Case Report

Hodgkin's Disease with Hyperferritinemia, Hepatic and Heart Failure

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ABSTRACT

Diffuse hepatic infiltration is an unusual form of Hodgkin's disease (HD). Its manifestation as progressive hepatitis or with hepatic failure is even rarer and can be difficult to diagnose. We aim to describe an unusual case of liver failure due to HD.

A middle-aged woman with a 10 month history of daily febrile episodes, constitutional symptoms and strikingly high levels of serum ferritin was admitted to our hospital with pancytopenia and jaundice. The patient rapidly deteriorated, and developed hepatic and heart failure. A liver biopsy revealed infiltration of the liver with mixed cellularity type HD that was confirmed by lymph node biopsy.

HD must be considered in the differential diagnosis of obstructive jaundice in adults. Liver biopsy early in the course of liver dysfunction may establish this diagnosis without a higher risk of bleeding complications seen once liver failure sets in.

Keywords: Hodgkin's disease; Hepatic failure; Heart failure; Ferritin

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INTRODUCTION

Hodgkin's disease (HD) sometimes can present as fever of unknown origin. Febrile cholestatic disease is a rare initial presentation of HD.(1-8), We, herein, report an unusual presentation of HD in whom the presence of cholestasis deteriorated into the development of hepatic and heart failure. This led to a liver biopsy and subsequent diagnosis of HD. Also discussed are the challenges of the diagnostic workup and treatment.

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CASE REPORT

A 38-year old female with an unremarkable past medical history presented with fever, constitutional symptoms and 12 kg weight loss during the previous 10 months. She was referred because of the continuance of her symptoms despite various antibiotic therapies and the recent development of jaundice. There was no history of intravenous drugs or hepatotoxic substance abuse. Her mother died from lung cancer and her father from laryngeal cancer. She had undergone extensive infectious disease work-up, computed tomography (CT) scan of the chest, abdomino-pelvic ultrasonography, technetium whole body scan, and upper and lower gastrointestinal endoscopy; all of which were completely normal. The patient underwent a bone marrow biopsy which was compatible with reactive/infectious marrow (Fig. 1).

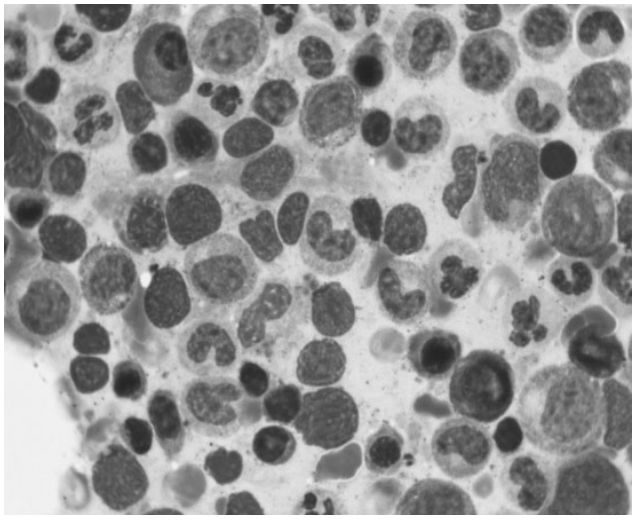

Fig 1. Bone marrow biopsy specimen showing red cell hypoplasia, mild eosionophillia and granulocyte hyperplasia with toxic granulation and mild lymphoplasmocytosis compatible with reactive/infectious marrow.

Laboratory studies were within appropriate reference ranges with the exception of an elevated erythrocyte sedimentation rate (ESR>100 mm in 1 h), lactate dehydrogenase and serum ferritin levels. Laboratory test results before and during hospitalization are shown in Table 1.

Blood studies showed normocytic anemia. Serum protein electrophoresis and immunoelectrophoresis showed low levels of total protein and albumin. Despite all the above mentioned studies, no explanation was found for her symptoms.

