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Clinicopathological Conference Report: PM 26154

Myeloproliferative Neoplasm with Extensive Myeloid Metaplasia: A Diagnostic Dilemma

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This case (PM 26154) was discussed on 16-3-2015, as a student clinicopathological exercise at PGIMER, Chandigarh, India.

Clinical details and case analysis: Dr Pruthvi CR, Junior Resident (Department of Internal Medicine PGIMER, Chandigarh).

CLINICAL DETAILS

Date of Admission: 03-07-2014
Date of Death: 07-07-2014

Mr PC, 58-year-male resident of Faridkot, Punjab was admitted to PGIMER on 3 July 2014 with complaints of progressive increase in shortness of breath for 1 month and yellowish discoloration of eyes for 2 days. The shortness of breath was insidious in onset and progressive, which required oxygen supplementation at presentation. This was associated with bilateral pedal edema and low grade intermittent fever. There was no history of cough, expectoration, paroxysmal nocturnal dyspnea, palpitation, abdominal distension or facial puffiness. Jaundice was noted and was associated with pruritus. No clay colored stools or high colored urine was noticed. There was history of generalized weakness and easy fatigability for 6 months. There was history of loss of weight/appetite and blurring of vision for 2 months.

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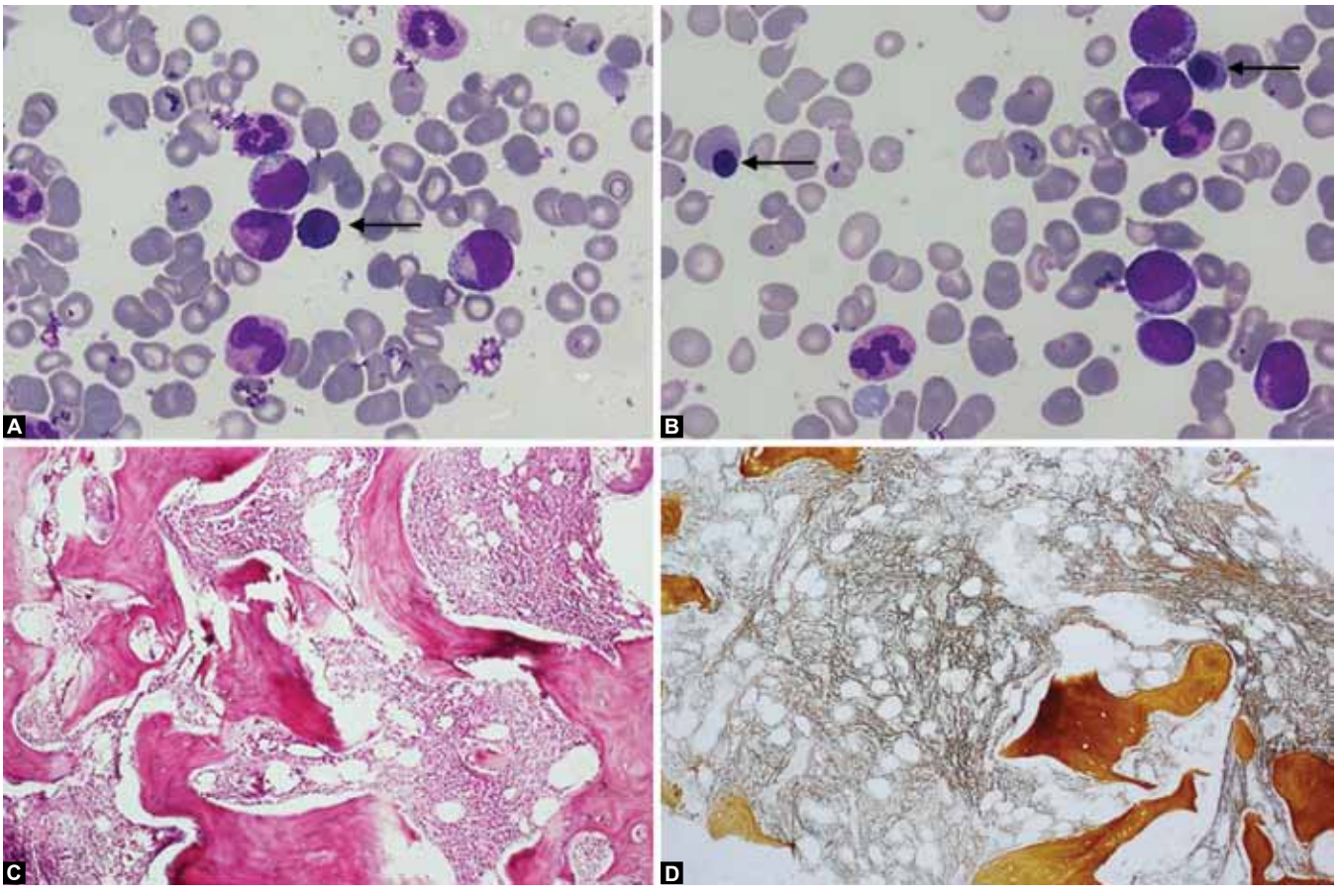
BACKGROUND HISTORY

