ABSTRACT

Long term treatment with tyrosine kinase inhibitors (TKIs) are known to produce serositis resulting in minimal pericardial and pleural effusion but massive pericardial effusion causing tamponade is very rare. In this case, we report on a case of 60 yrs old female, who was on imatinib for last 4 yrs for postoperative treatment for GIST stomach, who presented in a state of cardiac tamponade, due to massive pericardial effusion. After emergency pericardiocentesis, malignant and infectious etiologies were ruled out. Patient treated symptomatically and the effusion subsided on withdrawal of offending drug and there was no recurrence of effusion on follow up. In this report we highlight on the rare but important side effect of imatinib therapy and the importance of its early recognition.

CASE REPORT

History

Our patient is a 60 yrs old house wife from Vythiri, with past history of systemic hypertension and with history of surgery for GIST of stomach on imatinib as postoperative adjunctive therapy, who was apparently normal till present admission, attended our casualty with history of stabbing pain in the interscapular region, sudden in onset, worsening gradually, with no radiation, but associated with shortness of breath, sweating and vomiting. No associated chest pain / cough / hemoptysis / syncope / loss of consciousness / limb pain / abdominal pain / hematuria / decreased urine output.

A Case Of Imatinib Induced Massive Pericardial Effusion Causing Cardiac Tamponade

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No history of trauma or fever. No history of significant loss of weight or loss of appetite. She gives history of systemic hypertension for past 5 years and was on losartan tablets. She gives history of GIST of stomach which was treated with wedge resection in November 2012, and she was on postoperative adjuvant treatment with imatinib tablets 400 mg twice daily dosage, and she was asymptomatic till present admission. No past history of coronary artery diseases. No significant family history or no history of contact with tuberculosis.

EXAMINATION

On examination she was drowsy, with pulse rate of 118/min, feeble, peripheries were cold with systolic blood pressure of 70 mmHg, Resp rate - 34/min, JVP was elevated with prominent x descent, Generalized hypopigmentation with patchy hyperpigmentation on face. CVS examination showed non palpable apex beat, and muffling of heart sounds and respiratory system examination revealed decreased intensity of breath sounds in bilateral infraaxillary, infrascapular with decreased VF and VR with stony dullness on percussion in the above areas suggestive of bilateral pleural effusion. Midline laparotomy scar seen on abdominal examination. No focal neurological deficits.

The possibilities considered from emergency department were cardiac tamponade with bilateral pleural effusion in view of hypotension, tachypnoea, raised JVP and muffled heart sounds and respiratory system findings. Considering her past history of malignancy it could be a malignant effusion. Also could be a tuberculous as she s from an area where incidence is high. Sudden stabbing pain and hypotension could be due to dissection of aorta. Hypotension with raised JVP could be acute myocardial infarction especially affecting right ventricle. It could be also pulmonary embolism, her previous history of GIST might be contributing to a prothrombotic state and might lead to embolism even in the absence of immobilization. Other rare causes like esophageal rupture, pancreatitis was kept lower in the list.

INVESTIGATIONS

ECG showed low voltage complexes, sinus tachycardia (figure 1 and figure 2)

A screening echocardiogram was done in ED confirmed significant pericardial effusion, 36 mm posteriorly, no RWMA, Concentric LVH, good LV function, with RA and RV diastolic collapse.

Pericardiocentesis was done immediately and drained 450 ml of haemorrhagic fluid and pigtail
catheter was inserted, which drained 400 ml of haemorrhagic fluid for 4 days. Later thoracotomy was done, a pericardial window created, and a drainage tube was inserted. A pericardial biopsy was also taken. Routine blood investigations were within normal limits (table 1)

Figure 2

Figure 3

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<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Hemoglobin</strong></td>
<td>10.8</td>
</tr>
<tr>
<td><strong>WBC count</strong></td>
<td>11700</td>
</tr>
<tr>
<td><strong>Platelet count</strong></td>
<td>214000</td>
</tr>
<tr>
<td><strong>ESR</strong></td>
<td>16</td>
</tr>
<tr>
<td><strong>Blood Urea</strong></td>
<td>34mg</td>
</tr>
<tr>
<td><strong>Serum Creatinine</strong></td>
<td>1.2</td>
</tr>
<tr>
<td><strong>Serum Sodium</strong></td>
<td>132mg</td>
</tr>
<tr>
<td><strong>Urine microscopy</strong></td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Serum Potassium</strong></td>
<td>4.2</td>
</tr>
<tr>
<td><strong>Random blood sugar</strong></td>
<td>102mg</td>
</tr>
<tr>
<td><strong>Serum bilirubin (total)</strong></td>
<td>1.8mg</td>
</tr>
<tr>
<td><strong>ALT</strong></td>
<td>42</td>
</tr>
<tr>
<td><strong>AST</strong></td>
<td>36</td>
</tr>
<tr>
<td><strong>ALP</strong></td>
<td>82</td>
</tr>
<tr>
<td><strong>Serum Protein</strong></td>
<td>6.4</td>
</tr>
<tr>
<td><strong>Serum Albumin</strong></td>
<td>2.9</td>
</tr>
<tr>
<td><strong>Prothrombin time/INR</strong></td>
<td>16/1.2</td>
</tr>
<tr>
<td><strong>Peripheral smear</strong></td>
<td>Normal</td>
</tr>
</tbody>
</table>
Chest x ray showed enlarged cardiac silhouette and left sided pleural effusion (figure 3)

