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Dasatinib-induced chylothorax: a clinical laboratory's perspective

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ABSTRACT

Dasatinib is a tyrosine kinase inhibitor drug used for chronic myeloid leukaemia (CML) treatment. Chylothorax has been rarely reported as a secondary effect of dasatinib occurring especially in long-term treated patients, although its pathophysiology is not yet fully understood. Laboratory analysis of the pleural effusion is crucial for chylothorax diagnosis. We report a case of a 53-year-old male patient presenting a chylothorax after 14 years of dasatinib therapy where the clinical laboratory was key in the diagnosis.

INTRODUCTION

Dasatinib is a second-generation tyrosine kinase inhibitor drug used for chronic myeloid leukaemia (CML) treatment. It is commonly prescribed to adult patients with the following types of CML: newly diagnosed patients who are 'Philadelphia chromosome positive (Ph+)', 'accelerated' and 'blast' phases when other treatments do not achieve remission. In addition, it is prescribed in Ph+ acute lymphoblastic leukaemia (ALL) or 'lymphoid blast' crisis when patients do not tolerate previous treatments (1,2).

The most common side effects of dasatinib therapy are skin rash, dyspnoea, abdominal pain, pancytopenia, hypertension, bleeding events that may require dose interruption or transfusion, and liquid retention including pleural effusion (1).

Pleural effusion occurs in as many as 28-33% of long-term treatments (3). However, pleural effusion in the form of chylothorax has rarely been reported and its pathophysiology is not fully understood (4,5).

We describe a case of a patient who presented with chylothorax after being treated with dasatinib for 14 years.

CLINICAL-DIAGNOSTIC CASE

A 53-year-old male with a 16-year history of CML and ongoing dasatinib treatment for 14 years presented to the emergency department with symptoms of fever, dyspnea, and abdominal pain. Physical examination revealed a blood oxygen saturation level of 95% and chest radiography showed pleural effusion on the left lung (Figure 1). Consequently, a chest ultrasound-guided left thoracentesis was performed for evacuation and diagnosis. The extracted fluid exhibited a turbid and milky white appearance. Biochemical analysis using AU5800 (Beckman Coulter®) revealed a total protein concentration of 50 g/L (<30 g/L is suggestive of transudate), adenosine deaminase activity of 22 U/L (>45 U/L is suggestive of tuberculosis), cholesterol concentration of 1.29 mmol/L, and triglyceride concentration of 6.58 mmol/L (>1.25 mmol/L is suggestive of chylothorax) (Table 1).

Table 1 Results of biochemical analysis of pleural fluid by AU5800 and automatized cytological analysis by Sysmex XN-1000

Biochemistry		Cytology	
Glucose	6.72 mmol/L	Cells	3.45 x10^3 cell/L
Protein	50 g/L	Erythrocytes	2x10^5 cell/L
Lactate dehydrogenase	142 U/L	Lymphocytes	75 %
Cholesterol	1.29 mmol/L	Mesothelium cells	0 %
Triglycerides	6.58 mmol/L	Macrophages	21 %
Adenosine deaminase	22 U/L	Neutrophils	3 %

Automated cytological analysis using Sysmex XN-1000 revealed 3.45x103 cells/L and 2x105 erythrocytes/L. Cytocentrifugation, staining with May Grünwald-Giemsa and microscopic observation showed 75% mature lymphocytes, 21% macrophages and 3% neutrophils (Figure 2). Microbiological cultures, pathological anatomy, and immunophenotype studies yielded negative results.

The elevated triglyceride concentration (Table 1) and mature lymphocyte predominance (Figure 2) suggested the presence of chylothorax, which may result from trauma, surgery, infection, or malignancy; however, these causes were not apparent in this case. Although rare, the treatment with kinase inhibitors is a possible cause of chylothorax. Therefore, a drug-related chylothorax was suspected, and the patient's dasatinib treatment was discontinued, resulting in clinical improvement. After draining the pleural effusion, treatment with octreotide, an analogue of somatostatin that inhibits digestive secretions and reduces lymphatic flow, was prescribed to prevent chylothorax.