June 2013: The patient was evaluated in Ludhiana for complaints of easy fatigability, loss of weight, left upper quadrant heaviness. He was found to have anemia, leukocytosis with shift to left and massive hepatosplenomegaly. Bone marrow examination was suggestive of chronic myeloproliferative disorder, possibly chronic myeloid leukemia-chronic phase. Patient was started on Imatinib, hydroxyurea and allopurinol. Following this BCR-ABl testing was done which was negative. In view of persistently elevated total leukocyte count patient was referred to PGIMER, Chandigarh.

August 2013: Bone marrow (BM) done in PGI. Antemortem Bone Marrow (A-1368/13, 27-08-2013): Hb—9 gm/dl, TLC—1,48,300/µl, platelet count—1,76,000/µl, DLC N 49, L01, M 02, Basophils 02, Blasts 05, Promyelocytes 02, Myelocytes 30, Metamyelocytes 09. N-RBCs 04/100 WBC, LAP score 3 [Normal 40–110] (Figs 1A and B). The trephine biopsy showed thickened trabeculae with focal osteomyelosclerosis and sinusoidal dilatation. The intervening marrow spaces were narrowed and showed granulocytic preponderance along with few small hypolobated megakaryocytes. Erythropoiesis was reduced. No clusters of blasts seen. Reticulin fibrosis was grade 3 (Figs 1C and D). Findings were of a chronic myeloproliferative neoplasm with myelofibrosis and osteomyelosclerosis, possibly CML-MF. BCR-ABL1 (common transcripts—p190 and p120) and JAK2/V617F mutations (Done at PGI by RT-PCR) were negative, karyotyping (Done at PGI)—No metaphases on two occasions, karyotyping done outside (Oncquest, 17/04/14)—Negative for the Philadelphia chromosome. Imatinib was stopped, hydroxyurea and allopurinol were continued.



Figs 1A to D: Peripheral blood film shows leukocytosis with marked shift to left. Basophils (2%) were noted, seen in (A) (arrow). Nucleated red blood cells (4/100WBC) are seen in (B), (C) bone marrow trephine biopsy shows thickened trabeculae with focal osteomyelosclerosis (10×) and (D) intervening marrow spaces show grade 3 reticulin fibrosis (reticulin stain, 10×)

September 2013: Patient evaluated in Ludhiana and was found to have elevated total leukocyte count. He was started on steroids.

November 2013: He developed transfusion dependence.

March 2014 (outside facility–Ludhiana): The patient was continued on the same treatment till March 2014 in Ludhiana. A repeat BM examination was performed which was suggestive of Myelodysplastic syndrome (MDS). Dacitabine was given for 5 days, following which he developed anemia and thrombocytopenia. He again came to PGIMER, Chandigarh and was started on thalidomide and steroids. Myelodysplastic syndrome panel was done which was negative. Thalidomide was stopped and continued on hydroxyurea.

Past history: Patient was a known case of type II Diabetes mellitus for 13 years on oral hypoglycemic agents. There were no history of hypertension, pulmonary tuberculosis, coronary artery disease and seizures.

EXAMINATION

General Examination

Patient was conscious and oriented. He was tachycardiac with a pulse rate of 102 beats/minute and tachypneic with a respiratory rate of 24 cycles per minute. There was hypoxemia with a SpO_2 of 88% and respiratory acidosis. Jugular venous pressure was elevated. Pallor, icterus and bilateral pedal edema were noted. The patient was afebrile. There was no cyanosis, clubbing or lymphadenopathy.

Systemic Examination

Respiratory system examination revealed equal air entry on both sides and normal vesicular breath sounds. Bilateral basal crackles were present. Abdomen was soft and nontender on palpation. Liver was palpable 18 cm below right coastal margin with a span of 32 cm. It was firm to hard in consistency. Spleen was palpable, 14 cm below left coastal margin and was firm to hard to feel. No free fluid was present. Bowel sounds were heard. Cardiovascular system and central nervous system examination were within normal limits.

