International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Case Report: Dasatinib Induced Pulmonary Hypertension in a Case of CML

Dr. Abhishek Padhiar[1], Dr. Ankit Agarwal[2]

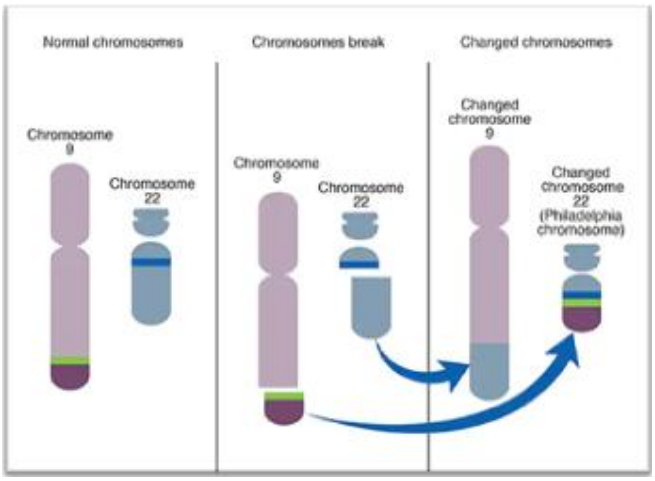
Department of General Medicine, Department of Oncology, Geetanjali Medical College and Hospital, Udaipur - 313001, India

Abstract: ***Dasatinib was identified to be associated with pulmonary arterial hypertension. There is still very little data on clinical characteristics of this severe complication. When a 51 - year - old male presented with worsening dyspnea was diagnosed with pulmonary arterial hypertensionin a background of CML and managed with standard comprehensive care, including replacement of other tyrosine kinase inhibitor, administration of pulmonary vasodilators. Our case suggests that dasatinib - induced pulmonary arterial hypertension may be partially reversible when diagnosed early, managed with target therapy of pulmonary arterial hypertension, providing new insight into the rare complication.***

Keywords: CML - Chronic myelogenous leukemia, TKIs - tyrosine kinase inhibitors, DASA - Dasatinib, PAH - Pulmonary artery hypertension

1. Introduction

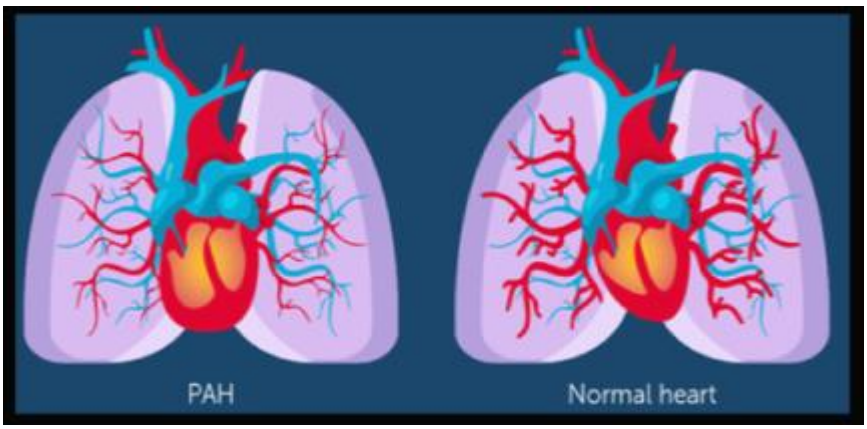
Chronic myelogenous leukemia (CML) is a clonal myeloproliferative disorder, is caused by the constitutively active BCR - ABL tyrosine kinase resulting from the translocation that produces the Philadelphia (Ph) chromosome (Figure 1). The course of CML is typically biphasic or triphasic, with an early indolent or chronic phase, followed often by an accelerated phase and a terminal blastic phase. Before the era of selective BCR - ABL1 tyrosine kinase inhibitors (TKIs), the median survival in CML was 3–7 years, and the 10 - year survival was 30% or less. The worldwide TKIs have revolutionized the treatment, natural history, and prognosis of CML. Today, the estimated 10 - year survival rate with first BCR - ABL1 TKI approved, is 85%.1



Philadelphia chromosome

Dasatinib, a second - generation tyrosine kinase inhibitor (TKI), was approved as a first - line therapy for CML and for patients unresponsive to, or intolerant to imatinib. It is effective in both chronic as well as accelerated phases of the disease.

