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Clinico-Pathological Corelation : A Search for the Cause of Myelofibrosis


A 26 year old unmarried female came with complains of menorrhagia since 2 months and swelling in right vulval area since 1 month (March 2013). She had a history of ileocaecal tuberculosis with abdominal lymphadenopathy (with appendicitis) in 2006 for which she underwent appendectomy and took 3 months of AKT (no documents provided to support the diagnosis of either disease). There was no history of fever, rash or bleeding from any other sites. The patient was following up with the gynaecologist for the above complaints and was being investigated for the same.

With the above presentation the likely causes could be local gynaecological namely fibroids, endometriosis or local genital infections. Though presentation without fever is unlikely for infections; genitourinary tuberculosis could be a possibility. The patient had history of incomplete treatment for abdominal tuberculosis in the past. Also, a bleeding disorder due to thrombocytopenia or von Willebrand disease or coagulopathy should be kept in mind.

On investigations, patient was found to have pancytopenia with haemoglobin 4.4 g/dl, WBC 2000/cumm (N42 L56 M2) and platelets 23000/cumm. Her PT/INR and APTT were normal. MCV was 85. Her CT abdomen plus pelvis was suggestive of left adnexal hemorrhagic cystic lesion and right vulval infected Bartholin’s cyst. In view of the above reports she was referred to medicine unit for the evaluation of pancytopenia.

Now with the above lab reports and imaging studies, the likely cause of the presenting complains could be the ovarian cyst which could have undergone hemorrhagic transformation aggravated by thrombocytopenia. But the adnexal lesion required further conformation of etiology, especially to rule out a carcinoma.

Tumour markers were normal [alpha fetoproteins (2.76 IU/ml), CA 19.9 (< 0.6 U/ml), CEA (1.2 ug/ml), CA 125 (5.32 U/ml)]. With these reports a carcinoma of ovaries was ruled out. Also it was necessary to evaluate the cause of pancytopenia (Table 1).

Reticulocyte count was 1-2% (corrected retic count was 0.3-0.6%). USG abdomen
showed normal liver and spleen. Iron and vitamin B12 levels were normal. Coomb’s test (direct and indirect) was negative. Oesophagogastroduodenoscopy (OGDscopy) was normal. Stool for occult blood was negative. Uric acid and lactate dehydrogenase (LDH) levels were normal. Peripheral smear showed pancytopenia.

In the work up for pancytopenia, nutritional deficiencies were ruled out, so was a blood loss anemia from gastrointestinal tract. Pancytopenia secondary to hypersplenism was ruled out as there was no evidence of portal hypertension. Now our differentials for pancytopenia were narrowed down to hypoplastic marrow especially aplastic anemia as corrected reticulocyte counts were low. Though the atypical RBCs on peripheral smear could be secondary to bone marrow infiltration or myelofibrosis.

A Bone marrow aspiration with biopsy was done. The marrow aspiration was diluted with blood and imprint showing scanty material with megaloblastic erythropoeisis. Biopsy showed increase in reticulocytic fibres and fibrosis with reduction in erythroid and myeloid islands (Figure 1). Megakaryocytes were noted of which some appeared small in size, with some lymphocyte and plasma cells. Macrophages showed erythropagocytosis in 5%. Impression of biopsy was suggestive of Myelofibrosis. Masson trichrome staining for marrow collagen showed grade 3 fibrosis (Figure 2).

Imprint and biopsy were suggestive of myelofibrosis. Now the next step was to evaluate the cause of myelofibrosis. Primary myelofibrosis was unlikely as the patient was young and her liver and spleen were normal in size. So the diagnosis was more likely to be secondary which needed further evaluation (Table 2).

Immunohistochemistry of bone marrow was inconclusive due to extensive fibrosis. HIV 1 and 2, HBsAg and anti HCV were negative. Serum ANA and dsDNA levels were negative. JAK2 V617F mutational analysis was negative. Blood cultures for bacteria, fungi and tuberculosis were negative.

With these available investigations collagen vascular disorders and infections were ruled out. Cultures from marrow could not be sent as aspirate was dry. Sarcoidosis was ruled out as there was no granuloma formation in bone marrow biopsy. Carcinomatous infiltration of bone marrow was unlikely as to the cause of secondary myelofibrosis. To rule out a lymphoproliferative disorder, a repeat marrow was planned but patient did not consent for the same. Patient was discharged with symptomatic medications. The patient did not follow up for 2 months.

She got readmitted 2 months later in view of severe anemia requiring transfusion. There was history of bleeding per rectum and was transfused 2 units of packed cells and 6 bags of platelets. She also complaint of fever during this admission. Her investigations revealed pancytopenia with absolute neutrophil count of 197. She was given antibiotics, antivirals and antifungals and G-CSF. She came out of neutropenic sepsis. Repeat bone marrow biopsy was done during this admission. Aspirate was dry again with imprint suggestive of suppression of myeloid and erythroid cells as well as megakaryocytes with increased promyelocytes and auer rods i.e. faggot cells (Figure 3). Biopsy showed few marrow spaces with cellularity increased for age with supression of megakaryocytes, normal myeloid and erythroid cells (Figure 4). Proliferation of cells resembling promyelocytes were seen with small foci of infarction.