On admission, her oral temperature was 39°C, pulse 100/min and she was jaundiced. The remainder of the examination was unremarkable. Initial labs were significant for mildly elevated transaminases, direct hyperbilirubinemia and pancytopenia with normocytosis, which resolved spontaneously after 5 days. Over the next several days following admission, she became more icteric and progressed to subfulminant liver failure, associated with grade I-II encephalopathy and coagulopathy. Echocardiogram was normal. CT scan of the abdomen and pelvis detected mild heterogenecity of the liver, with normal-appearing intra- and extrahepatic bile ducts. Magnetic resonance cholangiopancreatography (MRCP) was also normal. The patient underwent a needle biopsy of the liver. Upper cuts of the abdominal CT showed left axillary lymphadenopathy whilst a previous CT scan of the thorax was reported to be normal in another center. Upon further review of this CT scan, a suspicious soft tissue mass in the left axilla was noted (Fig. 2). Since no superficial lymphadenopathy was palpable, a diagnostic exploratory excisional lymph node biopsy via guide wire marking was performed. Histopathological examination revealed HD of mixed cellularity type with involvement of the lymph nodes and liver (Fig. 3). About 2 weeks after her admission, the patient developed symptoms of heart failure in the form of tachycardia, gallop rhythm, tachypnea, pulmonary rales and hypotension. Chest radiography was consistent with interstitial pulmonary edema. Repeated transthoracic two-dimensional echocardiograms revealed depressed left ventricular function with an ejection fraction of 30-35% and a mild-sized pericardial effusion. Electrocardiograms showed only sinus tachycardia and cardiac enzymes were normal.

The final diagnosis was advanced mixed cellularity type

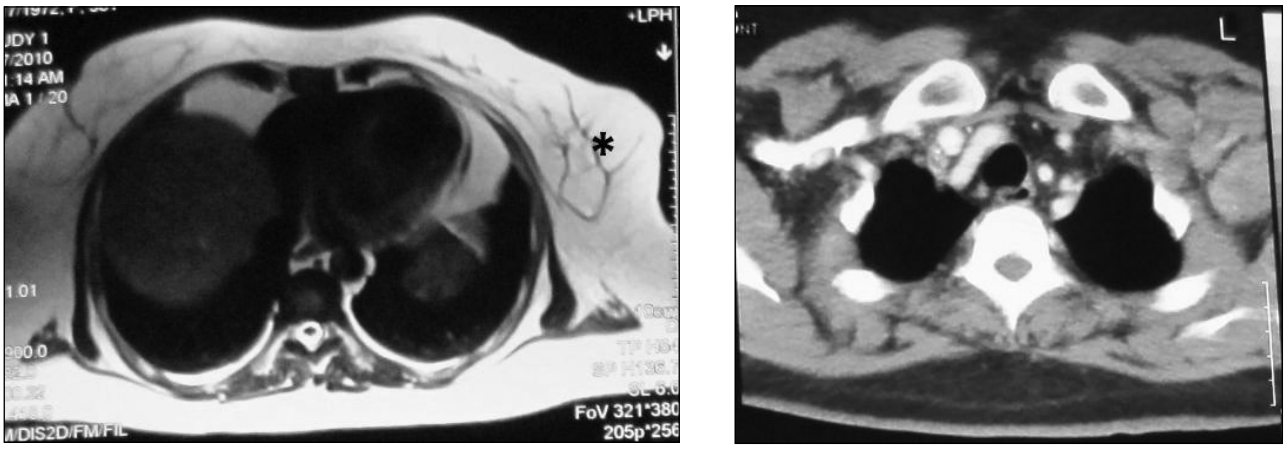

Fig 2. Contrast enhanced computed tomography scan of upper abdomen (A), and chest(B) showing left axillary lymphadenopathy (star).

