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DASATINIB INDUCED PLEURAL EFFUSION TREATED WITH LOW DOSE PREDNISOLONE

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Abstract: **A 45 year old male patient diagnosed case of chronic myeloid leukemia (CML) in 2003 being treated with dasatinib since 2010 came to the emergency department with complaints of fever, cough and breathlessness. On examination bilateral pedal edema was present and chest X-ray showed right sided pleural effusion. Pleural tap has been done with which his breathlessness was improved. Patient was initially started on antibiotics but not responded to the therapy. Now pleural effusion was considered as dasatinib induced and started on a trial of low dose oral prednisolone. Then patient shown improvement dramatically and successfully treated with short course of low dose oral prednisolone.**

Keywords: **Imatinib resistant, chronic myeloid leukemia, tyrosine kinase inhibitors, pulmonary arterial hypertension.**

I. INTRODUCTION & BACKGROUND

Dasatinib is an approved novel drug for treatment of primary and imatinib resistant CML. As this patient is a known case of CML and being treated with dasatinib for 4 years, now he has been diagnosed to have dasatinib induced pleural effusion. Incidence of dasatinib induced pleural effusion is not a rare adverse event but the condition is life threatening. So this case is the reminder of important clinical lesson. This case report shows the patients on dasatinib require more regular follow ups in the form of serial chest roentgenogram to avoid a life threatening situation. Clinicians should be aware of this complication for timely intervention; we are reporting this case for the same purpose.

II. CASE PRESENTATION

A 45 year old male patient came to the emergency department with chief complaints of cough, breathlessness and fever for two days. Medical history reveals that the patient is known case of CML first diagnosed in 2003, it is imatinib resistant CML. So patient was on dasatinib 100 mg once daily since 2010. Physical findings shows bilateral pedal edema and chest X-ray showed the pleural effusion. [figure 1] Hematological investigations were showing slightly high total leucocytes count and low hemoglobin. Pleurocentesis has been performed to analyze the pleural fluid that was showing high glucose level, LDH level and high total leukocytes count. Cytology of pleural fluid showed no malignant cells, polymerase chain reaction (PCR) for tuberculosis and culture for gram stains were negative. Now patient was initially started on antibiotics but no response had seen with the therapy. So dasatinib induced pleural effusion was considered and trial of prednisolone 20 mg twice a day started for 3 days. Dasatinib has been stopped on the same day and nilotinib 400 mg twice a day was started for CML. Patient improved dramatically and successfully treated with short course of prednisolone 20 mg twice daily. Patient also having severe pulmonary arterial hypertension (PAH) and hepatitis B surface antigen (HBsAG) positive status along with CML so patient is taking sildenafil and lamivudine for respective conditions. Dasatinib also caused PAH in this patient which is treating by sildenafil continuously and patient showing improvement. Other manifestations treated symptomatically.

III. INVESTIGATIONS

We went through the following diagnostic procedures

1. Chest X-ray was showing right sided pleural effusion.[figure 1]
2. Hematological investigations: hemoglobin – 11.6 gm/dL, Total WBC count – 11800 cell/micL.
3. Pleural fluid analysis:-

- Color – reddish, pH – 6.5
- Glucose level – 178 mg/dL
- Lactate dehydrogenase (LDH) – 366 IU/L
- WBC Count – 1860 cells/micL (N: 58%, L:42%)
- Cytology – no malignant cells
- Polymerase chain reaction for tuberculosis – negative
- Culture for bacterial detection – sterile and no gram stains present

4. Bone marrow aspiration: hematological response with no blasts crisis
5. Thyroid stimulating hormone: 1.900 mIU/mL.

IV. DIFFERENTIAL DIAGNOSIS

Bilateral pedal edema, breathlessness and chest X-ray were the supportive evidence to pleural effusion as primary diagnosis. Congestive heart failure (CHF) and esophageal rupture are the most common differential diagnosis. When we went through the investigational procedure of CHF, serum N-terminal pro brain natriuretic peptide (NT-proBNP) level was high but CK-MB(mass) & creatinine phosphokinase (CPK) were in normal range so possibility of CHF was ruled out. The pH of pleural fluid less than 6 is a best marker of esophageal rupture [1] but here it was above 6. Diaphragmatic injuries, hypothyroidism and TB are the other differential diagnosis of pleural effusion but all are ruled out in investigations.

V. TREATMENT

When patient came to hospital he was on dasatinib 100 mg once daily, sildenafil 20 mg twice in a day lamivudine 100 mg per day for CML, PAH and HBsAG status respectively. In emergency department on the basis of chest X-ray and subjective evidences patient was diagnosed to have pleural effusion. So he was initially started on antibiotics (cefepine, clindamycin and azithromycin) but condition not responded for the therapy. Now physician started a trial of prednisolone 20 mg for 3 days. Patient was showing improvement and effusion disappeared. Dasatinib stopped and nilotinib 400 mg twice in a day was started. Sildenafil and lamivudine are given continuously with other symptomatic therapies.

VI. OUTCOME AND FOLLOW-UP

As patient was started on prednisolone 20 mg twice in day, he had shown the improvement by first day only. Pleural effusion disappeared only in 3 days with prednisolone. As patient having severe PAH and CML, improvement would be slow. Fever, cough and breathlessness are the symptomatic conditions those were treated successfully on discharge. Now patient was discharged on nilotinib, sildenafil and lamivudine with supportive drugs like vitamins.

