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Myelofibrosis secondary to Hodgkin's lymphoma: A case report

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Abstract:

A 23-year-old male was misdiagnosed as a case of tubercular lymphadenitis based on fever with B-symptoms and finding of epithelioid granuloma on fine-needle aspiration of mesenteric lymph node and was started on antitubercular treatment from an outside hospital. Since the patient had progression of symptoms, we re-evaluated the case. Contrast-enhanced computed tomography showed multiple conglomerated necrotic cervical, peritoneal lymph nodes, hepatosplenomegaly, and multiple mixed sclerotic lytic lesions in multiple vertebral bodies and pelvis. An excision lymph node biopsy was suggestive of a nodular sclerosis variant of Hodgkin's lymphoma. A bone marrow study was performed subsequent to new-onset bicytopenia. Bone marrow aspiration was dry and bone marrow biopsy showed myelofibrosis. Thus, a diagnosis of myelofibrosis secondary to Hodgkin's lymphoma was made.

Keywords:

B-symptoms, generalized lymphadenopathy, Hodgkin's lymphoma, myelofibrosis

Introduction

Hodgkin's lymphoma is a rare disease with a prevalence of 0.98 per 1 lakh.[1] The exact etiology is unknown. There is a tendency for familial predisposition to Hodgkin's lymphoma.[2] There is a bimodal distribution with incidence rates in two peaks in the age groups of 15–34 years and older than 55 years.[3]

Myelofibrosis is characterized by intramedullary fibrosis and extramedullary erythropoiesis. Primary myelofibrosis is a clonal myeloproliferative neoplasm and affects middle aged. Secondary myelofibrosis is more common than primary and is seen with other myeloproliferative neoplasms, various leukemias, and rarely lymphoid neoplasms.[4]

Case Report

A 23-year-old male patient, a teetotaler and never smoker, had a history of fever – mostly evening rise of temperature, loss of weight, and appetite for 4-month duration and was evaluated for the same at an outside hospital. At the beginning of the illness, there was mild anemia, lymphopenia, and thrombocytosis. Liver enzymes were slightly increased. Alkaline phosphatase and gamma-glutamyl transferase levels were elevated [Table 1]. Contrast-enhanced computed tomography of the abdomen showed hepatomegaly with fatty infiltration of the liver and multiple discrete conglomerated mesenteric and retroperitoneal lymph nodes. Ultrasound-guided fine-needle aspiration cytology from the mesenteric lymph node was suggestive of epithelioid granuloma, negative for malignant cells and Ziehl–Neelsen staining. A possibility of abdominal Koch's was considered. He was started on antitubercular treatment with

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Table 1: Blood investigations