Table 1. Laboratory testing of the patient before and during hospitalization

Parameters studied (normal values)			value
Cr (mg/dl)			1
T3(0.4 – 1.82 ng/dl)			8.4
T4 (4.5 – 11.2 µg/dl)			1.2
TSH(0.4 – 4.2 mIU/ml)			2.5
β2-microglobulin (0.9 - 2 mg/dl)			2.31
Lactate dehydrogenase (207–414 IU/L)			538
Serum ferritin levels (8.9–233.7 nmol/l)			2961.5 - 14268.5
Total protein (60-78 mol/l)			36
Albumin (36-48 mol/l)			16.3
Autoimmune studies	direct and indirect Coombs		NL
	rheumatoid factor		
	antinuclear antibody		
	antismooth muscle antibody		
	antimitochondrial antibody		
	perinuclear antineutrophil cytoplasmic antibody (p-ANCA)		
	anti-LKM antibody		
Tumor markers	α-fetoprotein		NL
	carbohydrate antigen 19-9		
ESR (mm in 1 h)			>100
	Before admission	**At admission**	**During hospitalization**
Hb (g/dl) [MCV(fl), MCH (pg)]	11.9 [81, 26.3]	3.9 [85.2, 23.6]	9.1 [85.7, 27.7]
WBC (10^3/µL)	12	3.1	12.5
PLT (10^3/µL)	370	100	367
AST (<31 IU/l)	32	76	31
ALT(<31 IU/l)	30	87	30
ALP (64–240 IU/l)	337	1065	930
Total. bilirubin (0.2–1.2 mg/dl)	1.5	6	17
Direct. bilirubin (\0.2 mg/dl)	0.2	3.6	12.9
γGT (>38 IU/l)	-	190	-

Cr, Creatinine; T3, Triiodothyronine; T4, Total thyroxine; TSH, Thyroid stimulating hormone; ESR, Erythrocyte sedimentation rate; Hb, hemoglobin; MCV, Mean corpuscular volume; MCH, Mean corpuscular hemoglobin; WBC, White blood cell count, PLT, platelets count; AST, aspartate transaminase; ALT,alanin transaminase ; ALP, alkaline phosphatase ; γGT, γglutamyl transpeptidase.

HD (clinical stage IV B) and the patient was referred for chemotherapy. Since adriamycin is excreted via the biliary tract, a combination chemotherapy which included vincristine, bleomycin, cyclophosphamide and prednisone was started instead of the ABVD regimen. Unfortunately, no response to therapy was achieved. The patient's liver function tests deteriorated, hepatic encephalopathy progressed and fulminant hepatic failure occurred. The patient was transferred to the intensive care unit for supportive care, but despite these interventions the patient died. A request for autopsy was declined by the family.

DISCUSSION

We presented a case in which prolonged fever, nonspecific symptoms and strikingly high levels of serum ferritin preceded the presentation of hepatic and cardiac failure. Her final diagnosis was HD as evidenced by liv-

