inhibitora kinazy tyrozynowej – imatynibu w dawce 100 mg dziennie. Obserwowano spadek eozynofilii do 0,8 x 10^9/L z ustąpieniem objawów po tygodniu leczenia imatynibem. Badanie molekularne wykonane miesiąc później nie wykazało obecności genu F/P. Obecnie, pacjent nie zgłasza objawów choroby. Liczba eozynofili jest prawidłowa, a chory stale pobiera imatynib w dawce 100 mg 1x na tydzień.

Słowa kluczowe: przewlekła białaczka eozynofilowa, imatynib, kaszel, FIP1L1-PDGFRA

INTRODUCTION

Hypereosinophilic syndromes (HES) comprise a heterogeneous group of conditions characterized by sustained, non-reactive hypereosinophilia and eosinophilic tissue damage (1). There is little known about lung involvement in HES, but it was estimated that about 25% of patients demonstrated pulmonary manifestation (2). The FIP1L1-PDGFRA (F/P) fusion gene results from an interstitial deletion in chromosome 4q12 and is present in about 10% of patient fulfilling HES criteria. These cases are currently classified as chronic eosinophilic leukemia (CEL) (3).

Herein we report a rare case of CEL F/P+ with a cough as the sole clinical disease manifestation.

CASE DESCRIPTION

A 51-year old male developed a cough in 2001. He was investigated in Outpatient Pulmonary Unit using computed tomography of the lungs, bronchoscopy and spirometry with no abnormalities found. He was treated with several agents including inhaled and oral steroids with no effect. In 2009 his hematology revealed an increased white blood cell (WBC) count (14 x 10^9/L) with 60% of eosinophils in blood smear. No further

investigations were implemented. Two years later he was admitted to Hematological Unit, his eosinophil count was 9.4 x 10^9/L and 61% of marrow was occupied by eosinophils. Reactive causes of hypereosinophilia were excluded. Biochemistry was normal, his serum vitamin B12 level was 645 pg/ml (normal range: 189-883 pg/ml) and serum immunoglobulin (Ig) E level was slightly increased: 187 IU/ml (normal range: < 100 IU/ml). Serum tryptase level was normal: 10.9 ug/L (normal range: < 11.4 ug/L). There were no aberrant lymphocytes T in flow cytometry. Bone marrow trephine biopsy revealed fibrosis of grade I and II with eosinophilic predominance. The picture was consistent with the diagnosis of chronic eosinophilic leukemia. Molecular studies using reverse-transcription polymerase chain reaction (RT-PCR) performed on blood cells detected the presence of F/P fusion transcript. BCR-ABL and JAK2V617F mutations were negative. Imatinib was initiated at a daily dose of 100mg with slow tapering of bronchodilatators. One week later, patient was free of symptoms with a drop in eosinophil count. He was discharged from hospital while on imatinib at a dose of 100mg daily. The other therapies were stopped. One month after that he started imatinib, a repeated RT-PCR was done and F/P fusion was undetectable. Imatinib dose was reduced to 100mg weekly. Currently, 6 months after imatinib initiation patient remained free of cough with normal eosinophil count.

DISCUSSION

Cough as the sole clinical manifestation is rarely seen in patient with F/P-positive chronic eosinophilic leukemia. Only 2 out of 16 studied patients in Multicenter Polish Study demonstrated constitutional symptoms; there was cough in both cases. However, it should be highlighted that cough was not the sole clinical feature in this patient subgroup (4). Up-to-date there are two case studies presenting patients with a cough as a predominant manifestation of CEL. First report described a male with cough, gastro-oesophageal reflux and hepatosplenomegaly on physical examination. Of note is, that high dose steroids controlled the cough, but on steroid tapering the disease symptoms recurred. The second case presented a 42-year old patient who developed cough followed by a significant increase in WBC count and further appearance of anemia and thrombocytopenia. Hepatosplenomegaly was also demonstrated. Oral steroids, hydroxyurea and interferon alpha were ineffective. Imatinib appeared to be highly successful in both cases resulting in rapid disappearance of peripheral blood eosinophilia and symptoms resolution. The results of endobronchial biopsy showed goblet cell hyperplasia and submucosal infiltration of eosinophils in both cases (5, 6). It may suggest that these findings represent the key features of respiratory tract inflammation in HES leading subsequently to persistent cough. Unfortunately, the results of bronchial biopsy were inconclusive in our case. Of note is, that we demonstrated elevated serum IgE levels whereas in abovementioned patients these levels were at normal range. It may suggest partially reactive condition responsible for cough in our case, but on the other hand steroids were ineffective. It should be mentioned that cough as the sole sign is rarely seen in CEL thus the diagnosis protracted and lasted 10 years from first disease manifestation. Moreover, other disease features were absent. Notwithstanding, we should keep in mind that in half of CEL cases the diagnosis is accidental (4). It should be stressed that low dose of imatinib is a treatment of choice in F/P-positive CEL patients and its administration results in striking response.

In conclusion, non-reactive, sustained hypereosinophilia may be accompanied by unexplained cough and in a such case, the molecular assay towards the presence of the FIP1L1-PDGFRA fusion transcript is highly recommended. The further studies are needed to explain the role of eosinophils in pathogenesis of cough.

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