INVESTIGATIONS

Peripheral blood (2/7/14) showed severe anemia with a hemoglobin of 7.4 gm/l and RBC count 2.36 million/l. The total leukocyte count was 3 lac/l. Platelets were 13000/l. Differential count was N47, L8, M3, E4, Basophils 7, Blast

8 Myelocytes 14 Metamyelocytes 9. Bone marrow biopsy (A-1080/14) (5/7/14)—Hypercellular sapces with granulocytic hyperplasia. Megakaryocytic series of cells were proportionately seen along with dwarf megakaryocytes/micromegakaryocytes and some showing lobe separation. Background fibrosis, sinusoidal dilation and osteomyosclerosis were present. Reticulin was 3+. Diagnosed as case of myeloproliferative neoplasm with myelofibrosis—not in remission. *Biochemical examination* revealed hyperkalemia and progressive worsening of renal function tests. There was hyperuricemia, hyperphosphatemia, conjugated hyperbilirubinemia and elevated lactate dehydrogenase. *Arterial blood gas analysis* showed severe mixed acidosis, predominantly respiratory component in the first 2 days of hospital stay, followed by mixed acidosis. PaO_2/FiO_2 ratio of <100. *Coagulogram* showed an INR of >1.57 and PTI 63%. *Blood and urine culture* were sterile. *Chest X-ray* showed cardiomegaly with perihilar infiltrates. *Electrocardiogram (ECG)* showed a normal sinus rhythm with ST depression and T inversion in V_5-V_6. *2D Echo* showed left ventricular ejection fraction of 60% with concentric left ventricular hypertrophy and mild pulmonary arterial hypertension. Mild pericardial effusion was present with no evidence of tamponade. *High resolution computed tomography of chest* showed mild right sided pleural effusion and possibly pulmonary edema. *Ophthalmic examination* (done elsewhere) was suggestive of leukemic retinopathy.

Course and Management

Patient was treated with IV fluids, diuretics for cardiac failure, IV antibiotics, IV antifungals and antitumorlysis syndrome measures. Received leukapheresis, developed hypotension and altered sensorium, sustained cardiac arrest. Final clinical diagnosis was myelofibrosis, congestive cardiac failure and type I respiratory failure with hyperleukocytosis, leukostasis and tumor lysis syndrome.

CLINICAL ANALYSIS

The following clinical aspects are to be considered:

Primary disease: The primary disease is a myeloproliferative neoplasm (MPN). The possibilities include primary myelofibrosis (PMF) or chronic myeloid leukemia (CML) with secondary myelofibrosis. Features favoring the diagnosis of CML are high total leukocyte count (>100,000/μl), massive splenomegaly, peripheral blood examination consistent with CML with basophilia and low LAP score. Presence of dwarf megakaryocytes in bone marrow. The points against the diagnosis of CML are BCR-ABL1 (common transcripts) and Ph chromosome negative. Also, there was a lack of response to imatinib mesylate at another center. The points favoring primary myelofibrosis are a clinically aggressive course, massive splenomegaly, marrow fibrosis (grade 3) with osteomyelosclerosis and negative BCR-ABL1 transcripts, Ph-chromosome and JAK2.

Hyperleukocytosis/Leukostasis: Points favoring this are predisposing hematological condition with very high leukocyte count >1,00,000/l. There was dyspnea and hypoxemia, which may indicate pulmonary leukostasis. Visual blurring, leukemic retinopathy and altered sensorium could be indicative of CNS leukostasis. Also, there was worsening of renal functions and features of fluid overload. But the patient did not respond to leukapheresis.

Tumor lysis syndrome: The index case had a predisposing myeloproliferative disorder along with hyperuricemia, hyperkalemia and hyperphosphatemia. There was worsening of renal functions. But there was no documented hypocalcemia.

Congestive heart failure: The patient had an elevated *jugular* venous pressure, bilateral basal crackles, cardiomegaly, pulmonary edema and dyspnea on exertion. There was bilateral pedal edema and pleural effusion.

Sepsis: This could be bacterial, fungal or viral in etiology. The patient had tachypnea, tachycardia, dyspnea with altered sensorium. He had hypotension preterminally. Also, he was immunocompromised and had long standing type 2 diabetes mellitus. The points against sepsis are the afebrile state of patient. Also, the cultures were sterile and HRCT chest was not suggestive of an infective pathology.

The terminal events in the patient were likely leukostasis or leukemic thrombosis leading to type I respiratory failure in lungs. Also causing ? acute myocardial infarction or acute coronary syndrome ? cerebrovascular accident and increased intracranial tension. The cause of death being leukostasis, tumor lysis syndrome, type I respiratory failure with acute kidney injury and heart failure ? superadded sepsis. Final clinical diagnosis was myelofibrosis, congestive cardiac failure and type I respiratory failure with hyperleukocytosis, leukostasis and tumor lysis syndrome.

OPEN HOUSE DISCUSSION

Chairperson: The case is open for discussion. I invite treating unit SR for comments.

