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Impact Factor: 4.428

Common Presentation of a Rare Etiology: A Case Report of Drug-Induced Bilateral Pleural Effusion

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Abstract
A 64-year-old patient with chronic myeloid leukemia presented with a three-month history of cough and shortness of breath. She had no fever, paroxysmal nocturnal dyspnea, edema, or other sinister symptoms. She was mildly dyspnoic at rest with clinical features suggestive of bilateral pleural effusions, predominantly on the right side. Biochemical investigations adequately ruled out ongoing infections, hypoproteinaemias, organ insufficiencies, and D-dimer was negative. Radiologically, bilateral moderate pleural effusion was detected with a normal 2D echocardiography. Pleural fluid analysis revealed exudative effusion with reactive cytology and abundant red blood cells with no detectable leucocytes. Pleural fluid adenosine de-aminase level was within normal. Further evaluation with fibro-optic thoracoscopy exhibited a nodular pleura of the right costo-phrenic angle, with no adhesions or fibrotic bands. Chronic and acute bacterial infections were excluded with microbiological examination including gram staining, bacterial cultures, and mycobacterial investigations of pleural fluid and thoracoscopic biopsy specimens of the pleura. Malignant infiltrations were sufficiently excluded. The possibility of drug-induced effusion was considered. The drug dasatinib was suspected as the possible course of the effusion. The drug was changed over to Imatinib. Drastic improvement and complete resolution of the effusion were achieved. Finally, the diagnosis of dasatinib-induced pleural effusion was confirmed, thus concluding as the first such reported case in Sri Lanka.

Keywords: *Rare Etiology, Drug-Induced Bilateral Pleural Effusion*

Introduction

Pleural effusion is a common clinical finding with various underlying etiologies which is characterized by the accumulation of fluid in the pleural cavity [1]. Drug-induced pleural effusions are recognized as a rare but crucial adverse event associated with several medications, including dasatinib, a potent tyrosine kinase inhibitor used in the treatment of hematological malignancies [2]. While dasatinib-induced pleural effusion has been infrequently reported in the literature, pathogenesis and management strategies remain a subject of ongoing discussion and may need further assessment [3,4,5].

In this case report, we present a rare condition of dasatinib-induced pleural effusion in a patient with chronic myeloid leukemia. We aim to shed light on the clinical characteristics, diagnostic measures, therapeutic interventions, and subsequent outcomes of this adverse drug reaction. Since the events can significantly impact treatment decisions, patient outcomes, and quality of life, understanding the incident and management of dasatinib-induced pleural effusions is of ultimate importance for healthcare providers

[3,4,5]. we focus on contributing to the existing literature and enhancing awareness among health personnel regarding the potential risks and management considerations associated with dasatinib therapy by explicating the specific clinical manifestations, diagnostic challenges, and treatment options associated with this adverse event.

Case Report

A 62-year-old retired teacher, diagnosed with hypertension and chronic myeloid leukemia presented with a three-month history of non-productive cough and shortness of breath that worsened over one week. The shortness of breath had escalated from Modified Medical Research Council (mMRC) Dyspnea Scale grade 1 to 3. She also complained of orthopnea and a loss of appetite for the same duration. However, she had no paroxysmal nocturnal dyspnea, lower limb edema, facial puffiness, fever, chest pain, hemoptysis, loss of weight and night sweats. Her urinary and bowel habits were within normal. No features of connective tissue disease were found.

On further inquiry, she had no significant exposure to organic or chemical substances. There had been a recent switch in her leukemic drug to an alternative following a BCR-ABL 1 test. On examination, she was well-looking except dyspnoic on inspection, afebrile, no dependent edema, and palpable peripheral lymphadenopathy. Her vitals were normal. Examination of her lungs revealed bilaterally reduced air entry in the lower zones with a stony dull percussion note. Inward investigations including full blood count, inflammatory markers, liver and renal function tests were normal. Sputum for acid-fast bacilli, and MANTOUX test were negative. Ultrasound chest and abdomen showed bilateral pleural effusion, right more than left with collapse of the bilateral lower lobes. Moreover, 2D echocardiography was normal. Chest X-rays are shown below (Figure 1,2).

