Case Report

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Diving Deep into Diagnosis: Unveiling High Grade B-cell Lymphoma

Internal Medicine Section

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ABSTRACT

The term "lymphoma" comprises a heterogeneous group of biologically and clinically distinct neoplasms that arise from cells in the lymphoid organs. Based on the identification of Reed-Sternberg cells (RS cells), it is divided into Hodgkin and Non-Hodgkin's Lymphoma (NHL). Lymphadenopathy is a common presenting feature of lymphoma. Extranodal involvement may show gastrointestinal, cutaneous, neurological, or other symptoms. Hereby, the authors present a case report of 76-year-old male with non-Hodgkin's lymphoma whose symptoms were masked by the abdominal pain of emphysematous pyelonephritis. Although the infection was treated, the patient continued to complain of dull, aching, persistent abdominal pain. As a result, the patient underwent additional radiological examinations, including a contrast-enhanced Computed Tomography (CT) scan of the abdomen-pelvis, which disclosed multiple lymphadenopathies. Hence, an endoscopic ultrasound-guided biopsy was performed from the lymph node between the portal vein and inferior vena cava, revealed High-grade B-cell Lymphoma (HGBL). The prognosis for HGBL with double- and triple-hit lymphomas is extremely bad. The patient that came to us had an early diagnosis of HGBL, which led to a favourable prognosis, in contrast to most cases of the disease, which usually manifest late in the course and are linked with a very grave prognosis.

Keywords: Emphysematous pyelonephritis, Lymphadenopathy, Non-Hodgkin's lymphomas

CASE REPORT

A 76-year-old male, who has been taking medication for type 2 diabetes for five years, presented with complaints of diffuse abdominal pain for 12 days, high-grade continuous fever with chills, and burning micturition for five days. He further reported a weight loss of about 5 kg over the past three months.

On general physical examination, the patient was febrile with a temperature of 101 degrees Fahrenheit and a pulse rate of 120 beats/min. There was no palpable cervical, axillary, or inguinal lymphadenopathy. There was no icterus, cyanosis, or pedal oedema. On systemic examination, the abdomen was diffusely tender without any organomegaly or free fluid.

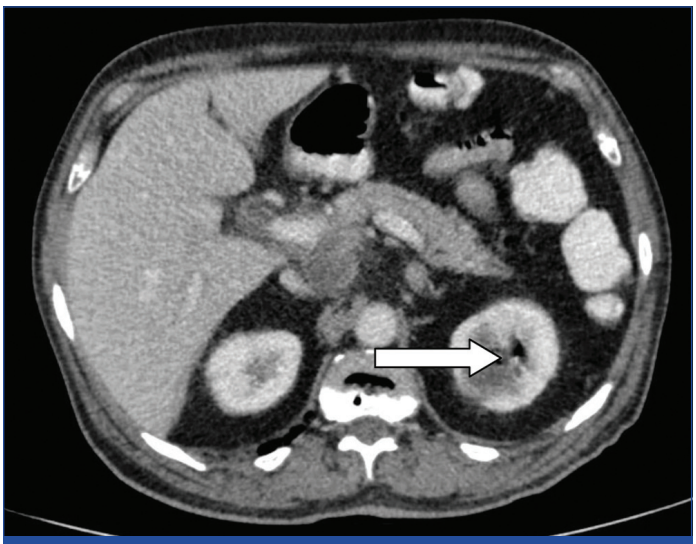
Increased white blood cells with a neutrophilic preponderance were found in the complete blood count. Urine routine microscopy revealed 80-90 pus cells, 8-10 red blood cells, trace protein, and the presence of glucose. Fasting and post-prandial plasma glucose were elevated with an Glycated Haemoglobin (HbA1c) of 8.9%. The urine protein creatinine ratio was 1.01, indicating moderate proteinuria. C-reactive protein, serum procalcitonin, and D-dimer were raised [Table/Fig-1].