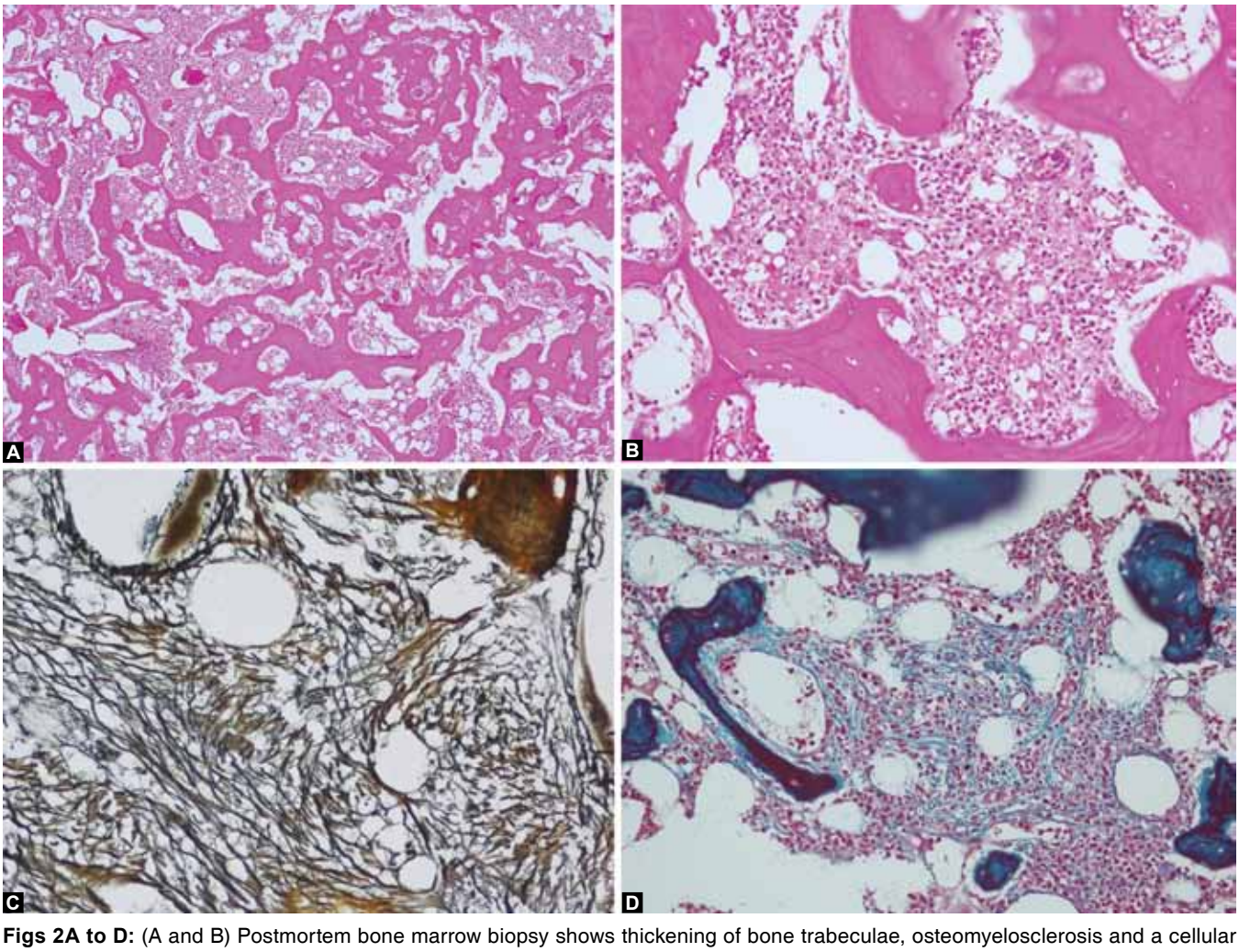
Treating unit SR: There are few important points about the clinical course of the patient. The diagnosis of BCR-ABL negative MPN is not straightforward. As you can see the diagnosis shifted from CML-MF to MDS elsewhere. The patient was kept on hypomethylating agents and finally a diagnosis of MF-osteomyelosclerosis was made.

Myelofibrosis does not always have an indolent course as aggressive forms are also present. Category with 9% blasts in peripheral blood, WBC count >1 lac behaves as badly as acute myeloid leukemia. Karyotype was not done for this patient. Patient died within 1 year of diagnosis and this shows that when the disease turns nasty, nothing works. Leukostasis though seen more in acute myeloid leukemias, can also be seen in chronic myeloid leukemias as was clinically suspected in this patient.

