INTERNATIONAL JOURNAL OF MEDICAL AND APPLIED SCIENCES
E-ISSN:2320-3137

Case Report

IMATINIB INDUCED PLEURAL EFFUSION: A CASE REPORT

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Abstract :
Tyrosine kinase inhibitors like imatinib have revolutionized the treatment of CML from being a supportive to a curative one. Side effects like fluid retention including pleural effusion are known to occur with therapy. We are reporting a case of imatinib induced right sided exudative pleural effusion, following 20 days of therapy with imatinib, which resolved spontaneously upon its withdrawal within a month.
Key words: CML, Imatinib, Pleural Effusion, Side effects of imatinib

INTRODUCTION

Chronic myeloid leukemia (CML) belongs to a heterogenous group of diseases that are characterized by infiltration of the blood, bone marrow and other tissues by neoplastic cells of the hematopoetic system. The diagnosis of CML is made by identifying a clonal expansion of hematopoetic stem cells that possess a reciprocal translocation between chromosomes 9 and 22(bcl-abr)[1]. Untreated, the disease is characterized by a transition from a chronic to an accelerated phase and finally a blast crisis (which is usually fatal) in around 4 years.

Tyrosine kinase inhibitors like imatinib have revolutionized the treatment of CML from being supportive to being one with curative intent. At present, the goal of therapy is to achieve prolonged, durable, non-neoplastic, non-clonal hematopoesis, signifying the eradication of all cells containing the bcl-abr mutation[1]. Imatinib, however, can cause a number of side effects like fluid retention, including pleural effusion. Severe fluid retention (e.g., pleural effusion, pericardial effusion, pulmonary edema, and ascites) events were reported in 0.7% of newly diagnosed CML patients taking Imatinib, and in 2%-6% of other adult CML patients taking imatinib[2]. However, the exact incidence of pleural effusion per se with imatinib use is still unknown.

Here, we are presenting a case of newly diagnosed (20 days ago) CML who developed right sided pleural effusion, 20 days of initiation of therapy because of imatinib.

CASE:

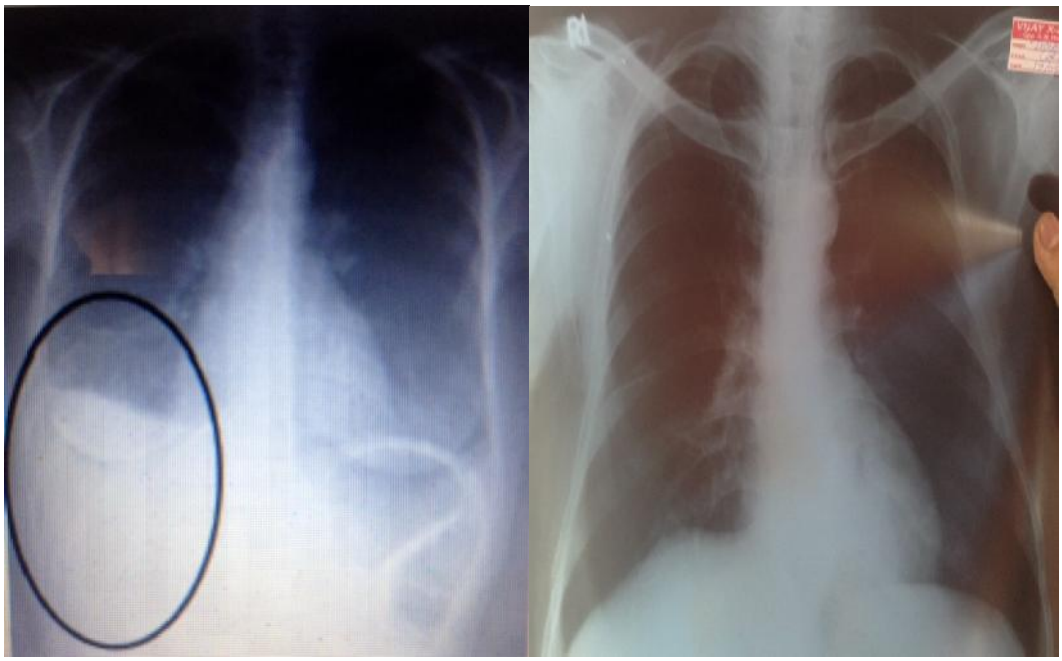
A 52 year male who was diagnosed as CML 20 days back, on treatment with imatinibmesylate 400 mg once daily, presented to us with chief complaints of breathlessness

on exertion (relieved by rest), right sided chest pain and dry cough for 5 days. There was no history of expectoration, fever, decrease in appetite, weight loss, decreased urine output or pedal edema. There was no history of diabetes mellitus, hypertension or ATT intake.

On examination, his vital signs were stable and there was no pallor, icterus, cyanosis, clubbing, edema or rise in JVP. Respiratory system examination revealed trachea to be shifted to the left side, decreased chest expansion on the right side, with a dull note on percussion and absent breath sounds in the right mammary, infra-mammary and axillary areas. Per abdomen examination revealed a massive spleen. Cardiovascular and neurological examination was within normal limits.