	Normal values	At the beginning of illness	Readmission with us (5½ months from symptom onset)					
			Day 1	Day 3	Day 5	Day 6	Day 7	Day 9
Erythrocyte sedimentation rate (mm/h)			68		65			43
Hemoglobin (g/dL)	14–18	11.8	4.9	7.5	5.7	4.6	6.6	6.7
Total leucocyte count (cells/mm^3)	4000–11,000	5100	3200	2000	1000	900	1000	500
Differential leucocyte count	$P_{40–60}$ $L_{20–40}$	$P_{78}L_{15}$	$P_{44}L_{41}$	$P_{41}L_{50}$	$P_{60}L_{30}$	$P_{39}L_{54}$	$P_{48}L_{50}$	$P_{20}L_{70}$
Platelets (cells/mm^3) (lakh)	1.5–4	6.16	1.7	1.5	1.6	1.5	1.2	1.5
Total bilirubin (mg/dL)	0.1–1.2	0.3	7.8	12.2	10	8.6	17.1	12.7
Direct bilirubin (mg/dL)	0–0.3	0.1	4.4	6.8	5	4.3	10.7	6.6
Indirect bilirubin (mg/dL)	0.1–0.9	0.2	3.4	5.4	5	4.3	6.4	6.1
Alanine aminotransferase (U/L)	<50	64	20	75	89	48	44	35
Aspartate aminotransferase (U/L)	<50	71	21	62	120	75	56	50
Alkaline phosphatase (U/L)	<150	1230	624	1440	1920	2215	2024	1995
Gamma-glutamyl transferase (U/L)	5–40	169		197			277	
Total protein (g/dL)	6–8	8.1	6.8	4.8	4.3	5.1	4.9	5
Serum albumin (g/dL)	3.5–5.5	4.3	3.8	2.6	2.7	3	2.9	3
Serum globulin (g/dL)	2–3.5	3.8	3	2.2	1.6	2.1	2	2
Urea (mg/dL)	5–20	32	34	71	68	42	53	36
Creatinine (mg/dL)	0.7–1.4	0.8	1	1.1	0.9	1.1	0.9	1.08
Uric acid (g/dL)	3.5–7	4	5.3	4.1	2.5	4.2	3.3	2.3
Calcium (mg/dL)	8.5–10.5	9.5	11	12.5	11.8	12.5	10.6	9.5
Phosphorus (mg/dL)	3.4–4.5	4	6.5	4.6	4.8	4.8	4.0	4.7
Prothrombin time (s)					16 (10–14 s)			
INR					1.1 (<1)			
Activated partial prothrombin time (s)					34 (21–35)			
Angiotensin-converting enzyme (ng/dL)					105 (normal<40 mg/dL)			
Direct Coombs test					Negative			
Human immunodeficiency virus					Nonreactive			
Hepatitis B and C					Nonreactive			
VDRL					Negative			
Epstein–Barr virus					Negative			
Antinuclear antibody					Negative			
Mantoux test					Negative			
Vitamin D levels (ng/mL)					15 (30–60)			
Parathyroid hormone (pg/mL)					8 (10–65)			

INR=International normalized ratio, VDRL=Venereal disease research laboratory

rifampicin, isoniazid, pyrazinamide, and ethambutol. However, the patient did not have any improvement in his symptoms despite receiving an intensive phase of antitubercular treatment for a total of 3 months. Multiple blood transfusions were given during this period in view of anemia, but no hemogram reports were available. He was then referred to our center. On admission and examination, he had pallor, icterus [Figure 1], generalized lymphadenopathy, and hepatosplenomegaly. There were multiple enlarged nontender, rubbery cervical, axillary, and inguinal lymph nodes, and a few of the cervical lymph nodes were matted. The rest of the system examination was normal. The blood investigation reports showed anemia, leukopenia with lymphocytosis, and direct hyperbilirubinemia with elevated alkaline phosphatase [Table 1]. The erythrocyte sedimentation rate was 68 mm at the end of 1st h. Peripheral blood smear showed normocytic normochromic red blood cells with few microcytes. White blood cells showed leukopenia and were negative for malignant cells. Antitubercular treatment was modified in view of jaundice. Packed red blood cells were transfused. A detailed family history revealed the death of two of his brothers and a sister in their second decade, and both the brothers had similar complaints and were diagnosed to have some hematological malignancies, but no records were available.

Contrast-enhanced computed tomography of the chest and abdomen showed multiple conglomerated necrotic cervical, intra- and retroperitoneal lymph nodes but no mediastinal lymph nodes [Figure 2a and b], hepatosplenomegaly, and mixed lytic sclerotic lesions involving multiple vertebral bodies and bilateral iliac blades [Figure 2c]. Cervical lymph node excision biopsy was done. Jaundice deepened, there was a marked elevation in serum alkaline phosphatase. He started to run fever on day 3; a repeat hemogram showed

leukopenia with neutropenia (absolute neutrophil counts – 820 cells/mm^3) [Table 1]. Antibiotics were upgraded in view of febrile neutropenia. Despite treatment, there was a fall in hemoglobin and total leukocyte counts. Antifungals were added to the therapeutic regimen in view of the febrile illness.