Pulmonary hypertension (PH) is defined as an increase in mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest as assessed by right - sided heart catheterization (RHC). (Figure 2) Normal mPAP at rest is 14 ± 3 mmHg with an upper limit of normal of approximately 20 mmHg.3

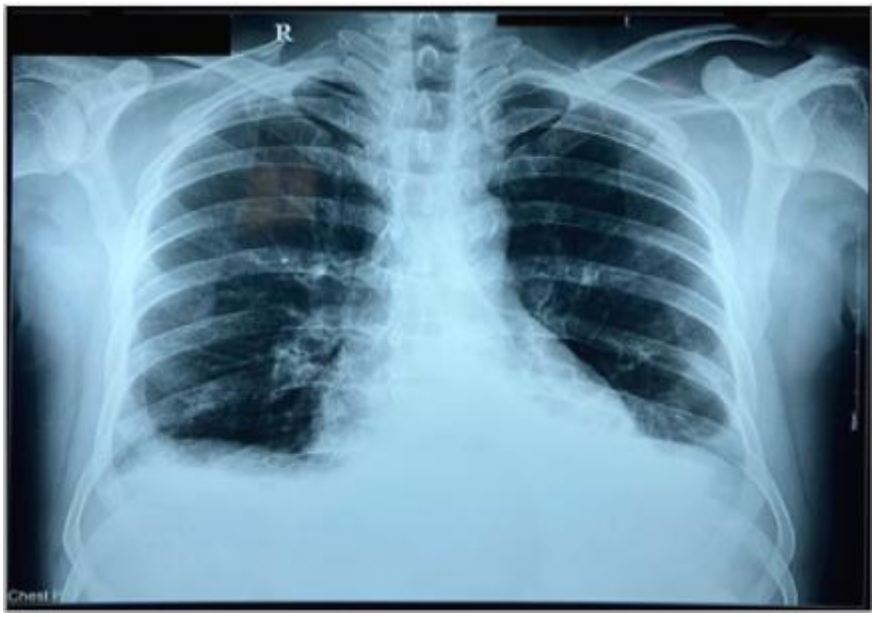


Change in hemodynamics of vasculature in PAH compared to normal

2. Case Report

A 51 - year - old male patient, teacher by occupation and non - smoker. He was diagnosed CML on 18th June 2018 and was on medication (Tab. Dasatinib 50mg twice/daily). He presented on 14th July 2022 with shortness of breath (SOB) which is progressive initially on exertion but for past one month SOB on rest, dry cough aggravated on exertion and relieved on rest and medication and 3 episodes of brief loss of consciousness (approx.15 seconds) with last episode on 12th June 2022. On examination his pulse was 110/min, respiratory rate was 24/min, Coarse creeps in bilateral basal lung fields, elevated JVP 15cms and 6 - minute walk test of 150 meters.

A X - ray chest was done, it showed decreasedbroncho - vascular markings and pulmonary oligemia dilated pulmonary artery, bilateral blunting of costo - phrenic angle. (Figure 3)

