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5th Combined Gulf Cancer Conference
Sharjah, United Arab Emirates

**CONTINUUM OF CARE
IN CANCER CONTROL
& MANAGEMENT**

Awareness & Prevention | Early Detection & Screening | Diagnosis
Treatment | Palliative Care | Survivorship | Research

SAVE THE DATE **21-23 NOV 2022**

The banner features a dark blue and purple gradient background with a white circular seal containing the text '5th Combined Gulf Cancer Conference' and 'Sharjah, United Arab Emirates'. Below the seal, the main title 'CONTINUUM OF CARE IN CANCER CONTROL & MANAGEMENT' is written in bold black letters, followed by a list of topics: 'Awareness & Prevention | Early Detection & Screening | Diagnosis Treatment | Palliative Care | Survivorship | Research'. At the bottom, a white box contains the text 'SAVE THE DATE' and a calendar icon showing '21-23 NOV 2022'.

Gulf Guidelines for Colorectal Cancer Workshop

**Updating
Colorectal Cancer
Guidelines**

8-9 November 2022

State of Kuwait

A circular graphic with a blue background and a white border. The text 'Updating Colorectal Cancer Guidelines' is written in yellow and white. Below it, a white box contains the text '8-9 November 2022'. At the bottom, the text 'State of Kuwait' is written in white.

MONKEY POX
ALL YOU NEED TO KNOW

A graphic featuring several red, spiky virus particles of varying sizes against a white background. The text 'MONKEY POX' is written in bold black letters on a red background, and 'ALL YOU NEED TO KNOW' is written in bold black letters on a white background below it.

The Official Journal of the Gulf Federation For Cancer Control

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Case report

Dasatinib–induced Chylothorax in Chronic Myeloid Leukemia

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Abstract

Dasatinib is a potent second–generation tyrosine kinase inhibitor (TKI) used in the first– and second–line treatment of chronic myeloid leukemia (CML). Chylothorax is a rare presentation that results in chyle leakage from the lymphatic system into the pleural space as a consequence of thoracic duct damage. Pleural effusion has been reported frequently in patients treated with Dasatinib however chylothorax has been rarely reported. Here we report an 18year old female presenting with chylothorax

after 63 months of Dasatinib intake along with a review of the relevant literature. Currently there are no standard guidelines regarding the approach to chylothorax management after the initial discontinuation of Dasatinib. Since the TKI options after stopping Dasatinib are limited, and most patients would have already failed the trial of first generation TKI, we suggest implementing a complete treatment strategy for this patient population.

Key words: chronic myeloid leukemia, Dasatinib, Pleural effusion, Chylothorax

Introduction:

Dasatinib is a potent second–generation tyrosine kinase inhibitor (TKI) used in the first– and second–line treatment of chronic myeloid leukemia (CML). Pleural effusion has been reported in around 28% of cases treated with Dasatinib^[1], yet Chylothorax is rarely reported. Here, we are presenting a young female with Chylothorax due to Dasatinib and review the literature about this entity and optimal management.

Case Presentation:

An 18 years old female, known case of Hypothyroidism on Eltroxin, diagnosed with chronic phase CML in 2012, was started on Imatinib initially then switched to Dasatinib 100 mg daily due to non–compliance and persistence of high BCR–ABL transcripts. Dasatinib was commenced on August 2015, achieving major molecular response (MMR) soon after, and maintaining MMR since then. In November 2020, she presented with fever, progressive shortness of breath and abdominal pain.

On Examination she was dyspneic, with decreased oxygen saturation. Chest examination showed a decreased air entry bilaterally. Complete blood count (CBC) WBC 10.3 x 10⁹/L, Hemoglobin 95 g/L, Platelet 334 x 10⁹/L, Neutrophils # 2.7 x 10⁹/L, Lymphocyte # 6.2 x 10⁹/L,

Retics % 2.1%. Serum electrolytes: creatinine 45 umol/L, sodium 134 mmol/L, potassium 4 mmol/L, total protein 62 g/L, albumin 35 g/L, calcium 2.4 mmol/L. Coagulation profile within normal limits. Last quantitative polymerase chain reaction (q–PCR) for BCR–ABL gene was 0.003%.

A Chest radiograph was suggestive of a bilateral pleural effusion (Figure 1) followed by a chest Computed Tomography scan (CT scan) which confirmed the effusion, more on the right side. A chest drain was inserted, draining around seven liters of a thick, milky–appearing fluid (figure 2). Fluid analysis showed 56% lymphocytes, Albumin 21630 mg/L, protein 49073 mg/L, LDH 161 IU/L total Triglycerides 6.6 mmol/L, pH 7.4 mmol/L, cholesterol 2.05 mmol/L, protein ratio 0.64, LDH ratio is 0.6, suggesting exudative nature (Chylothorax).