Bone marrow studies were done, and aspiration was dry. A liver biopsy was planned, but the same was deferred by the patient. Packed red blood cells and platelet transfusions were given. Excision biopsy of the cervical lymph node showed a nodular growth pattern with fibrocollagenous bands surrounding some of the nodules [Figure 3a], Reed–Sternberg cells [Figure 3b], and lacunar cells [Figure 3c], which were seen in a mixed inflammatory background with lymphocytes, plasma cells, and eosinophils. These were suggestive of a nodular sclerosis variant of Hodgkin's lymphoma. Immunohistochemistry was positive for CD30 [Figure 3d] and PAX5 [Figure 3e] in tumor cells. Immunohistochemical staining was negative for CD45, CD15, CD3, and CD20 in tumor cells. Cytokeratin and vimentin staining were also negative. Thus, a nodular sclerosis variant of Hodgkin's lymphoma was made. CBNAAT from lymph node biopsy was negative. He was referred to an oncology center and was planned for the initiation of chemotherapy. However, his general condition worsened, developed bilateral pneumonia with type 1 respiratory failure and septic shock, and succumbed to death. Bone marrow biopsy reports (collected posthumous) showed diffuse fibrosis in bony trabeculae enclosing marrow spaces. There was no invasion by lymphoma cells. This was suggestive of myelofibrosis [Figure 4]. There were no granulomas or malignant cells, and AFB stain was negative. Thus, a diagnosis of myelofibrosis secondary to Hodgkin's lymphoma was made.

Figure 1: Icterus in the patient

Discussion

Fever, night sweats, and weight loss (more than 10% of total body weight over a 6-month period) are referred to as "B-symptoms." These are associated with 40% of Hodgkin's lymphoma cases and are significant in staging and prognosis of the disease.[5]

This case had generalized lymphadenopathy with B-symptoms. Hypercalcemia, elevated serum alkaline phosphatase, gamma-glutamyl transferase, and fine-needle aspiration cytology finding of epithelioid granuloma were the other leading clues. Computed tomography of the chest and abdomen showed multiple conglomerated necrotic bilateral cervical, retro- and intraperitoneal lymph nodes with hepatosplenomegaly and mixed sclerotic and lytic lesions in the vertebra and pelvis.

Tuberculosis, lymphoproliferative neoplasms, and sarcoidosis were the differential diagnoses considered. All the three granulomatous diseases can be associated with hypercalcemia and cholestatic jaundice Cholestatic jaundice can be the sign of granulomatous hepatitis seen in association with the above diseases.

Mediastinal lymphadenopathy is seen in 75%–90% cases of sarcoidosis, 80% cases of lymphoma and 10% of nodal tuberculosis at the initial presentation.[6-8] Mediastinal lymphadenopathy was absent in this case.

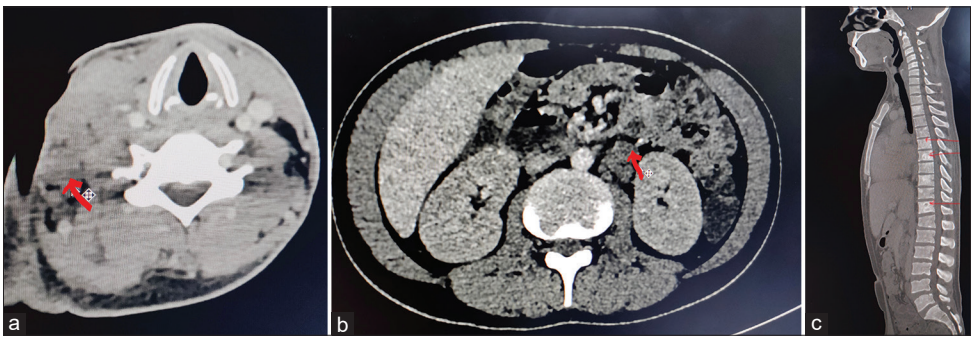

Figure 2: (a) CT scan of the neck showing cervical lymphadenopathy (red arrow), (b) CT scan of the abdomen showing abdominal lymphadenopathy (red arrow), (c) CT scan showing multiple lytic lesions on vertebral bodies (red arrows). CT: Computed tomography