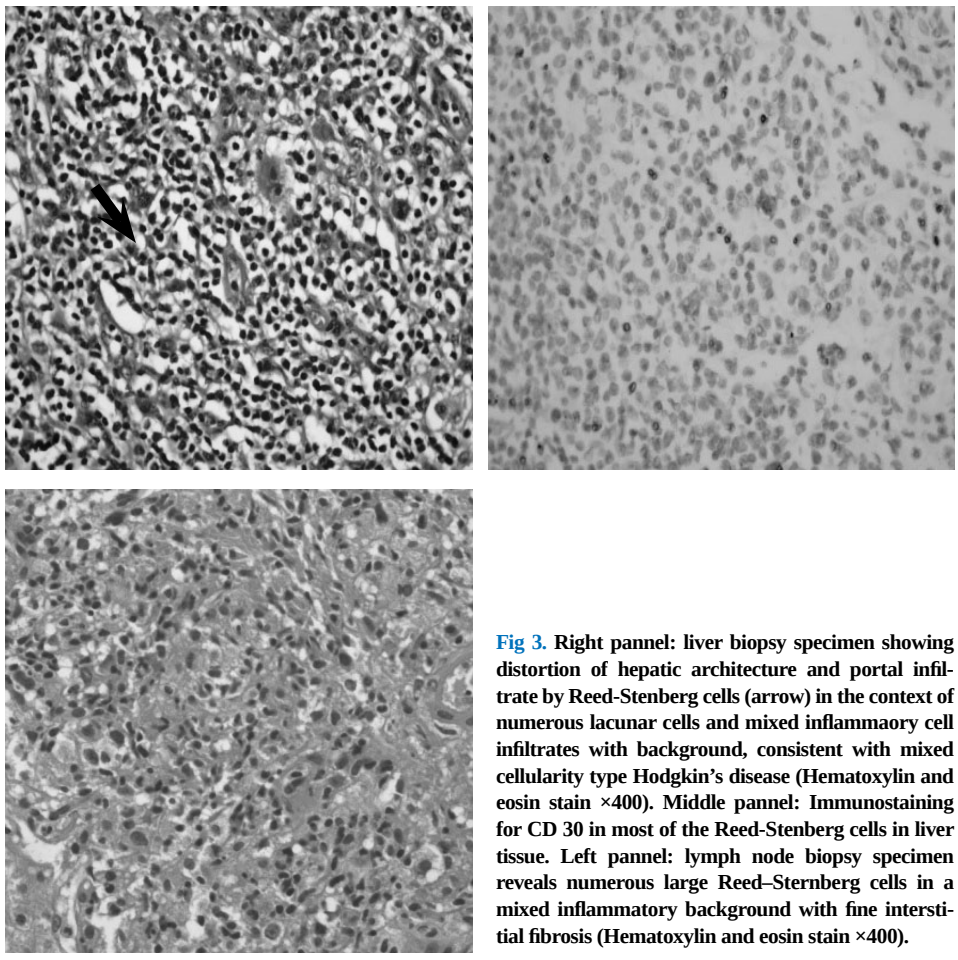

Fig 3. **Right pannel: liver biopsy specimen showing distortion of hepatic architecture and portal infiltrate by Reed-Stenberg cells (arrow) in the context of numerous lacunar cells and mixed inflammaory cell infiltrates with background, consistent with mixed cellularity type Hodgkin's disease (Hematoxylin and eosin stain ×400). Middle pannel: Immunostaining for CD 30 in most of the Reed-Stenberg cells in liver tissue. Left pannel: lymph node biopsy specimen reveals numerous large Reed–Sternberg cells in a mixed inflammatory background with fine interstitial fibrosis (Hematoxylin and eosin stain ×400).**

er and lymph node biopsies. The case described above was interesting in that it was diagnosed by liver involvement of HD.

Although liver infiltration in the advanced stages of HD is common (up to 60% postmortem), only 5%-14% of patients have liver involvement at presentation, depending on the method of sampling and the sample size (1, 9, 10). Jaundice is a rare initial presentation of HD and febrile cholestatic liver disease as a first symptom is unusual (1). Cholestasis in HD can be the result of parenchymal infiltration by the tumor, extrahepatic obstruction (9), paraneoplastic (8), or vanishing bile duct syndrome (4). Parenchymal infiltration is the most common underlying mechanism which is more common in the aggressive types of HD such as mixed cellularity and lymphocytic depletion (11). In our case, the mechanism of liver injury was parenchymal infiltration, manifested as increased transaminase activity with intra-hepatic cholestasis. It is distinctly uncommon for acute liver failure to be the initial manifestation of a malignant process with hematological malignancies, especially non-Hodgkin lymphoma being the most common etiology (7). Several mechanisms have been reported to be involved in hepatic failure caused by lymphoma, including tumor infiltration of the intrahepatic bile ducts, vasculature or parenchyma (7). A few patients have been described without other diagnostic features of the disease, in whom the presence of liver enlargement, cholestasis, or hepatic failure led to a liver biopsy and the subsequent diagnosis of HD (1, 2, 6, 12). In the only published series of 421 HD patients, 6 initially had cholestasis (with frank jaundice being noted in 4) and fever with no peripheral adenopathies, of whom only 3 patients were younger than 40 presented with primary liver involvement (3). It is also of note that in 3 of the 6 patients, HD was apparently limited to the liver (1).