DISCUSSION

Chylothorax is a rare condition that results from damage to the thoracic duct, leading to leakage of chyle from the lymphatic system into the pleural space (6). The diagnostic test for chylothorax involves the analysis of pleural fluid obtained by thoracentesis. Macroscopically, the fluid appears milky due to the high content of chylomicrons. However, this appearance is not specific to chylothorax, and a differential diagnosis is needed to rule out empyema and pseudochylothorax, which are cholesterol-rich pleural effusions commonly associated with chronic

Figure 1 Thorax radiography performed as the patient arrived at the emergency room. The patient showed pleural effusion on the left lung

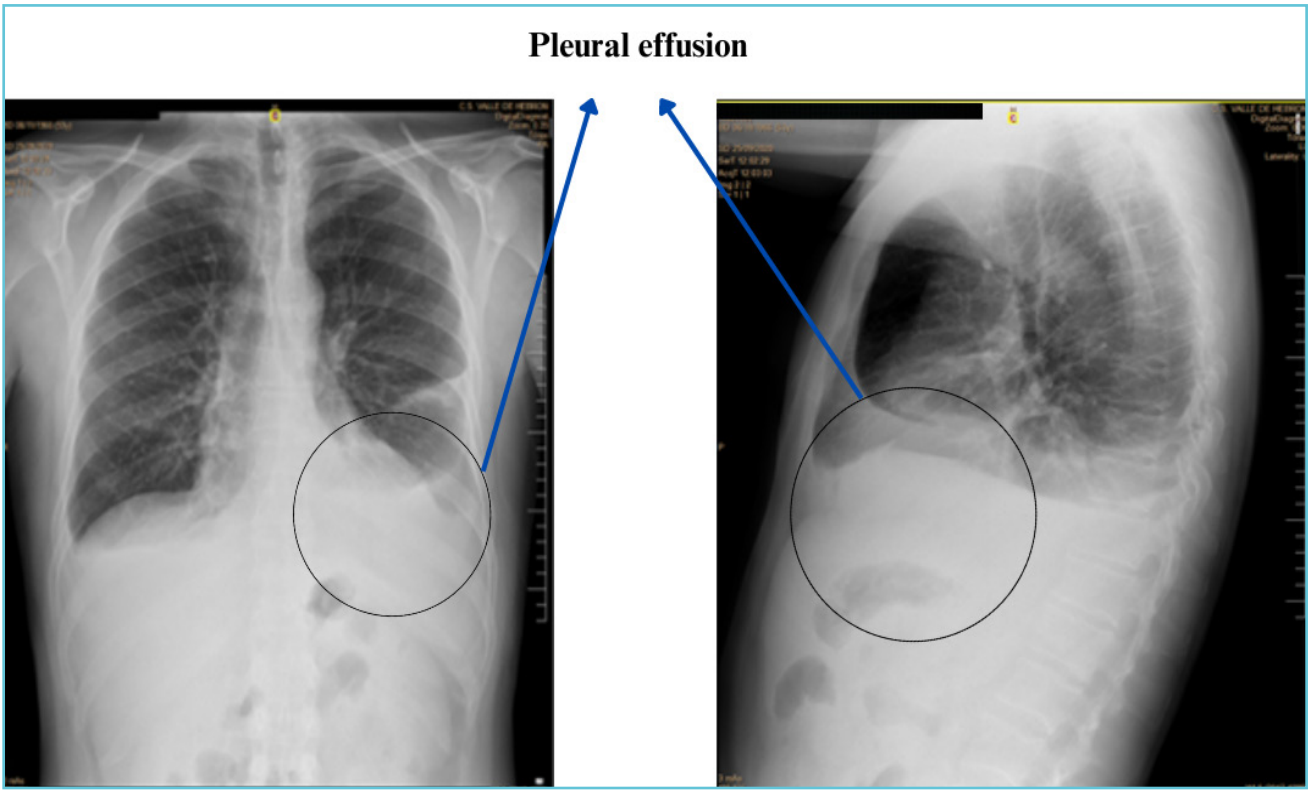
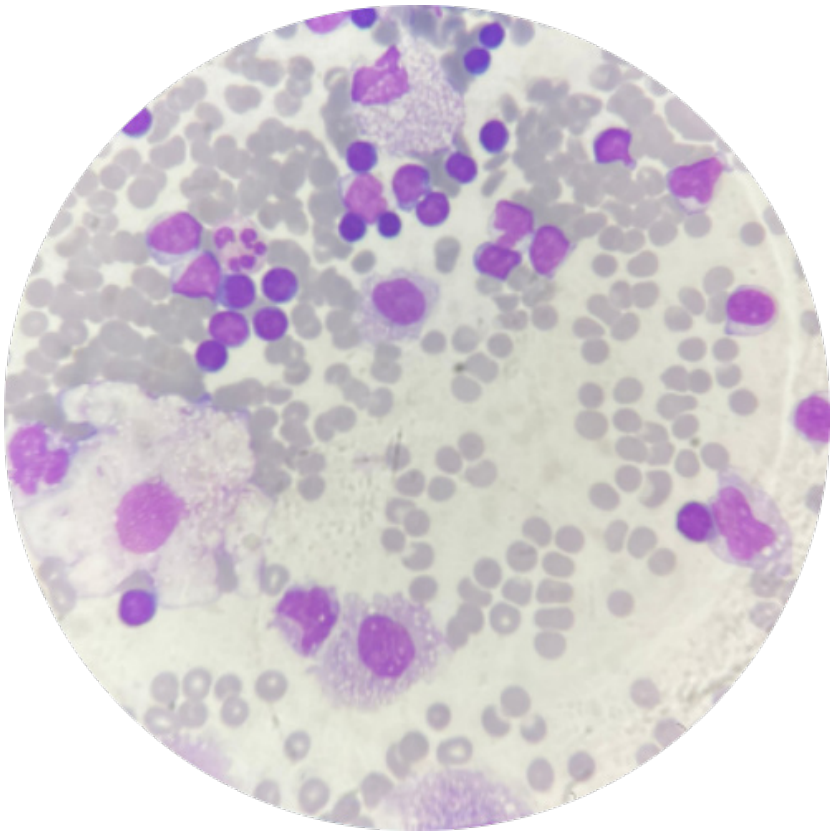