VII. DISCUSSION

CML is a myeloproliferative disorder characterized by a unique reciprocal translocation between chromosomes 9 and 22 resulting in deregulated tyrosine kinase activity. This is largely treated with targeted drugs called tyrosine kinase inhibitors like imatinib, dasatinib and nilotinib. Imatinib is most commonly used first line drug. Dasatinib is a second generation tyrosine kinase inhibitor approved for clinical use as first line and in imatinib failure CML. It is more potent

than imatinib in the treatment of Ph positive leukemias (including acute lymphocytic leukemia).[2] Apart from its known antileukemic activity dasatinib produces several side effects including third space exudative fluid collection.[3][4] This is known as "a sign of dasatinib response"[5] and triggered by activated T-lymphocytes. This fact is illustrated by pleural effusion in this case. The main symptoms of dasatinib induced pleural effusion are dyspnea, cough and fever with chest pain;[6] this patient had dyspnea, cough and fever on admission. The possible mechanism of dasatinib induced pleural effusion has been described as inhibition of PDGFRβ by Dasatinib.[4][7] Dasatinib inhibits more PDGFRβ in compared to imatinib and nilotinib that's why its incidence to cause pleural effusion is high. Incidence of dasatinib induced pleural effusion ranges from 20% - 40% depending on duration, dose and response.[8][9][10] According to literature pleural effusions/pericardial effusions triggered by T-lymphocytes can be treated effectively by glucocorticoids. Glucocorticoids counteract IgE-dependent and dasatinib enhanced histamine release in basophils. Prednisolone has strongly supportive evidences in treatment of nilotinib/dasatinib induced pleural effusion [7][11] and we did a successful trial of that. For further evaluation when we went diagnosed to CHF, NT-proBNP level was high but CK-MB(mass) and CPK were in normal range. These evidences ruled out the CHF but higher NT-proBNP supported to PAH as patient is a known case. According to Allanore et al NT-proBNP is a suggestive predictor of PAH.[12] So finally patients on tyrosine kinase inhibitors require more regular follow ups to avoid any life threatening event like pleural effusion and clinician should be aware of this complication for timely intervention.

VIII. FACTS TO LEARN

1. Dasatinib is an approved novel drug for the treatment of primary and imatinib resistant CML.
2. Dasatinib induced pleural effusion though life threatening is a sign of good response.
3. The patients on dasatinib or imatinib require more regular follow ups in form of roentgenogram to avoid life threatening situations.
4. Clinicians should be aware of this complication for timely intervention.
5. Low dose prednisolone for short duration is having good response against dasatinib/imatinib induced pleural effusion.

IX. AUTHORSHIP CONTRIBUTION

All authors are contributed equally in preparing of manuscript and eligible for authorship.

X. ACKNOWLEDGMENT

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Conflicts Of Interest

All authors have declared no conflicts of interest.

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Appendix-A

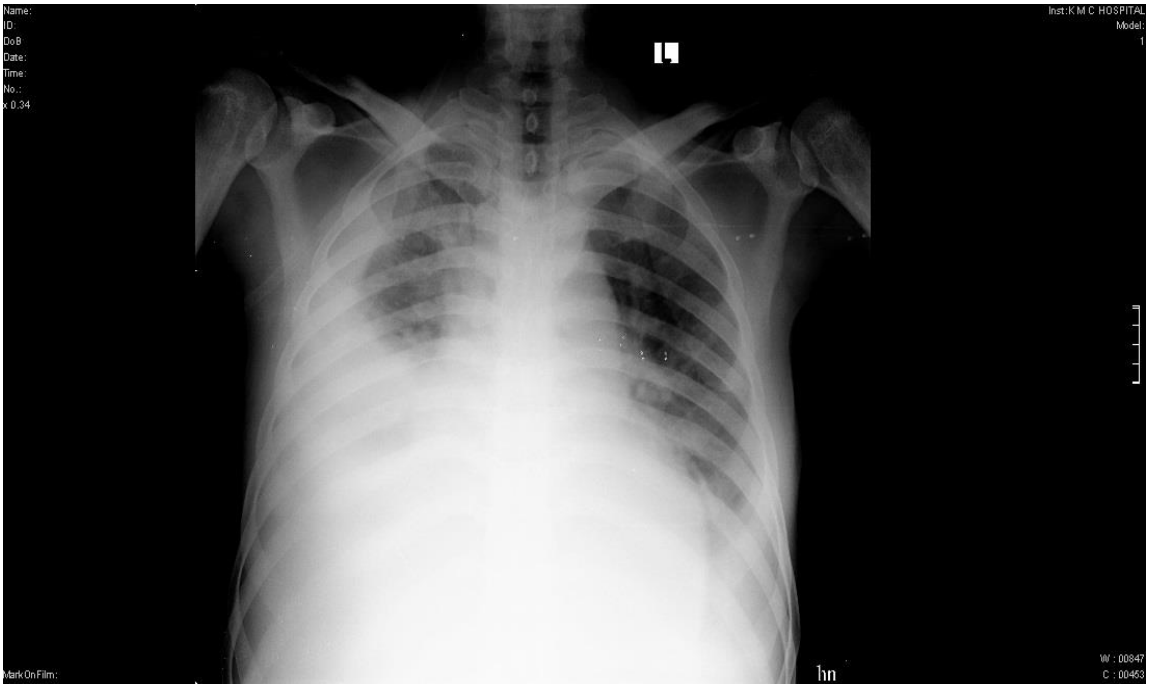

Figure1. Chest X-ray showing a right side pleural effusion (left side of the image).