Although cardiac involvement by malignancy is relatively common, it is unusual to be detected premortem. In large autopsy studies, involvement by malignant lymphoma has been reported to account for up to 17% of the total metastases from malignant neoplasms to the heart (13), and 16%–26% of patients dying from lymphoma are found to have mostly minor cardiac involvement (14).Primary cardiac lymphoma is exceedingly rare, accounting for 1% of primary cardiac tumors. The histology of these tumors is usually diffuse large B cell type non-Hodgkin lymphoma (14). Amirimoghaddam et al.(15) have reported a case of cardiac involvement by nodular sclerosing type HD presenting with heart failure and involvement of the bone marrow and cervical lymph node. Pericardial effusion is the most common echocardiographic findings in cardiac metastasis (13-15).It may be difficult to determine whether the heart failure in this patient was secondary to the underlying malignancy or another cause such as ischemia or myocarditis. The lack of electrocardiographic changes and normal cardiac enzymes was not compatible with myocarditis or an ischemic cause of heart failure in our case. Chronic tachycardia can result in reduction in myocyte contractility and impressive left ventricular dilatation, but cardiomyopathy has been reported in patients with chronic supraventricular tachycardias with ventricular rates of 130 to 200 beats/minute (16).

Despite advances in knowledge and development of many new diagnostic techniques, making a diagnosis of hepatic infiltration by HD in patients presenting with liver failure is generally difficult. However, early diagnosis is very important because quick institution of specific chemotherapy could reverse the liver disease (5). In the presence of lymphadenopathy, enlarged liver and high lactate dehydrogenase, lymphoma should be taken into consideration. However, as with our case, preceding findings such as prolonged fever, constitutional symptoms, hyperferritinemia, hematological abnormalities, altered acute phase reactants or pancytopenia may be seen in a number of primary liver diseases or other alternative diagnosis such as infection, acute hepatitis, hemophagocytic syndrome and adult onset Still's disease (AOSD), all of which can complicate diagnostic evaluation. Pancytopenia should alert the clinician to consider hemophagocytosis, however hemophagocytosis in the biopsy (bone marrow, lymph nodes, liver or spleen) is a prerequisite for diagnosis (17). Liver enlargement is present in almost 80% of patients with hepatic involvement of lymphoma. Common patterns are solitary or multiple discrete masses , and diffuse infiltration is rare and more common in the Chinese population (18).Ultrasonography and CT seem to be inadequate for the diagnosis and the technetium scan showed no focal uptake of tracer, despite literature supporting its use in lymphoma staging (19). In those patients with jaundice, cholestasis, transaminitis and/or coagulopathy upon diagnosis of HD, we stress the importance of pretreatment liver biopsy, specially for patients with evidence of persistent cholestasis of 1 month or longer. However, the diagnosis of HD in a liver biopsy is difficult due to the small size of the specimen and scarcity of the diagnostic Reed-Sternberg cells or its variants. Only 5% of samples taken by percutaneous liver biopsy display histologic changes consistent with tumor involvement, but a twofold increase is registered when peritoneoscopy-guided biopsy is performed, especially in presence of gross abnormalities on the liver surface (20). In our subject, Reed-Sternberg cells demonstrated by careful search in multiple sections of Liver biopsy specimen.

The prognosis for patients with liver disease as the initial manifestation of HD is generally poor (1, 3, 6) but not the rule, since some case reports show favorable response to chemotherapy (2, 8). Studies have demonstrated that lymphoma patients with cardiac involvement identified early were treated successfully (15, 21). Our patient was classified as stage IV, because of diffuse liver and probable cardiac involvement. In her case, it would be expected that she have a remission rate of over 50% and a 5-year survival rate of around 25% (22). Standard chemotherapy can be challenging with hepatic and cardiac dysfunction, and substantial dose reduction may be required(23). We believe such cases will help to establish the best approach to this very rare entity.

This case emphasizes the broad clinical spectrum with which HD can present and highlights the need to consider this diagnosis early with unexplained liver failure, especially with persistent fever. If the clinical picture is suspicious for HD, a liver biopsy should be attempted as soon as there is evidence of hepatitis, because rapid progression can cause fulminant hepatic failure and refractory coagulopathy with bleeding complications. Furthermore, early detection and timely initiation of appropriate combination chemotherapy can improve survival (15).

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