Pericardial fluid study showed haemorrhagic fluid with 760 cells, predominantly neutrophils, exudative, with low ADA, and a negative study for malignant cytology and cultures were sterile, and a gene xpert for M. tuberculosis was negative. (table 2)

Pleural fluid was straw coloured, transudative, with 300 cells, predominantly neutrophils, and with low ADA, and a negative study for malignant cytology and cultures were sterile, and a gene xpert for M. tuberculosis was negative. (table 2)

<table>
<thead>
<tr>
<th>Tests</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericardial fluid study</td>
<td>Haemorrhagic TC – 760 , P60, L40Prot - 5.5 ,Alb - 3.4 ADA - 11.9 (&lt;30) Cytology - few mesothelial cells and lymphocytes, no malignant cells Culture - sterile</td>
</tr>
<tr>
<td>Pleural fluid study</td>
<td>TC - 600, DC - P70 , L30Sug - 68Prot -1.3, alb -0.7ADA - 24 (&lt;30) Cytology - mesothelial cells +, no malignant cell Culture - sterile</td>
</tr>
<tr>
<td>USG Doppler abd aorta</td>
<td>Diffuse atheromatous changes</td>
</tr>
<tr>
<td>CT aortogram</td>
<td>No evidence of dissection/ aneurysmal dilatation Normal lumen and contrast opacities .B/l renal arteries – normal Mesenteric arteries - atheromatous changes ? Aortic root ulcer</td>
</tr>
<tr>
<td>MR angiogram</td>
<td>No significant abnormality detected in the present angiogram of aorta Mild bilateral pleural effusion Moderate pericardial effusion Collapse and bronchiectatic changes in left lower lobe.</td>
</tr>
<tr>
<td>Thyroid function tests</td>
<td>Normal</td>
</tr>
<tr>
<td>Trop I</td>
<td>Negative</td>
</tr>
<tr>
<td>HIV, HBsAg</td>
<td>Negative</td>
</tr>
<tr>
<td>HCV, VDRL</td>
<td></td>
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</tbody>
</table>

A CT aortography and MR aortography was also taken in a strong suspicion of aortic dissection which does not revealed any evidence of dissection or aneurysmal dilatation.

Malignant work up with USG breast and abdomen, CECT thorax, and upper GI endoscopy were negative. Pericardial biopsy showed fibrinous inflammation and few lymphocytes, and no malignant cells or granuloma. Other autoimmune work up and thyroid function tests were also within normal limits. (table 3)
Pleural and pericardial fluid gene expert for TB Negative
Mantoux Negative

Pericardial biopsy
- Dense fibrosis with congested vessels.
- Fibrinous exudates with reactive mesothelial cells
- No granuloma or evidence of malignancy

USG Abdomen
- Normal study
- No ascites

USG breast Normal

CECT thorax and abdomen
- Moderate pericardial effusion
- Minimal bilateral pleural effusion

Repeat echo
- No RWMA, Good LV function, EF – 55%

ANA (IF), RA factor
- Negative

Upper GI endoscopy
- Negative

Pericardial pigtail catheter drained >400 ml haemorrhagic fluid per day for 4 days, later thoracotomy and pericardial window created and an intercostal tube was inserted. Drained, blood stained fluid, which later became straw coloured. Fluid studies were repeated.

THE ROAD TO DIAGNOSIS

Here is a 60 yrs old housewife, with past history of systemic hypertension and with history of surgery for GIST of stomach on imatinib as postoperative adjunctive therapy, who was apparently normal till present admission, attended our emergency department with history of stabbing pain in the interscapular region, examination and subsequent investigations revealed massive pericardial effusion causing tamponade. The possibilities kept were,

1. Aortic dissection

In view of sudden severe pain in interscapular region, along with past history of hypertension, and examination showing hypotension and cardiac tamponade, we considered the possibility of aortic dissection. So we proceeded with CT aortogram after initial stabilization. It did not reveal any dissection or aneurysm but there was a suspicious aortic root ulcer. So we proceeded with MR aortogram which ruled out aortic dissection.