<table>
<thead>
<tr>
<th>Table 2 : Causes of secondary myelofibrosis</th>
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<tbody>
<tr>
<td>• Neoplastic – infiltration by cancer cells (primary is usually located in breast, lung or prostate)</td>
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<td>• Infective – tuberculosis, fungal infections, HIV</td>
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<tr>
<td>• Metabolic – Gaucher’s disease</td>
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<tr>
<td>• Hematological malignancies – chronic myeloid leukemia, multiple myeloma, lymphomas, acute myeloid leukaemia</td>
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<tr>
<td>• Radiation, radiomimetic drugs</td>
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<td>• Others – Sarcoidosis, congenital osteopetrosis</td>
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Features of bone marrow biopsy were suggestive of acute leukemia.

In view of increased promyelocytes, there was possibility of APML (AML-M3), but APML usually does not present as myelofibrosis. It is acute leukemia mostly megakaryoblastic lymphoma (FAB M7) that can present as myelofibrosis. Even Chronic Myelogenous leukemia, Myelodysplastic syndrome and Non Hodgkins lymphoma can present with myelofibrosis. Thus patient was investigated further.

APML is known to be associated with the complication of DIC (Table 3). Therefore, though she was not in DIC clinically, her PT/APTT were sent. PT=20.5 sec (Control=14), APTT=33.1 sec (Control=26 to 34); d Dimer levels were 6.3 mg/L (normal < 0.3). Fluorescent in situ hybridization (FISH) for PML-RARA was positive in 2% cells on peripheral blood. Real time Polymerase chain reaction (RT PCR) was done on PML-RARA quantified as 0.74% which showed mild to moderate positivity. Repeat immunohistochemistry showed diffuse Myeloperoxidase (MPO) positivity and negative for c-kit and CD 34.

Now the diagnosis of APML was confirmed based on the FISH and RT PCR reports. Also immunohistochemistry showed MPO positivity and negative for CD 34.

Thus the patient was started on differentiating agent for APML with injection arsenic trioxide 10 mg/day and tablet tretinoin 60 mg daily for 42 days and other symptomatic medications.

Repeat RT PCR after induction phase of 42 days of arsenic trioxide and tretinoin was negative for PML RARA. Subsequently the patient has undergone consolidation and maintenance phases of treatment and her symptoms and laboratory parameters have normalized. A third bone marrow was done at the end of treatment which shows normal cellularity and marrow consistent with her age (Figure 5).

Thus this patient who initially presented as myelofibrosis was eventually diagnosed to have Acute Promyelocytic Leukemia. Usually patients of APML may present with symptoms of Disseminated intravascular coagulation (DIC) but patient presenting with myelofibrosis is very rare.

**Discussion**

Increased marrow fibrosis has been reported to occur in acute myelogenous leukemias but seldom encountered in patients of APML. Myelofibrosis is a negative prognostic factor in Chronic Myelogenous

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**Table 3: Clinical features of APML**

- Fatigue, weakness, shortness of breath (from anemia)
- Easy bruising and bleeding (from thrombocytopenia and coagulopathy)
- Disseminated intravascular coagulation (DIC) characterized by rapid increase in the number of immature white blood cells, resulting in rapid progression of malignant cell counts and crowding of the bone marrow which results in very low red blood cells and platelet counts, which can cause serious bleeding.
- Fever and infection (from lack of normal white blood cells)
- Minor abdominal discomfort (from enlargement of the spleen)
leukemia, Myelodysplastic syndrome, Non Hodgkins lymphoma (NHL) and Acute Megakaryoblastic lymphoma (FAB M7). The possible mechanisms for development of myelofibrosis in APML is overexpression of transforming growth factor beta as reported by Mori et al. In the cases reported by Fukuno et al and Aventin et al there is expression of HLA DR and the promyelocytes were positive for CD 34. Even Batlle M et al have reported a case of APML presenting as myelofibrosis. The myelofibrosis is reversible after induction with chemotherapy as described by Mori et al; as well as with bone marrow transplant as described by Fukono et al. Pankhi Dutta et al have reported a case of APML with secondary myelofibrosis who underwent molecular remission following induction therapy. Thus, myelofibrosis may be present with AML-M3 and doesn’t appear to be associated with poor outcome as seen in above case reports.

In our patient, post treatment, bone marrow biopsy was repeated which has shown reversal of myelofibrosis and normal cellularity for her age (Figure 6). Clinically the patient has improved and RBC, WBC and Platelets have normalized. Post therapy, RT PCR shows molecular remission. Our patient has also shown reversal of myelofibrosis post therapy.

Bone marrow biopsy should be routinely done in all patients of AML-M3 to study the prevalence of myelofibrosis in APML. Long-term follow ups are necessary and larger number of cases should be studied to find out whether APML and myelofibrosis is just an association or APML can present as myelofibrosis.

References