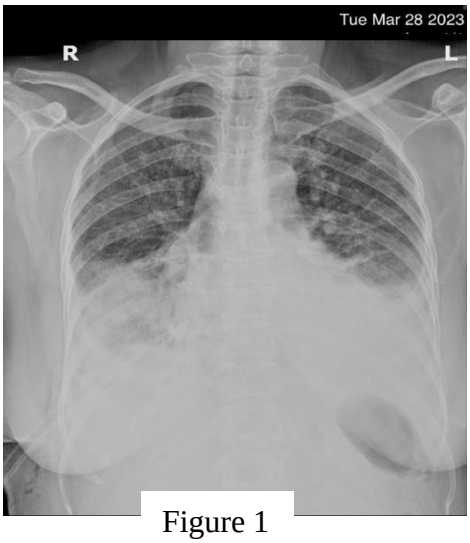

Figure 1

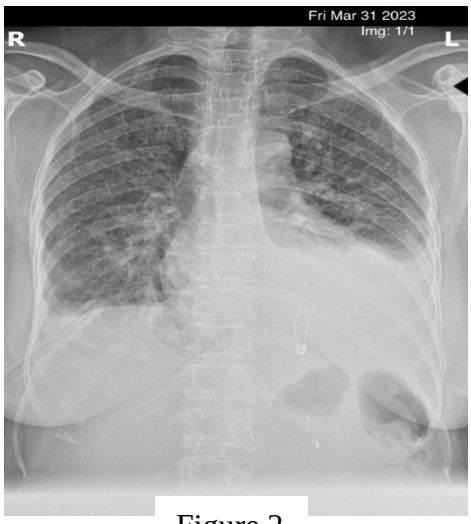

Figure 2

Further exploring the underlying etiology, she underwent Fibro-optic thoracoscopy which showed multiple pleural nodules in the right costo-phrenic angle with no fibrous bands or adhesions (Figure 3,4,5). Two liters of serous, blood-stained fluid was removed and sent for appropriate investigations.

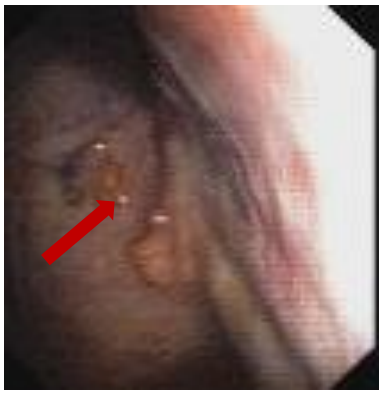

Figure 3

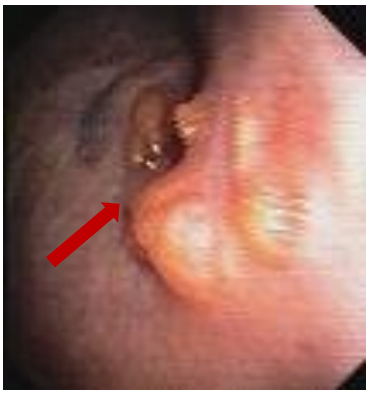

Figure 4

Figure 3, 4: Multiple pleural nodules of partial pleura in costophrenic angle.

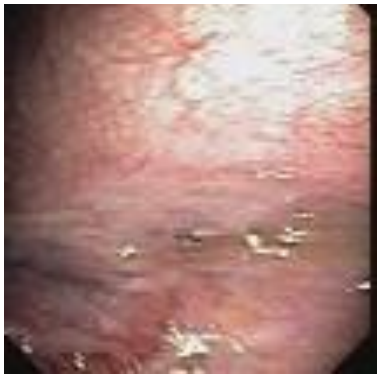

Figure 5: Pleural infiltration on diaphragmatic pleura

Table 1: Pleural fluid analysis.

Parameter	Values
Total protein	39 g/l
pH	7.5
LDH	307.7 IU/L
Amylase	65 U/L
Cholesterol	58.7 mg/dl
RBC	170 mm^3
Leucocyte Count	Nil

Bacterial and fungal staining and cultures were negative as well as mycobacterial investigations. Cytological analysis revealed Scattered lymphocytes, reactive mesothelial cells, and the absence of atypical cells. Histology of pleural nodules demonstrated non-specific inflammatory infiltrations with no evidence of chronic myeloid leukemia or other malignant infiltration.

As there is no other explainable underlying cause for bilateral pleural effusion, possible etiology was suspected as dasatinib-induced pleural effusion. This case was discussed in a multidisciplinary team meeting and decided to withhold dasatinib. The patient was completely improved clinically and radiologically (Figure 6), and finally, dasatinib-induced pleural effusion was confirmed. dasatinib was replaced with imatinib.