Parameters	Laboratory values	Normal values
Haemoglobin (g/dL)	12 g/dL	13.2-16.6 g/dL
Total leukocyte count (cells/cumm)	13000/cumm	4000-10000/cumm
Platelet count (cells×106/µL)	2.13×106/µL	4.35-5.65×106/µL
Serum urea (mg/dL)	35 mg/dL	17-49 mg/dL
Serum creatinine (mg/dL)	1.17 mg/dL	0.6-1.35 mg/dL
Fasting plasma glucose (mg/dL)	150 mg/dL	<100 mg/dL
Postprandial plasma glucose (mg/dL)	226 mg/dL	<140 mg/dL
Urine protein creatinine ratio	1.01	0.2
Urine routine microscopic examination	Protein-trace Glucose-2+ Pus cells- 80-90/hpf RBCs- 8-10/hpf	Protein-absent Glucose-absent Pus cells- 0-5/hpf RBCs- 0-2/hpf
Total serum bilirubin (mg/dL)	1.69 mg/dL	0.22-1.20 mg/dL
Direct bilirubin (mg/dL)	0.60 mg/dL	<0.5 mg/dL
AST (IU/L)	19 IU/L	8-48 IU/L
ALT (IU/L)	25 IU/L	7-55 IU/L
ALP (IU/L)	131 IU/L	40-129 IU/L
HbA1c (%)	8.90%	<5.7%
Total protein (g/dL)	7.20 g/dL	6.4-8.3 g/dL
Serum albumin (g/dL)	3.7 g/dL	3.5-5.2 g/dL
Albumin:globulin ratio	1.06	1.1-2.5
ESR (mm/hr)	95 mm/hr	<20 mm/hr
CRP mg/dL	10 mg/dL	<0.3 mg/dL
Procalcitonin (ng/mL)	5 ng/mL	<0.08 ng/mL
D-dimer (ng/mL)	>10000 ng/mL	0-500 ng/mL
HIV antibody	Negative	
Hepatitis B antibody	Negative	
Anti-hepatitis C antibody	Negative	
Culture report	*Escherichia coli* >105/mL colony forming units	

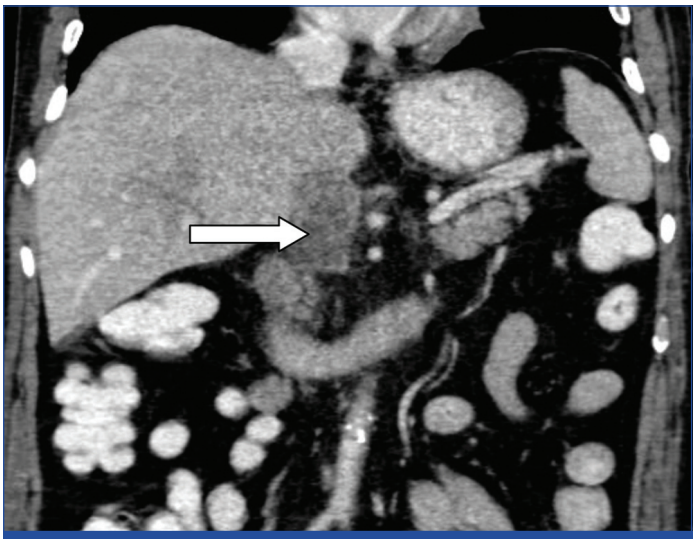
[Table/Fig-1]: Laboratory investigations.
RBC: Red blood cells; AST: Asparate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; ESR: Erythrocyte sedimentation rate; CRP: C-reactive reactive protein; HIV: Human immunodeficiency virus

A Ultrasonography (USG) of the abdomen and pelvis showed a few air foci in the left kidney's lower pole calyces, suggestive of emphysematous pyelonephritis with periportal and peripancreatic lymphadenopathy. The urine culture report showed *Escherichia coli* with >105/mL colony-forming units. As per the culture sensitivity, the patient was treated with i.v. injections of piperacillin-tazobactam for 21 days and amikacin for seven days, based on creatinine clearance. The patient no longer had a fever or burning micturition, but he continued to report diffuse abdominal pain. A CT scan of the abdomen and pelvis showed left renal calculi (16×11 mm in size) with air foci in the collecting system, suggestive of emphysematous pyelonephritis. Retroperitoneal necrotic lymphadenitis was observed in the peripancreatic, periportal, and para-aortic regions, with the largest lymph node measuring 4×5 cm, causing mass effect and

compression of the lower common bile duct and dilatation of the intrahepatic biliary radicles [Table/Fig-2,3]. The differential diagnoses given were tuberculosis and metastatic lymphadenopathy.