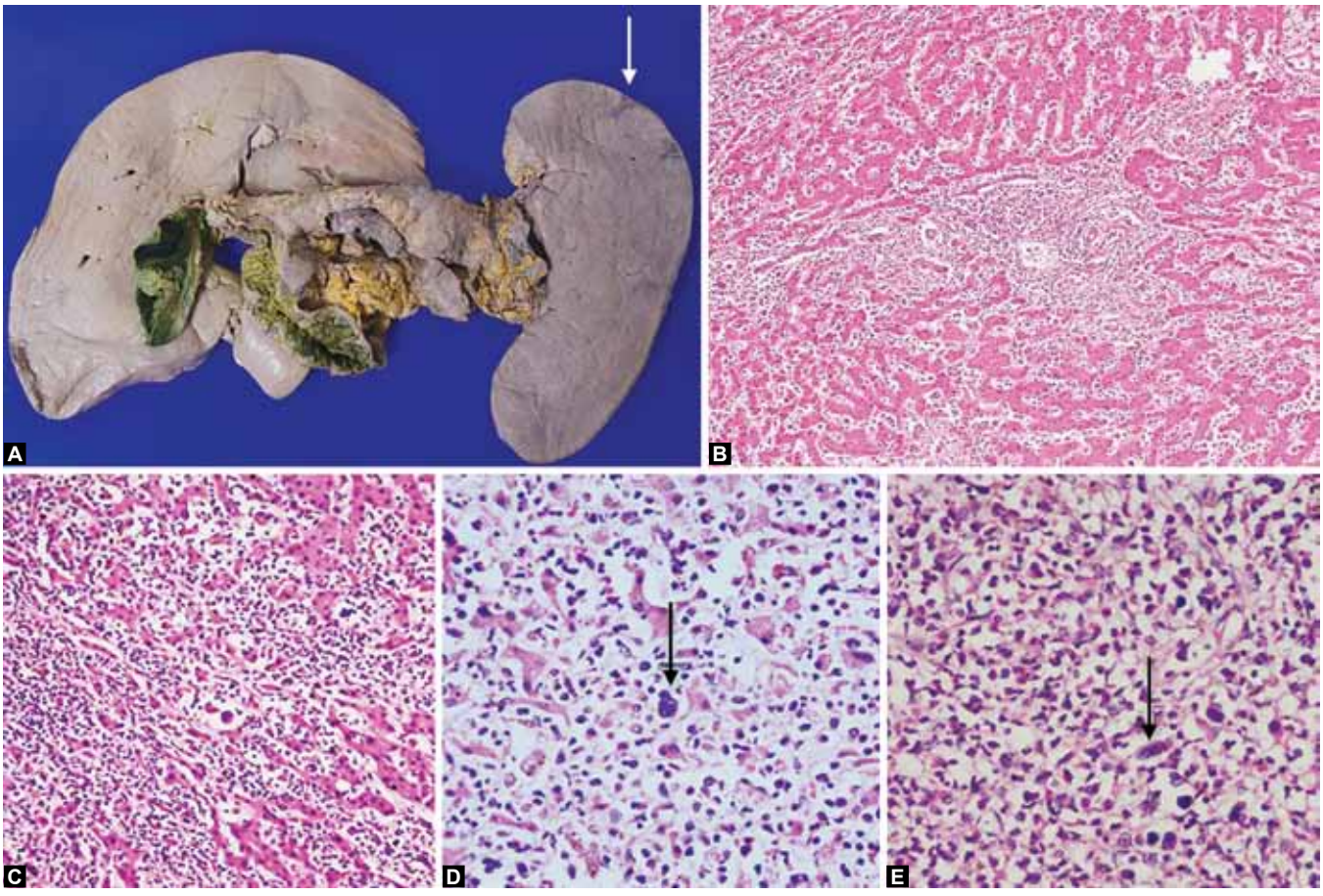
Dr Sachin: In a patient with leukemia with lung infiltrates, three kinds of leukemic manifestations need to be considered. Leukostasis which comprises of accumulation of WBCs in pulmonary circulation causing hypoxemia. Second is leukemic infiltration, which leads to consolidation and ground glassing. And third being lysis pneumopathy.

Autopsy Findings: PM 26154— Dr Vishrut K Srinivasan/Dr Vani Bharani

A partial autopsy was performed. The pericardial cavity contained 80 ml of straw colored fluid. Other serous cavities were within normal limits. The bone marrow showed hypercellular marrow spaces with granulocytic hyperplasia. Megakaryocytes were proportionately seen with some dwarf forms and a few with lobe separation. Erythroid series was relatively reduced. In addition, there was significant marrow fibrosis, thickening of bone trabeculae and osteomyelosclerosis. Reticulin fibrosis was grade 3/3 (EUMNET 0-3) (Figs 2A to D). The liver was enlarged and weighed 3050 gm (Fig. 3A). External and cut surface were unremarkable. Portal vein dissected did not reveal dilatation or thrombosis. On microscopic examination there was a maintained lobular architecture as highlighted by the reticulin stain. There was expansion of portal tracts and hepatic sinusoids due to the presence of extensive myeloid metaplasia seen as infiltration by hematopoietic precursors and megakaryocytes with lobe separation (Figs 3B to D). Some hypolobated forms were also seen. The spleen was enlarged and weighed 1650 gm. The outer surface was congested. Cut surface showed wedge shaped areas of subcapsular infarction (Fig. 3E). On microscopic examination there was depletion