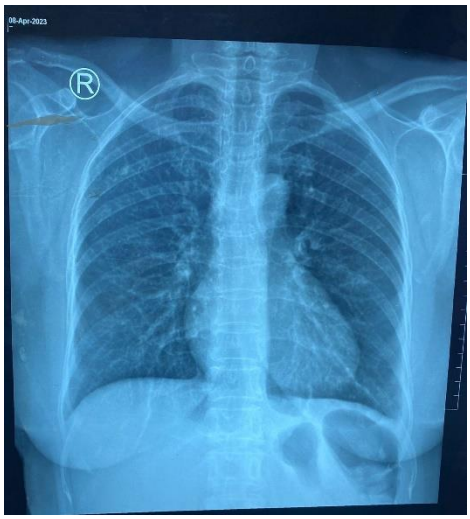

Figure 6

Discussion

Dasatinib is a potent second-generation BCR-ABL1 tyrosine kinase inhibitor that demonstrated exceptional efficacy in the treatment of various hematologic malignancies including chronic myeloid leukemia [6]. However, the use of dasatinib is associated with several adverse events including pleural effusion. The findings of this case report align with previous reports in the literature, which have indicated dasatinib-induced pleural effusion as a rare but recognized adverse event [3,4,5,7]. The incidence of pleural effusion in dasatinib-treated adult patients ranges from 20%-40% while some studies report a thin incidence rate among children receiving the dasatinib [8,9]. The development of pleural effusion has been observed at various time intervals during dasatinib therapy, with cases reported both early in treatment as well as after months to years of drug exposure.

Age, advanced-stage of the disease, cardiac diseases, hypertension, higher daily dose, prolonged disease duration, previous interferon therapy, anemia, autoimmune disease, hypercholesterolemia, and dermatitis during imatinib treatment were reported as the risk factors for dasatinib-related pleural effusion [10,11,12]. The pathological process of dasatinib-induced pleural effusion remains poorly understood [10,13]. Several mechanisms were postulated and one potential mechanism involves direct endothelial involvement, damage, and increased capillary permeability caused by dasatinib, leading to the accumulation of fluid in the pleural space [13]. Another suggested mechanism involves dasatinib-induced inhibition of Src family kinases, which may disrupt tight junction integrity and contribute to increased vascular leakage. Additionally, immune-mediated mechanisms and alterations in lymphatic drainage have been suggested but require further investigation [13].

Diagnosing dasatinib-induced pleural effusion can be challenging, as it often presents with nonspecific clinical features [10]. Imaging studies, such as chest X-rays or ultrasounds, play a crucial role in evaluating pleural effusions [10,14]. Thoracentesis with pleural fluid analysis is essential for confirming the diagnosis and ruling out other potential etiologies [10,14]. Pleural fluid analysis typically reveals an exudative effusion, with lymphocyte predominance and low glucose levels [14]. These biochemical features mimic several common etiological causes like tuberculous pleural effusion [14]. As tuberculosis is endemic in third-world countries like Southeast Asia, misdiagnosis as tuberculous pleural effusion can be a common occurrence unless a definitive etiological analysis. Hence it is mandatory to rule out common etiological causes for lymphocytic exudative pleural effusion with appropriate investigation.

The management of the dasatinib-induced pleural effusion depends on the severity and persistence of the pleural effusion [15]. Dasatinib treatment should be temporarily stopped for medium-sized or large pleural effusions and patients with substantial symptomatology or those with risk factors such as advanced age, pulmonary or cardiac comorbidities, or a history of autoimmune illness suggestive of increased adverse event intensity or related morbidity until the adverse event is resolved and then resumed at lower dosages

[10,16]. Symptomatic effusions may require therapeutic interventions such as thoracentesis or chest tube drainage to relieve respiratory distress and facilitate lung re-expansion [10,17]. Although diuretics and corticosteroids have been used to manage pleural effusion in some instances, their efficacy remains uncertain, and further investigation is required [10,14,16,17]. Health personnel need to be aware of this complication and close monitoring of the patients receiving dasatinib therapy to reduce the events of pleural effusions. Early detection and tailored intervention can help mitigate symptoms, prevent complications, and optimize treatment outcomes.

Conclusion

Exploring all the possibilities of bilateral pleural effusion is mandatory to arrive at a definitive diagnosis. Appropriate invasive investigation should be offered in situations of undiagnosed pleural effusion to ascertain the final diagnosis. Otherwise, the wrong diagnosis will be entertained, and unnecessary medication may be prescribed to these patients, particularly in countries where tuberculosis is prevalent. Extrapulmonary tuberculosis would be the most probable diagnosis to consider, leading to anti-tuberculosis treatment. More harm, including inappropriate medication with or without side effects, as well as psychological trauma, could be inflicted on the patients. Drug-induced lung diseases, including pleural effusion, should be considered in a given clinical scenario whenever appropriate. Further studies are required to explore the underlying mechanisms, identify risk factors, and assess the role of diuretics and corticosteroids in the management of dasatinib-related pleural effusions

Conflict of interest

There is no financial interest or any conflict of interest related to this paper.

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