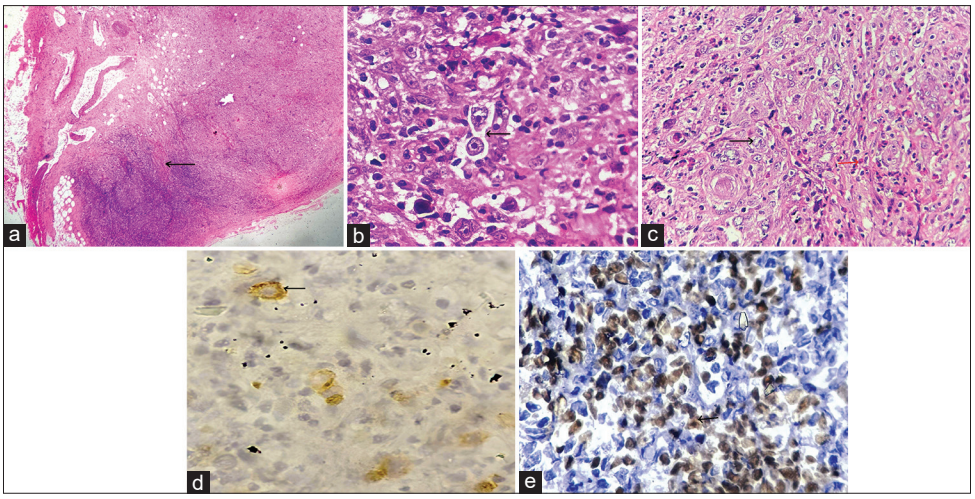

Figure 3: (a) Cervical lymph node biopsy showing nodules and fibrocollagenous bands (black arrow) separating them on H and E staining, (b) lymph node biopsy showing two mononuclear Reed–Sternberg cells (Black arrow), (c) lymph node biopsy showing lacunar cells (black arrow) in an inflammatory background of eosinophils (red arrow) predominantly, (d) immunohistochemistry of lymph node showing CD30 positivity in tumor cells, (e) immunohistochemistry of lymph node biopsy showing PAX5 positivity in tumor cells

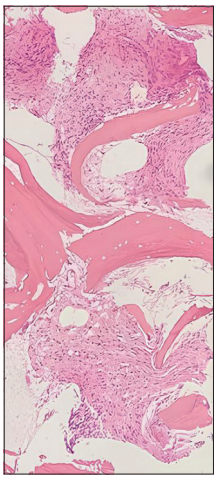

Figure 4: Bone marrow biopsy showing marrow spaces enclosed by dense fibrosis

Conglomerated necrotic lymph nodes are common in tuberculosis and lymphomas. Only rare cases of sarcoidosis exhibit extensive necrosis in lymph nodes.[9]

The ancillary findings in this case were many, and we worked up for them before proceeding with invasive procedures. Hypercalcemia in granulomatous diseases is usually mediated by Vitamin D. However, Vitamin D levels and serum parathyroid hormones were low. Parathyroid hormone-related peptide assay was not available.

Lytic vertebral lesions can cause hypercalcemia. Hypercalcemia in turn serves as a negative feedback loop and decreases the parathyroid hormone secretion. Such lesions are rare but can be seen in lymphoma and very rarely with sarcoidosis.[10] Although considered rare, a collation of large case series showed that 10%–15% of Hodgkin's lymphoma cases have radiographic evidence of secondary skeletal lesions at autopsy.[11]

Raised alkaline phosphatase levels were then worked upon. Alkaline phosphatases are found in different body tissues. More than 80% of the serum alkaline phosphatase is released from the liver and the bone. The sources of raised alkaline phosphatase in this case could be the following;

a. Bone isoenzyme (in view of raised serum calcium and lytic bone lesions)
b. Liver isoenzyme (due to worsening cholestasis with elevated gamma-glutamyl transferase levels)
c. Regan isoenzyme – rare variant of placental alkaline phosphatase (seen in association with various tumors including Hodgkin's lymphoma).[12]

Worsening cholestasis in the absence of any lymph nodes at porta hepatis raised a possibility of granulomatous hepatitis. However, we could not proceed with a liver biopsy as a negative consent was given by the patient.