Figs 2A to D: (A and B) Postmortem bone marrow biopsy shows thickening of bone trabeculae, osteomyelosclerosis and a cellular marrow. Marrow (10×, 20×), (C) reticulin fibrosis was grade 3/3 (Reticulin stain, 10×) and (D) areas of fibrosis highlighted on Masson trichrome stain (20×)



Figs 3A to E: (A) Organ complex comprising of slice of the diffusely enlarged liver and spleen with no focal lesions. The spleen shows wedge shaped infarcts (arrow). The gallbladder and pancreas are unremarkable, (B to D) microscopic examination of liver showing extensive myeloid metaplasia in the sinusoids and portal tracts. Abnormal megakaryocytes are seen in abundance (arrow), (E) microscopic examination of spleen showed extensive myeloid metaplasia. Some hypolobated megakaryocytes were seen (arrow)

of white pulp with red pulp showing diffuse myeloid metaplasia as seen in the liver (Figs 3D and E). In addition, areas of infarction and collections of hemosiderin-laden macrophages were also seen. The lungs were heavy and together weighed 1550 gm. Pleura was dull and opaque. The tracheobronchial tree did not reveal any aspirated material. The pulmonary vasculature was within normal limits. Lungs were subcrepitant to feel. On microscopic examination marked interstitial expansion due to myeloid metaplasia and infiltration by hematopoietic precursors was seen (Fig. 4A). The cells were seen within blood vessels as well as focally within alveolar spaces (Fig. 4B). Pulmonary edema was also noted. Tracheobronchial tree was within normal limits. The heart weighed 250 gm. There was left ventricular hypertrophy. Atherosclerosis (grade 3) of aorta was present. On microscopic examination, the myocardium was unremarkable. No features of myocardial infarction were seen. The kidneys were swollen and together weighed 280 gm. The external surface was dull. The cut surface showed an indistinct corticomedullary junction. On microscopic examination myeloid metaplasia was noted in the interstitium, renal sinus and perinephric fat (Figs 4C and D). Tubules showed changes of mild acute tubular necrosis. Glomeruli and blood vessels are essentially normal. The lymph nodes (perihilar and peripancreatic) also showed myeloid metaplasia in the sinuses (Fig. 4E). Other organs were within normal limits.