Dasatinib was held on admission, steroids were commenced. The patient's symptoms and oxygen saturation gradually improved, chest tube drained the

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No.	Age	Gender	Disease phase	Dasatinib dose	Time to chylothorax	Treatment measures	Plan and Recurrence	Ref.
1	40	Female	CP	100 mg daily	40 months	Dasatinib held, steroids, diuretics	Switched to Nilotinib, no recurrence	[6]
2	21	Female	CP	100 mg daily	44 months	Dasatinib held, Steroids, diuretics, tube–drainage, octreotide,	Recurred 2 weeks after 1 st episode while off–Dasatinib. Shifted to Nilotinib	[7]
3	69	Male	CP	100 mg daily	10 months	Thoracocentesis	Continued Dasatinib, chylothorax recurred few months later, switched to bosutinib	[9]
4	71	Female	Ph + ALL	140 mg daily	2 months	Dasatinib dose reduction, steroids, diuretics, thoracocentesis	Dasatinib dose reduction	[10]
5	73	Female	CP	70 mg daily	12 months	Dasatinib held Steroid Diuretics Thoracocentesis	Bosutinib → imatinib Goreisan	[8]
6	63	Female	CP	100 mg daily	12 months	Dasatinib held Drainage Steroids	Switched to imatinib No recurrence	[11]
7	5	Female	CP	150 mg daily	10 months	Dasatinib held Drainage	Definitive treatment with bone marrow transplantation	[12]
8	Pt 1: 47 Pt 2: 46 Pt 3: 49	Pt 1: M Pt 2: M Pt 3: M	NR	NR	Pt 1: 8 mo Pt 2: 19 mo Pt 3: 24 mo	Pt 1: continued Pt 2: discontinued Pt 3: discontinued	Pt 1&2: diuretics, steroid and thoracocentesis Pt 3: ligation of thoracic duc	[13]
9	51	Male	CP	70 mg twice daily	84 months	Dasatinib held Drainage	Switched to nilotinib	[14]
10	71	Male	CP?	100 mg per day	6 months	Thoracocentesis switched to different class of drugs?	Recurrence of Chylothorax after resuming Dasatinib in two days	[15]
11	18	Female	CP	100 mg daily	63 months	Dasatinib held, thoracocentesis, steroids, diuretics	Switched to Nilotinib	Presented case

effusion, the tube was eventually removed after which the patient was discharged home after 18 days in the hospital. When followed up as an outpatient, she was switched to Nilotinib.

Discussion:

Dasatinib is a potent second generation small molecule multi–target kinase inhibitor of BCR–ABL, and other kinase proteins such as PDGFR which might be

responsible for pleural effusion in CML patients (pts)^[2]. Although Dasatinib is generally well tolerated, there are some documented non-hematological adverse events in clinical trials with Dasatinib, such as gastrointestinal symptoms, headache, peripheral edema, and pleural effusion^[1]. Dasatinib alters pulmonary endothelial permeability in a ROS-dependent manner in vitro and in vivo leading to pleural effusion^[3]. Pleural effusion is seen in 14–32% of pts receiving Dasatinib in clinical trials, usually of grade 1–2 but grade ≥ 3 is rare (3%)^[1]. The pleural effusion is usually lymphocytic exudative effusion^[4].

Chylothorax was documented to be rare in Dasatinib treated pts and its pathophysiology is not fully understood. Dasatinib was found to be the only TKI associated with the development of chylothorax in CML pts.

Chylothorax is a rare presentation that results in chyle leakage from the lymphatic system into the pleural space as a consequence of thoracic duct damage, usually on the right side. It was noted that pleural fluid triglyceride levels >1.24 mmol/l (110 mg/dl) with a cholesterol <5.18 mmol/l (200 mg/dl) is diagnostic of chylothorax^[5]. Chylothorax is most commonly caused by surgery or trauma. There are other non-traumatic causes including malignancy, amyloidosis, sarcoidosis, superior vena cava thrombosis, benign tumors, congenital duct abnormalities, diseases of the lymph vessels, and retrosternal goiter. Non-Hodgkin's lymphoma is the most common hematological malignancy resulting in chylothorax^[6].

Given the proven efficacy of Dasatinib in pts with CML and the rarity of the complication of chylothorax, efforts are made to treat the chylothorax with a plan to resume Dasatinib in a lower dose after resolution of this

adverse event. Despite the lack of literature, recurrence of chylothorax remains probable (table 1). It seems to be persistent and chronic, necessitating a switching to different TKI^[7]

Management of pleural effusion according to National comprehensive cancer network (NCCN) is by holding Dasatinib, administering diuretics and a short course of steroids. When the acute event resolves, Dasatinib may be resumed with dose reduction^[5]. However, in cases of Dasatinib induced chylothorax it is advised to switch TKI as the recurrence rate is extremely high.

Of note, Sasaki and his colleagues has reported one successful control of Dasatinib induced chylothorax with steroids and "Goreisan"; a herbal Japanese medicine that controls the aquaporin channels and regulate the water flow^[8]. There was a hypothesis suggesting that chylothorax can be a symptom of CML, however, recurrence of chylothorax happened only when Dasatinib was resumed with 2 days. This finding supports that chylothorax can be induced by Dasatinib in CML pts.

In conclusion, Dasatinib is one of the most potent and effective drugs for the management of CML. Although the risk of chylothorax-related pleural effusion is small, the sequelae of such an event may be detrimental on patients' quality of life and disease outcome. In the few reported cases, the general approach was to discontinue Dasatinib, or resume it at a lower dose which may have an unfavorable effect on the patient's molecular response. Therefore, it is crucial that similar cases are reported when diagnosed.

Abbreviations: chronic myeloid leukemia (CML), Tyrosine kinase inhibitor (TKI)



Fig. 1: shows a portable Chest X-ray with Bilateral effusion more at the right side



Fig. 2: showing chylothorax drainage from the patient's chest tube

Conflict of Interest Statement: The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

- Ref 1 = Authors names + institute
- Ref 2 = PMID: 27217448

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