A serum angiotensin-converting enzyme assay was done as sarcoidosis was one among the differential diagnosis. Although commonly associated with sarcoidosis, an elevated ACE level can also be seen in cases of military tuberculosis and lymphoma.[13,14] ACE is involved in the control of cellular proliferation. In a study by Koca *et al*., ACE staining was positive in histiocytes and vascular endothelium of tissues involved in Hodgkin's lymphoma.[15]

Noninvasive investigations did not resolve the dilemma and hence a tissue biopsy was needed to make a definitive diagnosis. An excision biopsy of the cervical lymph node was done as fine-needle aspiration can cause architectural distortion. Lymph node biopsy showed a nodular sclerosis variant of classical Hodgkin's lymphoma. The diagnosis of nodular sclerosis variant of Hodgkin's lymphoma

requires (a) nodular growth pattern, (b) broad fibrotic bands surrounding the nodules, and (c) lacunar cells Reed Sternberg cell variant with clear cytoplasm and sharply demarcated cellmembranes). Immunohistochemistry was positive for CD30 and PAX5. CD30 is expressed in nearly all cases of classical Hodgkin's lymphoma, whereas CD15 is found only in 75%–85% of cases.[16]

Vimentin is a cytoskeletal protein and is expressed in mesenchymal cells. However, it is overexpressed in various epithelial cancers including carcinomas of prostate, breast, gastrointestinal tract, lung, and malignant melanomas.[17] Cytokeratin stain was also negative (overexpressed in epithelial cell cancers). Thus, a possibility of secondary metastasis to the cervical lymph nodes was ruled out.

The absence of caseation necrosis, a negative cartridge-based nucleic acid amplification test for tuberculosis, and nonresponsiveness to antitubercular treatment ruled out coexisting tuberculosis.

Bone marrow studies done in view of bicytopenia were suggestive of myelofibrosis with no invasion by lymphoma cells. Thus, a diagnosis of myelofibrosis secondary to Hodgkin's lymphoma was kept.

Bone marrow involvement in Hodgkin's lymphoma is rare and is seen in 5%–14% of such cases.[18] Most cases with myelofibrosis secondary to Hodgkin's lymphoma are elderly with absent peripheral lymphadenopathy. Male gender, subdiaphragmatic lymphadenopathy, hepatosplenomegaly, and B-symptoms can all be associated with bone marrow involvement (as in this case). Direct invasion of bone marrow by lymphoma cells is rare. Reed–Sternberg cells are not seen on bone marrow biopsy. However, intramedullary fibrosis is seen, and these get reversed once Hodgkin's lymphoma gets treated.[19] In lymphomas, immune-mediated paraneoplastic syndromes are common and include autoimmune-mediated cytopenias.[20] No serological markers of autoimmunity was present in this case.

In a series[4] of seven cases of myelofibrosis secondary to Hodgkin's lymphoma, five had a classical variant of the disease (nodular sclerosis – 3, lymphocyte depleted – 1, and mixed cellularity – 1). Four of them had invasion of the marrow by lymphoma cells. All of them were subjected to chemotherapy and had a median time of survival between 3 months and 11 years.

Intramedullary fibrosis is mediated through cytokines produced by abnormal megakaryocytes and leukocytes in primary myelofibrosis. In myelofibrosis secondary to Hodgkin's lymphoma, platelet-derived growth factor produced by monocytes and transforming growth factor produced by T-lymphocytes drives the process.[21,22] Platelet-derived growth factor induces fibroblast proliferation and transforming growth factor induces synthesis of extracellular matrix proteins.[23]

Anemia is the most common and thrombocytopenia is the least common manifestation in myelofibrosis secondary to Hodgkin's lymphoma. Leukoerythroblastic picture is not seen in peripheral blood smear in such cases unlike primary myelofibrosis.[19]

Treatment for primary myelofibrosis ranges from careful follow-up of cases in asymptomatic cases to hematopoietic stem cell transplant in advanced cases with profound cytopenias. Contrary to this, myelofibrosis secondary to Hodgkin's lymphoma is reversible with remission of lymphoma.[19]

Conclusion

Fever with B-symptoms and an epithelioid granuloma (especially if obtained on fine-needle aspiration) needs further evaluation to pinpoint a diagnosis.

Although uncommon, bone marrow involvement can be seen in Hodgkin's lymphoma.

A bone marrow biopsy is warranted in all cases of Hodgkin's lymphoma with cytopenias and progressive systemic symptoms and also in the elderly.

Ethical considerations

the ethical clearance was obtained from the institutional committee and patient declaration was obtained and the same had been mentioned.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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