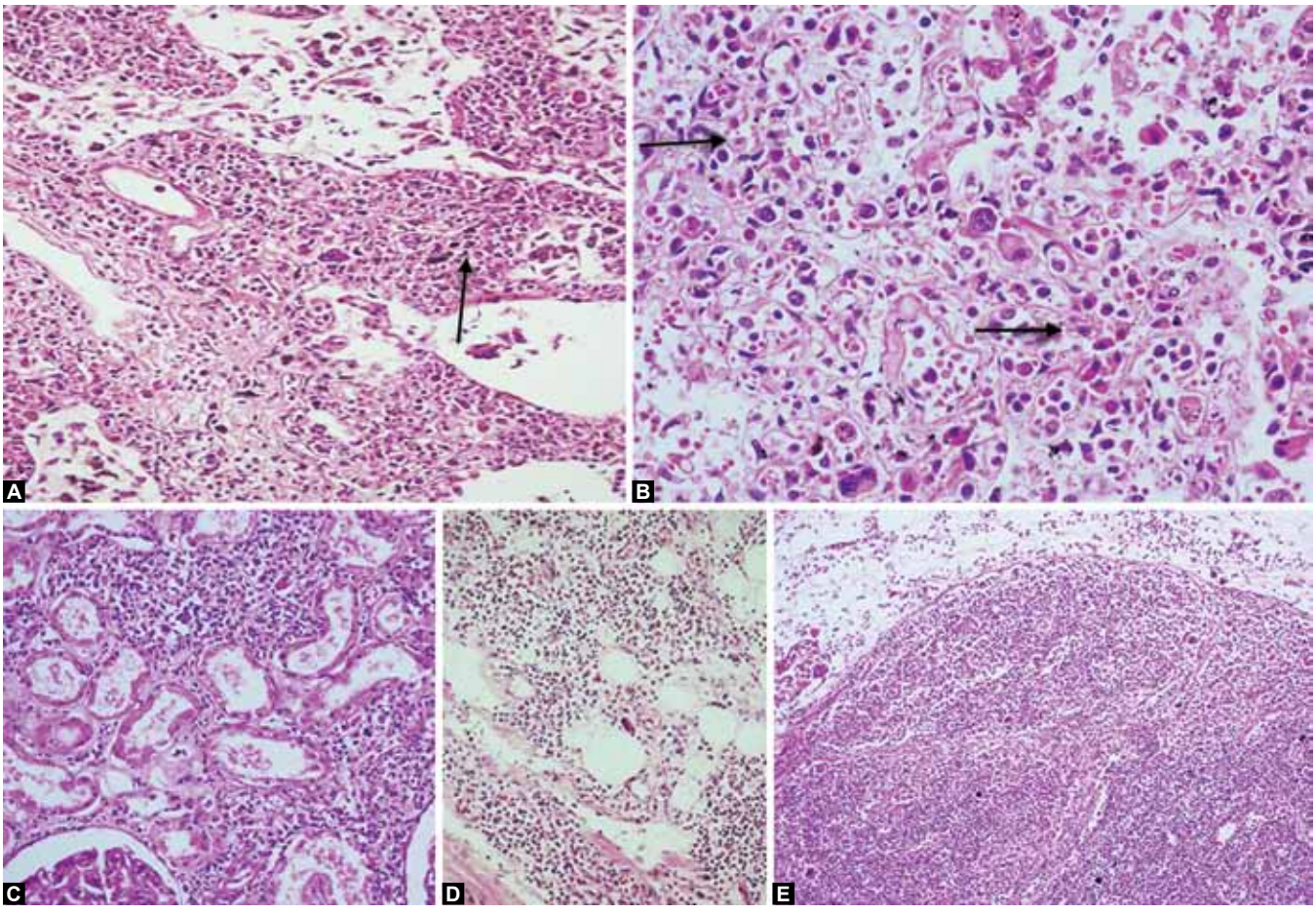
FINAL AUTOPSY DIAGNOSIS
PM 26154, 58 YRS M

- Myeloproliferative neoplasm (Philadelphia chromosome, BCR-ABL and JAK2 negative) with grade 3 myelofibrosis and osteomyelosclerosis—More likely to be a cellular phase of primary myelofibrosis with extensive myeloid metaplasia in the liver, spleen, lungs, kidneys, perinephric fat, lymph nodes
- Pulmonary edema
- Grade 3 atherosclerosis of aorta.

OPEN HOUSE DISCUSSION

Senior resident: The differential diagnosis in this case of MPN is cellular/accelerated phase of MF and accelerated phase of CML. The diagnosis of CML with other transcripts or BCR-ABL negative is a bit contentious.

Dr A Das: We have to take everything together. The peripheral blood picture looks, like CML, with leukocytosis,



Figs 4A to E: (A) Microscopic examination of lung shows marked interstitial expansion due to extensive myeloid metaplasia and infiltration by hematopoietic precursors. The cells are seen focally within alveolar spaces (20x), (B) hematopoietic precursors in the pulmonary capillaries (40x). Myeloid metaplasia seen in the (C) kidney, (D) perirenal fat and (E) sinuses of the lymph nodes

basophilia and low LAP score. Most of the times, MF presents with high platelet counts, whole organ infiltration by myelocytes, metamyelocytes, neutrophils and megakaryocytes. If only BCR-ABL negativity is considered, it can be fitted with MF. But I believe CML with other transcripts need to be excluded.

Dr S Verma: I think best would be to say we do not know what is the basic disease. Rather than saying BCR-ABL negative CML or alternate transcript CML. If we look at patients of CML, how many show the kind of osteosclerosis you see in the case. What is the explanation for osteosclerosis? But if you look at MF patients, most would have osteosclersosis. Also agnogenic myeloid metaplasia is seen. There is a high total leukocyte count which indicates an accelerated form of the disease. Therefore, I am not likely to say that this is only myelofibrosis, but surely it is not a garden variety of CML either. I am yet to see this kind of osteosclerosis in CML. If you look at the extensive myeloid metaplasia, it is seen more in MF than CML. It is described in CML, but not to this extent. So, I feel that this case is more like MF with extensive myeloid metaplasia.

Dr Gaurav: Just to add to what Dr Verma has said. It looks like MF considering the fact that Philadelphia chromosome was negative. pH negative or atypical transcripts with so much myelofibrosis is odd for CML. Overall picture, extensive myeloid metaplasia could cause the increase in total leukocyte count.

Dr Nandita Kakkar: This is an interesting case and we have seen a few such cases before as well. They were labeled as early cellular phase of MF with extensive myeloid metaplasia. One of them had a primary malignant pulmonary teratoma with yolk sac element. This degree of myeloid metaplasia can only be seen in MF.