Figure 2 Microscopic image of a cytological extension of pleural effusions stained with May Grünwald-Giemsa (100x)



inflammatory disorders. The typical cytology observed in chylothorax is a predominance of mature lymphocytes. In 1980, Staats and collaborators introduced criteria for the biochemical diagnosis of chylothorax, which is defined by the presence of chylomicrons in pleural fluid and is strongly suggested by a triglyceride concentration >1.25 mmol/L. When triglyceride levels are between 0.57-1.25 mmol/L, an electrophoresis of pleural fluid lipoprotein should be performed to detect chylomicrons (8).

Dasatinib exerts its mechanism of action by inhibiting tyrosine kinases, particularly the ABL family, platelet-derived growth factor receptor beta (PDGFR-β), KIT and Src. Although the physiopathology of chylothorax induced by dasatinib remains unclear, one possible mechanism proposed by Gorham is related to the inhibition of PDGFR-β (9). This receptor plays a role in the regulation of lymphangiogenesis, and its inhibition leads to the formation of abnormal lymphatic vessels and leakage into the pleural space. Another proposed mechanism is linked to the inhibition of Src kinase, whose activity is involved in the regulation of vascular permeability and stability of the pleural epithelium (4, 10).

In conclusion, chylothorax is a rare adverse effect of long-term dasatinib treatment. Our case report highlight the decisive contribution of the biochemical analysis and cytological study of the pleural fluid for the diagnosis and treatment of chylothorax.

LEARNING POINTS

- Dasatinib, a drug used for CML treatment, can rarely cause chylothorax as secondary effect.
- Macroscopic, cytological and biochemical study of a pleural effusion is crucial for differential diagnosis of chylothorax, pseudochylothorax and empyema.
- High triglyceride concentration together with low cholesterol concentration and a high proportion of matures lymphocytes support the diagnosis of chylothorax.

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