Investigations revealed Hb-8.5 gm%, TLC-8100/mm^3, DLC- $N_{64}L_{28}E_3M_5$, platelet count-184,000/mm3, PCV-27.3, MCV-107.5, MCH-33.5, MCHC-31.1 and the GBP showed macrocytic anemia. Liver function tests were normal with SGOT/PT-24/27, serum bilirubin T-0.9, D-0.5, I-0.4 and a serum albumin-3.8. The urine examination was normal, and so was the echocardiography of the patient. Chest X-ray revealed a right sided moderate pleural effusion and pleural fluid analysis revealed an exudative pleural effusion with the following values: protein-5.0 gm, sugar-101.0 mg, albumin-2.6 gms, WBC count-960, RBC count-120, DLC- lymphocytes 98%, monocytes 2%, ADA-52.4. BACTEC culture for AFB done on this fluid sample was negative.

Although, all criteria for it to be a tubercular pleural effusion were being fulfilled, but as the patient was on imatinib, we kept it as a possible case of imatinib induced pleural effusion. Imatinib was stopped and the patient kept on weekly follow up. After 3 weeks, the patient was totally asymptomatic and his chest x ray revealed total clearance of the effusion. Thus, our diagnosis was proved and the patient re-started on imatinib. Now, the patient is in regular follow up till date and has not had recurrence of his respiratory symptoms or effusion.



DISCUSSION:

Tyrosine kinase inhibitors have revolutionized the management protocols of chronic myeloid leukemia. However, fluid retention, including pleural effusion, is a troublesome side effect encountered with all of them, including imatinib. The frequency of imatinib induced pleural effusion is not known, but that of fluid retention is somewhere between 0.7-6%.

Some studies have found (eHealthMe) that reported that out of all the patients taking imatinib, 20,248 complained of side effects, out of which 651 had pleural effusion (3.22%) as on 18th June, 2014. These patients amounted to around 0.24% of the total number of pleural effusion patients on eHealthMe. On further analysis, it was found that most patients who develop pleural effusions on imatinib, do so within the 1st month of therapy (48.14%), with the percentage going down progressively thereafter to 30.48% between 1-6 months, 8.74% between 6-12 months and so on. A small female preponderance was found, with 55.56% patients being female. Analysis of the age of the patients revealed that increasing age of the patient increased the likelihood of development of pleural effusion, with the incidence as low as 0.31% between the ages 2-9 and as high as 73.60% above the age of 60 years. The percentage in the age group of our patient (50-59 years) was found to be 13.15%[3].

A study on the lung abnormalities after treatment with dasatinib 70 mg twice daily for CML (because of imatinib resistance or intolerance)[4], found that 6 out of the 40 patients under study developed pleural effusions. 4 of them had bilateral effusions and 2 were unilateral. Parenchymal lung changes were also found in 7 patients on dasatinib, 4 out of which also have pleural effusions. Protein content analysis done in these patients revealed all of them to be blood free exudates and cytological analysis found lymphocytes in 5 patients (61 +/- 33%) and neutrophils in the 6th. However, no pathogen was detectable in any case. Dasatinib was interrupted following the diagnosis of pleural effusion, and it was found that the respiratory symptoms resolved within one week of interruption of therapy. Pleural effusions resolved within 1 month of treatment interruption (completely in 4 and incompletely in the rest). Following this, dasatinib was re-introduced in a decreased dose of 40 mg BD in these patients, and they were found to be symptom and effusion free on regular follow up.

Since all pleural effusions analysed were exudative in nature, diuretics are unlikely to be effective in these patients. Also, high lymphocyte counts and the absence of infection in the pleural fluid analysis, suggests hypersensitivity or other immune mediated mechanisms as the possible cause of pleural effusion in such patients, as opposed to the general theory of fluid retention. The patient may therefore develop pleural effusion without the much more commonly anticipated pedal edema.

Drawing parallels from this study, our patient also had an exudative pleural effusion which resolved within one month of interruption of therapy with imatinib, and has been effusion free on re-introduction in the same dose. Thus, when a patient on imatinib (or any other tyrosine kinase inhibitor) develops pleural effusion, one should promptly discontinue the drug till the patient's symptoms and findings disappear, following which it can be safely re-introduced. Although, the temptation to start the patient on anti-tubercular drugs can sometimes be hard to resist, one should always wait and watch before jumping the gun.

To conclude, physicians should always be careful and attentive to the possibility of imatinib (or other tyrosine kinase inhibitors) induced pleural effusions, in patients in which they are being prescribed. We recommend stopping imatinib till the effusion subsides, and then restarting it under close observation. Corticosteroids may be used to aid in resolution of the effusion, but diuretics are mostly ineffective because of the suspected immune mediated mechanism of its formation.

REFERENCES

1. Harrison's Principles of Internal Medicine. Chapter 109. Pg 905-918
2. Gleevec, Novartis- Product Monograph,Pg 12, Fluid retention and Edema
3. eHealthMe: Review: Could Gleevec cause pleural effusion? 22nd June, 2014
4. Lung Abnormalities after Dasatinib Treatment for Chronic Myeloid Leukemia: A case series. Anne Bergeron, Delphine Rea et al