Dr Pankaj Malhotra: There is no possibility of CML in this case. This is agnogenic myeloid metaplasia with accelerated phase. With this, we can explain all the things. Patient was nonresponsive to imatinib. This also goes against the diagnosis of CML. Treatment options for such patients include JAK2 inhibitor solitinib and HLA matched transplant.

Dr Neelam Verma: The clinical picture and hemogram looks like CML. To add to the confusion we have low LAP scores. But if you go back in literature, low LAP scores have been described in MF. High counts was a little red hearing here. Otherwise, the picture in todays world, if BCR-ABL is negative, it has to be something other than CML. JAK

2 is seen in 50 to 60% of primary MF. But it can also be negative in MF. Extensive myeloid metaplasia is typical of the disease. Overall, the primary possibility would be of accelerated phase of PMF.

COMMENTARY—INDEX CASE

Primary myelofibrosis (PMF)[1] is a myeloproliferative neoplasm arising from the neoplastic transformation of early hematopoietic stem cells. Older terms for this disorder include agnogenic myeloid metaplasia with myelofibrosis and chronic idiopathic myelofibrosis. The disorder is characterized by anemia, myelofibrosis, extramedullary hematopoiesis,[2] leukoerythroblastosis and hepatosplenomegaly. Extramedullary hematopoiesis is a response to the erythropoietic failure and mostly involves liver, spleen and lymph nodes. The peripheral smear shows anisocytosis, poikilocytosis, teardrop cells, nucleated red blood cells, and variable degrees of polychromasia. Marked leukocytosis (WBC >30,000/µl) and thrombocytosis (platelet count >500,000/µl) occurs in approximately 11 and 13% of patients, respectively at the time of diagnosis. Eight and 26% patients have leukopenia and thrombocytopenia, respectively. Immature cells including myeloblasts are seen. Myeloblasts are usually <5% of the total WBC count. The bone marrow in PMF is often difficult to aspirate, usually yielding a 'dry' tap. Megakaryocytes are often morphologically abnormal with both micro and macromegakaryocytes. Granulocytes may show hyperlobulation, and erythroid precursors may be normal or increased. Bone marrow biopsy is necessary to demonstrate fibrosis which is typically extensive. Bone marrow sinusoids are expanded and there is intravascular hematopoiesis. There is osteosclerosis with thickening and distortion of the bony trabeculae. In some patients, however, the bone marrow is markedly hypercellular with scant bone marrow fibrosis. This is called the cellular phase of PMF.[3] The diagnosis in this setting is made from the clinical and peripheral smear findings after chronic myeloid leukemia and polycythemia vera (PV) have been excluded.

There is no gold standard for diagnosing PMF, but criteria have been proposed by WHO in 2008.[4] The diagnosis requires fulfillment of all three major criteria and two minor criteria. These are:

Major Criteria

1. Presence of megakaryocyte proliferation and atypia, usually accompanied by reticulin and/or collagen fibrosis.
2. WHO criteria for PV, CML, MDS, or other myeloid neoplasm not met.
3. Demonstration of a clonal marker (e.g. JAK2 or MPL).

Minor Criteria

1. Leukoerythroblastosis
2. Palpable spleen
3. Anemia
4. Increased serum lactate dehydrogenase level.

Primary myelofibrosis must be distinguished from the other chronic myeloproliferative neoplasms that can be accompanied by substantial bone marrow fibrosis. These include CML, MDS and mast cell disease. Thus, a careful morphologic and cytogenetic examination is required before a diagnosis of PMF is made.

The index case was finally labeled as a case of PMF—cellular phase. A possibility of CML-MF was considered because of high total leukocyte count (>100,000/µl), massive splenomegaly, peripheral blood basophilia, low LAP scores and dwarf megakaryocytes in the bone-marrow. But BCR-ABL (common transcripts) and Ph chromosome were negative. There was also a lack of response to imatinib mesylate. But the presence of massive splenomegaly, extensive marrow fibrosis (grade 3) with osteomyelosclerosis and the extensive myeloid metaplasia, strongly favors a diagnosis of PMF. The BCR-ABL transcripts and Ph-chromosome are negative. JAK2 was negative in index case, but the frequency of positivity in PMF ranges from 43 to 63%. Low LAP score have been demonstrated in PMF rarely. The extensive degree of EMH seen in the index case is highly suggestive of a diagnosis of PMF. Besides the involvement of liver, spleen and lymph nodes, there was infiltration into the lungs, kidneys and perirenal fat as well. The lung infiltration is seen in form of interstitial expansion, infiltration of alveolar spaces and capillaries.[5] The involvement of alveolar spaces and perinephric fat are rare manifestation of myeloid metaplasia.[6]

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