2. Malignancy

We considered a strong possibility of GI malignancy because she had past history of GIST, and we also suspected carcinoma breast or lung with metastasis or local invasion causing haemorrhagic pericardial effusion. But she had no history to suggest a malignancy like loss of appetite or weight, history of gastrointestinal bleed, cough, hemoptysis or breast lumps. We worked up for malignancy with imaging, also with an upper GI endoscopy. Pericardial fluid studies sent for cytological studies and a pericardial biopsy was also taken. But all malignant work up including biopsy came as negative.
3. Acute coronary syndrome with complications

Though rare, acute coronary syndrome, especially anterior wall MI with ventricular free wall rupture or VSR can present like this, and her age and hypertension being the risk factors. But ECG did not reveal any ST elevation and a normal troponin values ruled out a coronary event, and an echocardiography showed no regional wall motion abnormality.

4. Tuberculosis and other infections

We kept the possibility of infectious etiologies also, but there was no fever or systemic symptoms. No palpable lymph nodes. Pericardial fluid was transudate and repeated cultures were sterile. So the diagnosis of an infection was ruled out. Blood cultures were also negative and echocardiogram did not reveal any vegetations.

After reasonably ruling out other causes we considered Imatinib induced serositis causing pleural and pericardial effusion, though chance of massive effusions was rare. So we stopped the drug after discussing with oncology department.

She was treated with supportive measures only, Steoids and diuretics were not given.

She had improvement in symptoms in 2 weeks of stopping Imatinib. Pericardial drain was nil and drain removed. Repeat chest x-ray and echo were normal, with no evidence of pericardial or pleural effusion. There was no recurrence of symptoms on follow up. The pericardial and pleural effusions were attributed to imatinib therapy as all other causes were excluded and there was improvement in symptoms following discontinuation of treatment.

DISCUSSION

Imatinib is a tyrosine kinase inhibitor specific for abnormal BCR-ABL tyrosine kinase which is commonly given for Ph positive CML and ALL; it is also given in MDS with PDGFR gene rearrangements, eosinophilic leukemias, dermatofibrosarcoma protuberans. In GIST it is given for metastatic or malignant or unresectable tumours or as a part of post operative adjuvant treatment after complete resection. Adverse effects reported commonly are edema (53%), neutropenia (gr 3-27% and gr 4-48%), nausea (43%), muscle cramps (35%), rash (32%), fatigue (31%), diarrhea (30%), headache (29%), arthralgia (27%), abdominal pain (23%), myalgia (21%). Other common side effects reported are nasopharyngitis, haemorrhagic tendencies, vomiting, cough, URTI, fever, weight gain, hepatotoxicity.

Serositis following imatinib therapy is reported in about 7% cases. Usually it is manifested as minimal pleural or pericardial effusions or as minimal ascites which is detected on routine follow up and usually asymptomatic.

Isolated pericardial effusions following tyrosine kinase inhibitor therapy has been reported. Few cases of cardiac tamponade due to imatinib therapy has also been reported. Mechanisms causing serositis is not well understood, both hypersensitivity and autoimmune mechanisms has been proposed.

In all reported cases the symptoms resolved in average time period of 2 weeks and complete work up for malignancy and infective etiologies were negative.

So all patients on long term treatment with tyrosine kinase inhibitors should be followed up at regular intervals to look for treatment related side effects.

PEARLS

1. What is beck’s triad ?
   The triad of hypotension, raised JVP and muffled heart sounds constitute beck’s triad. Seen in cardiac tamponade.

2. Three causes for raised JVP with hypotension?
   Cardiac tamponade, pulmonary embolism and right ventricle myocardial infarction.
3. What are the uses of Imatinib?
   CML, ALL, myelodysplastic syndrome, GIST, mastocytosis

4. What are the causes of pericardial effusion?
   Infections like viral, tuberculosis, bacteria, malignancies like lung, breast, lymphoma and leukemia, post cardiac surgery, uremia, hypothyroidism, dissection of aorta, myocardial infarction, capillary leak syndrome and drugs

REFERENCES
1. Goodman and Gilman’s, The Pharmacological Basis of Therapeutics, 12th edition,
4. Vineet Agarwal et al, Annual Journal of The Johns Hopkins University School of Medicine, Baltimore, 2015 (PUBMED)