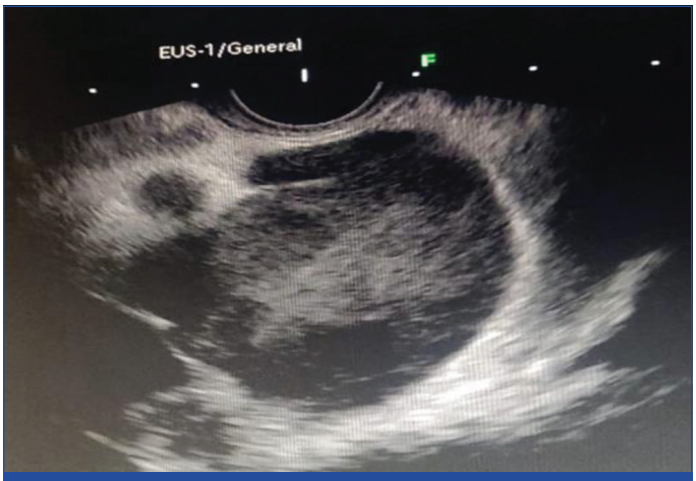


[Table/Fig-2]: CT scan of abdomen and pelvis shows left renal calculi (16×11 mm in size) with air foci in the collecting system- suggestive of emphysematous pyelonephritis.

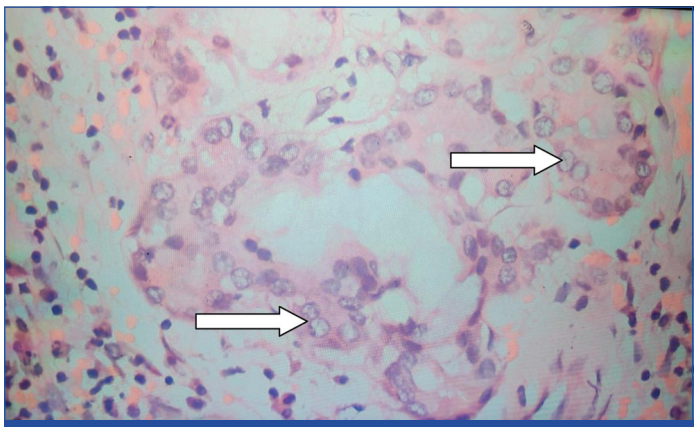


[Table/Fig-3]: CT scan of abdomen and pelvis shows retroperitoneal necrotic lymphadenitis in peripancreatic, periportal, and para-aortic region with largest being 4×5 cm, with mass effect and compression of lower common bile duct and dilatation of intrahepatic billiary radicles.

Endoscopic ultrasound-guided biopsy of the lymph node between the portal vein and inferior vena cava was performed to further assess the lymphadenopathy [Table/Fig-4]. The sample was then sent for histopathological examination {Haematoxylin and Eosin (H&E)}. It showed poorly differentiated malignant tumour cells arranged in different sheets. Tumour cells were enlarged in size and had hyperchromatic nuclei, prominent nucleoli, and scant cytoplasm with increased mitoses [Table/Fig-5]. The neoplastic cells on immunohistochemistry were positive for CD20, BCL2, and C-MycR, and negative for CD3, BCL6, and CD10, with a 90% MIB-1 proliferation index. Hence, it was suggestive of HGBL. Based on the diagnosis, the patient was given six cycles of chemotherapy which included the drugs Rituximab, Cyclophosphamide, Doxorubicin hydrochloride (Hydroxydaunorubicin), Vincristine sulfate (Oncovin), and Prednisone (R-CHOP regimen) at intervals of every 21 days, and the patient is under routine follow-up.



[Table/Fig-4]: Endoscopic ultrasound-guided biopsy of the lymph node in between the portal vein and inferior vena cava.



[Table/Fig-5]: Poorly differentiated malignant tumour cells arranged in different sheets. Tumour cells were enlarged in size and had hyperchromatic nuclei, prominent nucleoli, and scant cytoplasm with increased mitoses {Haematoxylin and Eosin (H&E) stain, 40X)}.

DISCUSSION

In 2016, World Health Organisation (WHO) added a novel category called 'HGBL' in its revised classification, which essentially replaces the previous category "B-cell lymphoma, unclassifiable", containing features that are in between a diffuse large B-cell lymphoma and Burkitt lymphoma. HGBL comprises two forms of lymphomas: HGBL, NOS and HGBL associated with Myelocytomatosis Oncogene (MYC) and B-cell lymphoma 2 (BCL2) and/or B-cell lymphoma 6 (BCL6) rearrangements (HGBL, R). HGBL, R is alternatively referred to as Double/Triple-Hit lymphoma (HGBL DH/TH) [1].