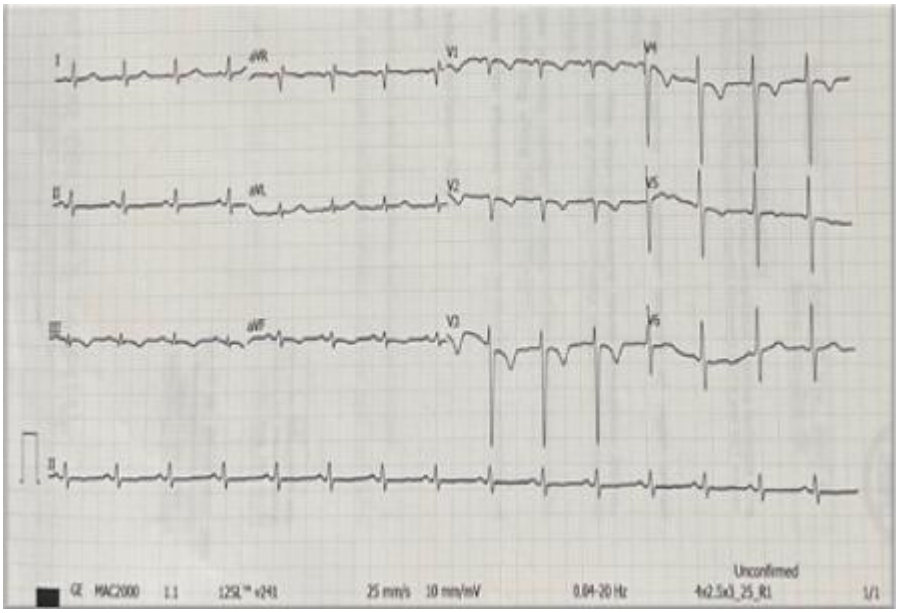


X - ray chest

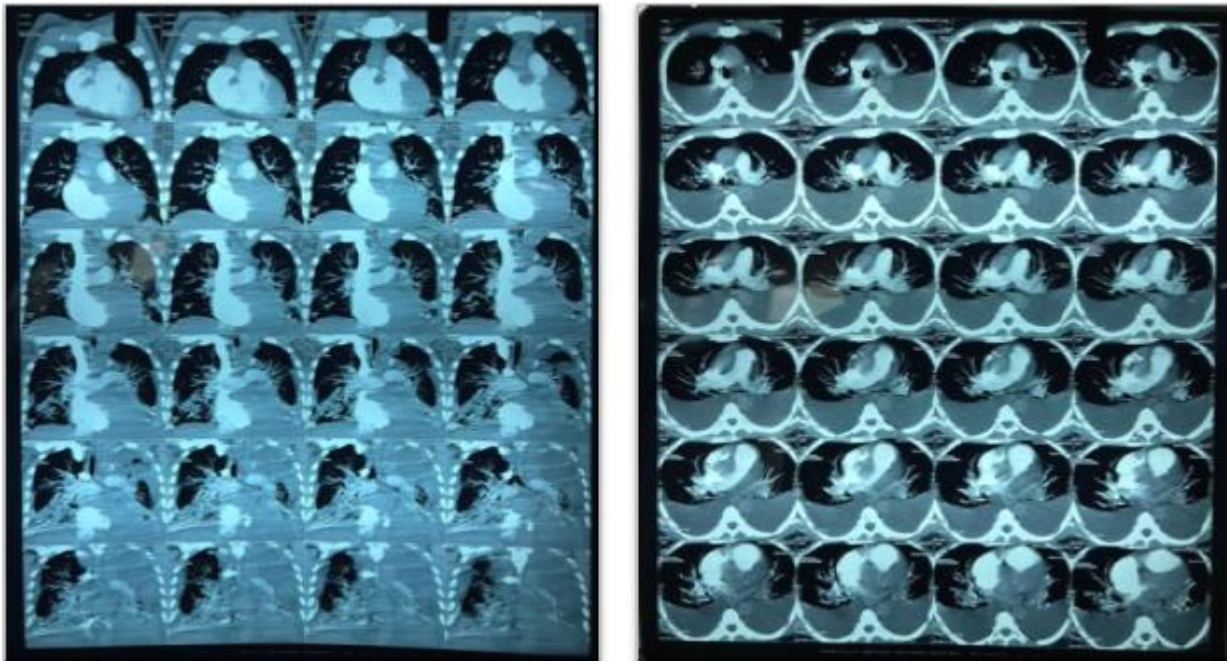
USG chest was done, it showed bilateral mild to moderate pleural effusion.

USG whole abdomen was done it showed Benign prostatomegaly.

An ECG was done, it showed sinus rhythm with inverted p - wave in V1 suggestive of right ventricular strain. (Figure 4)

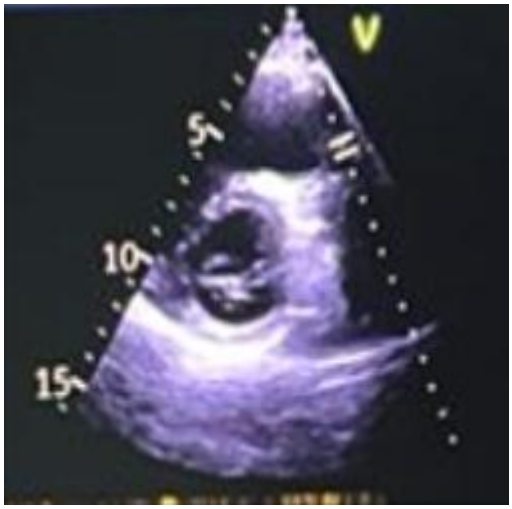


ECG with long lead.