Compared to individuals without diabetes, patients with diabetes have a moderately elevated risk of developing non-Hodgkin's lymphoma [2]. Since, obesity is present in most type 2 diabetes patients, metabolic abnormalities linked to obesity may act as a mediating factor in the relationship between diabetes and NHL [3]. The rise in NHL linked to obesity may be caused by modifications in the levels of circulating adipocytokines, including leptin and adiponectin. These cytokines are known to be involved in immunity and inflammation and can alter the balance between cell death and proliferation [3].

Common symptoms of HGBL include lymphadenopathy, fever, night sweats, lethargy, loss of appetite, and Central Nervous System (CNS) involvement [4]. Other extranodal areas that may get involved include the kidneys (13%), bone marrow (24%), peripheral blood (8%), gonads (4%), gastrointestinal tract (22%), liver (12%), and central nervous system (7%) [5]. Secondary Gastrointestinal (GI) tract involvement is highly prevalent, with one of the fatal consequences being upper gastrointestinal haemorrhage [6]. In the majority of cases, morphological, immunophenotypic, traditional cytogenetic, and fluorescence in-situ hybridisation reports can be combined to provide an appropriate diagnosis.

The Event-free Survival rate at 12 months (EFS) was 42% in HGBL associated with MYC and BCL2 and/or BCL6 rearrangements, while the median Overall Survival rate (OS)

was 21.7 months in a study conducted to determine the inferior survival in HGBL with these rearrangements [7]. Out of the three entities, HGBL with isolated MYC positivity and HGBL with Double Hit and/or Triple Hit (DH/TH) have the worst prognosis, followed by Diffuse Large B-cell Lymphoma (DLBCL), Not Otherwise Specified (NOS), and HGBL, NOS [8]. HGBL typically originates extra-nodally and has an extremely dismal prognosis. According to their initial staging, all patients with Double Hit Lymphoma (DHL) along with Double Expression (DE) lymphoma should have a diagnostic lumbar puncture. Additionally, CNS involvement in DHL patients is very high during the first three years; hence, prophylactic CNS therapy is advised for all DHL patients [9]. According to a study done by Mitobe M et al., drugs like Etoposide phosphate, Prednisolone, Vincristine sulfate (Oncovin), Cyclophosphamide, Doxorubicin hydrochloride (Hydroxydaunorubicin), and Rituximab {Dose-adjusted (DA) EPOCH-R} therapy have a far higher success rate than even the usual R-CHOP regimen for treating HGBL with MYC and BCL2 and/or BCL6 rearrangements, including those who have renal failure [10]. But occasionally, the symptoms of an acute infection can masquerade as the presentation of NHL [11]. Fever with dysuria is one of the commonest symptoms of emphysematous pyelonephritis. Emphysematous pyelonephritis is characterised by its common clinical features, which include fever with or without chills, dysuria, abdominal pain, renal angle tenderness, nausea, and vomiting [12]. Hence, the symptoms of NHL can be masked due to co-existing infection. Like in present case, the patient presented to us with the acute signs and symptomatology of emphysematous pyelonephritis. A similar case was reported by Mahapatra HS et al., in which the patient first presented with acute pyelonephritis with an ovarian tumour but was ultimately diagnosed with HGBL [11]. The patient was treated with appropriate antibiotics according to the culture and sensitivity. But the presence of continuous symptoms leads us to investigate further and ultimately it turned out to be lymphoma. Early diagnosis leads to the early commencement of chemotherapy and better prognosis. The patient is under regular follow-up without any events.

CONCLUSION(S)

Diabetes is linked to an increased risk of developing NHL. So, elderly diabetic patients with co-existing infections and B symptoms such as continuous low-grade fever, night sweats, and significant weight loss should be meticulously screened for underlying malignancy. The lymphoma can be overshadowed by the symptoms of an infection. High-grade B-cell NHL has an extremely bad prognosis and can be fatal, if treatment is delayed. Hence, there should be a high clinical suspicion to diagnose such atypical presentations of NHL, as they are treatable and have a good prognosis, if treated timely.

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