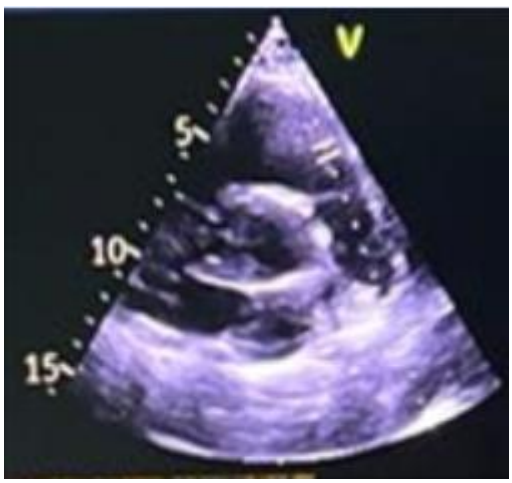


CT pulmonary angiography

A CT Pulmonary angiography was done which showed bilateral pleural effusion and dilated pulmonary vessels and non - enhancing filling defect in superior aspect of right atrial chamber of heart possibly thrombus. (Figure 5)



2D - ECHO at the time of admission



2D - ECHO after 6 months

A 2D - Echo was done, it showed dilated right atria and ventricle and Pulmonary hypertension with Pulmonaryartery systolic pressure 74mmhg. (Figure 6)

2D - ECHO study's findings		
Parameters	On admission	Follow - up after 3 months
Mitral valve (peak/velocity)	63/43 cm/s	43/71 cm/s
Aortic valve (peak/velocity)	114 cm/s	145 cm/s
Pulmonary valve (peak/velocity)	80 cm/s	79 cm/s
LVEF	60%	60%
RSVP	74mmhg	44mmhg

Blood Routine		
	On admission	Follow up after 3 months
Hemoglobin	13.6	13.2
TLC	6.4	4.7
Platelets	207000	172000
PT/INR	16.5/1.37	18.1/1.39
Serum Creatinine	1.43	0.99
Na^+/K^+	140/4.9	138/4.2
D - Dimer	1540 ng FEU/ml	380 ng FEU/ml
SGPT	208 U/L	76 U/L
SGOT	170 U/L	42 U/L
Blood cultures and viral markers were negative.		

Patient was admitted in ICU and dasatinib was stopped and patient treated with optimum medical therapy (Inj. Streptokinase 1.5 lakh international unit stat, Inj. Furosemide 20mg iv once daily, Inj. Heparin 5000 units iv thrice daily, T. tadalafil 20mg once daily, Oxygen inhalation, other symptomatic treatment) and discharged after 10 days on treatment (T. Rivaroxaban 15mg twice daily, T. Torsemide 10mg once daily, T. Ambrisentan 10mg once daily, T. tadalafil 20mg once daily).

Patient was followed up after 1, 3 and 6 months intervals, showed significant improvement clinically. A 6 - minute walk test showed significant improvement (370 meters).

6 - minute walk test		
On admission	Follow - up after 3 months	Follow - up after 6 months
150 meters	370 meters	600 meters

A 2D - Echo was done, it showed dilated RA and RV and decrease in pulmonary hypertension with pulmonary wedge pressure 44mmhg. (Figure 7). An X - ray chest was done, which showed clear bilateral CP angles. A CBC was done, it showed CML in remission phase and Routine blood biochemistry was normal. He was continued on treatment (T. Rivaroxaban 20mg once daily, T. Torsemide 10mg once daily, T. Ambrisentan 5mg twice daily).

3. Discussion

Dasatinib is an important TKI for patients with CML and Ph^+ ALL, providing high rates of response and reduced progression to advanced disease with an acceptable safety profile. In our case, patient had significant improvement in general condition and cardiac function with partial reversal of pulmonary hypertension and provided insight on the reversible remodeling of pulmonary vasculature in dasatinib treated patients of CML after dasatinib was stopped.

Patients usually presented with progressive dyspnea on exertion, cough and marked functional impairment in most of the studies. In a study by Shah NP et al, pleural effusion was most frequently found with PAH (68%).8 In our case the initial presentation like SOB and dry cough which was in line with other studies.

In our study possible mechanism involved in dasatinib induced PAH could not be assessed but possible mechanisms, Despite being a BCR - ABL TKI, dasatinib is also a potent inhibitor ofSrc kinase (Proto - oncogene tyrosine - protein kinase Src), Src kinase inhibition could be involved in DASA - PAH development observed by Montani D et al.6 A study reported that dasatinib treatment induces pulmonary endothelial cell apoptosis in a dose - dependent manner and endothelial dysfunction via increased production of reactive oxygen species, which occur independently of Src kinases. It was demonstrated that dasatinib exacerbates PAH only in a rodent model of PAH but not in control animals, supporting a two - hit theory of the pathophysiology of DASA - PAH observed by Guignabert C et al.7 In a report of 41 patients with RHC - confirmed DASA - PAH, 94% showed improvement, but only 58% achieved complete resolutionobserved by Shah NP et al.8

In a study by Liu et al, they reported with regard to the use of dasatinib, dasatinib induced PAH, a rare adverse reaction, should not negate the advantage of this drug in hematological field. Electrocardiography and TTE are the preferred non - invasive tests for screening PAH. If a hint of PAH occurs, dasatinib should be stopped immediately and for life, and target treatment for PAH should be considered according to the individualized situation.5 This was in line with our case.

In a study reported by Weatherald Jet al, long - term outcomes in 21 patients treated for dasatinib - PAH. Dasatinib was discontinued in all patients and pulmonary vasodilators were prescribed in 11; those treated with pulmonary vasodilators had worse baseline hemodynamics but could reach long - term hemodynamic outcomes similar to those in patients not treated with pulmonary vasodilators, though PAH persisted in 37% at the last follow - up (median 24 months). They followed an algorithm to treat patients presenting with more severe symptoms [e. g., New York Heart Association (NYHA) functional class (FC) III or IV] and those with severe hemodynamic compromise [e. g., cardiac index (CI) <3 L/min/m2] with pulmonary vasodilators, and to consider de - escalation of pulmonary vasodilators if normal hemodynamics persists at 1 year.9 In our case, the patient's initial presentation was severe (i. e., NYHA FC IV and CI 1.35 L/min/m2); therefore, his treatment with multiple pulmonary vasodilators was justified and eventually shown to be successful.

4. Conclusion

A dangerous and potentially fatal side effect of long - term dasatinib treatment is PAH. When receiving dasatinib for an extended period of time, patients should always be carefully monitored. Once PAH develops it indicates use of TKIs other than dasatinib. Here we saw a case of DASA - PAH with typical clinical characteristics and a partially reversible course, which was successfully controlled by a multimodal strategy and combination targeted therapy. To determine its risk factors and the function of the tyrosine kinase pathway in the pulmonary vasculature, which would aid in its early detection and potential treatment, more research is required.

5. Disclosure

We have no conflict of interest to disclose.

References

[1] CML. Harrison's Principles of Internal Medicine, 21st edition.2018; 101: 748 - 757.
[2] Anti - cancer drugs. Tripathi, K. D. Essentials of medical pharmacology (8th ed.). Jaypee Brothers Medical.2018; 64: 915 - 936.
[3] Galie N, Humbert M, Vachiery JL, Simon Gibbs, Irene Lang et al.2015 ESC/ ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J.2016; 37 (1): 67–119.
[4] Xu XQ, Jing ZC. The 6th world symposium on pulmonary hypertension: focus on updates on definition and clinical classification of pulmonary hypertension. Med J PUMCH.2018; 9 (3): 197–201.
[5] Liu R, Tang Y, Fu T, Zhou J, Ma L, Yuan J, Xu O. Dasatinib - Induced Pulmonary Arterial Hypertension: A Case Report. Research Reports in Clinical Cardiology.2021; 12: 33 - 39.
[6] Montani D, Bergot E, Günther S, Savale L, Bergeron A, Bourdin A, Bouvaist H, Canuet M, Pison C, Macro M, Poubeau P. Pulmonary arterial hypertension in patients treated by dasatinib. Circulation.2012 May 1; 125 (17): 2128 - 37.
[7] Guignabert C, Phan C, Seferian A, Huertas A, Tu LY, Thuillet R, Sattler C, Le Hiress M, Tamura Y, Jutant EM, Chaumais MC. Dasatinib induces lung vascular

toxicity and predisposes to pulmonary hypertension. The Journal of clinical investigation.2016 Sep 1; 126 (9): 3207 - 18.

[8] Shah NP, Wallis N, Farber HW, Mauro MJ, Wolf RA, Mattei D, Guha M, Rea D, Peacock A. Clinical features of pulmonary arterial hypertension in patients receiving dasatinib. American journal of hematology.2015 Nov; 90 (11): 1060 - 4.

[9] Weatherald J, Chaumais MC, Savale L, Jaïs X, Seferian A, Canuet M, Bouvaist H, Magro P, Bergeron A, Guignabert C, Sitbon O. Long - term outcomes of dasatinib - induced pulmonary arterial hypertension: a population - based study. European Respiratory Journal.2017 Jul 1; 50 (1).