Case Series

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Aggressive Non-Hodgkin's Lymphoma: A Case Series and Literature Review

Pathology Section

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ABSTRACT

Aggressive lymphoma of non-Hodgkin's type is uncommon. The most common clinical presentation is lymphadenopathy and fever. One-fifth of Non-Hodgkin's Lymphoma (NHL) present with serous effusions involves the body cavities like pleural, abdominal and pericardial cavities. Ten percent of aggressive lymphomas occur without an underlying immunosuppressive status. The NHL is more common in the elderly with a male preponderance. Paraneoplastic syndromes are rarely associated with non-Hodgkin's lymphoma. Peritoneal lymphomatosis is extremely rare and associated with a poor prognosis. Since clinical suspicion for underlying malignancy is higher with peritoneal carcinomatosis (than for serous effusion of body cavities), they get recognised early. However, peritoneal lymphomatosis can be neglected and misdiagnosed. This series is about five cases of aggressive non-Hodgkin's lymphoma. These cases are presented here for their rarity and diverse clinical manifestations. The case of angioimmunoblastic lymphoma was seen in an elderly male who presented with hypoglycaemia serous effusion and lymphadenopathy. Two patients were diagnosed with Natural Killer (NK) cell lymphoma and they presented with serous effusion with a jejunal thickening, as visible in the CT scan. One case of Diffuse Large B Cell Lymphoma (DLBCL) was seen in an elderly female presenting with inguinal lymphadenopathy. Lymphoma shows a varied clinical and radiological presentation and it should always be a differential diagnosis in the massive serous effusion and unexplained bowel thickening in Computed Tomography (CT) imaging with or without lymphadenopathy. The cases reported here emphasise the importance of early pathological diagnosis and immunohistochemical confirmation to ensure that the right treatment can be started at an appropriate time.

Keywords: Angioimmunoblastic lymphoma, Diffuse large B cell lymphoma, Natural killer cell, Serous effusion

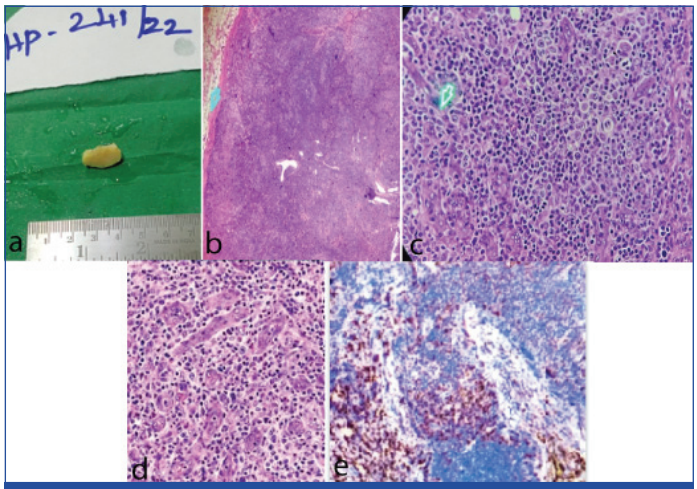
INTRODUCTION

Aggressive lymphoma of non-Hodgkin's type is rare and accounts for 10-15 % of Non-Hodgkin's Lymphoma (NHL) [1]. The most common clinical presentation is lymphadenopathy and fever. Only 20% cases present with serous effusions involving the body cavities like pleural, abdominal and pericardial effusions [2]. Only 10% of aggressive lymphoma occurs without an underlying immunosuppressive status [3]. It is more common in the elder age and shows a male preponderance. Paraneoplastic syndromes associated with NHL are extremely rare. Peritoneal lymphomatosis is extremely rare and associated with a poor prognosis. Clinical attention is more for peritoneal carcinomatosis. However, peritoneal lymphomatosis can be neglected and misdiagnosed. A careful histomorphological and immunophenotypical examination is required for the classification of more than 40 different subtypes of lymphoma, all with different behaviour and prognosis. The series is about five cases of aggressive NHL who reported to the institute from February 2022 to June 2022.

Case 1

A 55-year-old male presented with complaints of fever, abdominal distension and generalised weakness for six months. The patient was known to have diabetes and hypertension, since 15 years on regular medications. On examination, the patient had pallor, ascites, and inguinal lymphadenopathy. Ultrasound and computerised tomographic studies revealed massive ascites with generalised lymphadenopathy. Complete haemogram revealed haemoglobin of 8.0 g/dL, Packed Cell Volume (PCV) of 24%, platelet count of 3.50×10^9/dL and random blood sugar was 40 mg/dL. An excision biopsy of the inguinal node was done. Grossly, the node measured 3×4 cm. The cut surface of the node was grey white and fleshy [Table/Fig-1a]. The histomorphological picture revealed a completely effaced architecture and diffusely infiltrated by large and medium-sized lymphoid cells with vesicular chromatin and prominent nucleoli traversed by prominent blood vessels [Table/Fig-1b-d].

The differential diagnosis of Diffuse Large B Cell Lymphoma (DLBCL) and angioimmunoblastic T cell lymphoma was considered. On conducting Immunohistochemistry (IHC), the cells were positive for Cluster Differentiation 43 (CD43), CD30 (IMMUNOBLAST), BCL2 and CD4-predominance, BCL-6-focal positive, CD3 positive [Table/Fig-1e]. The tumour cells were negative for CD10, CD68, CD20, CD15, EBER, PAX5 and CD7. The final diagnosis of angioimmunoblastic lymphoma was given based on the immunohistochemical findings. The patient was started on chemotherapy and subsequently, his hospital stay was uneventful. The patient was lost to follow-up.

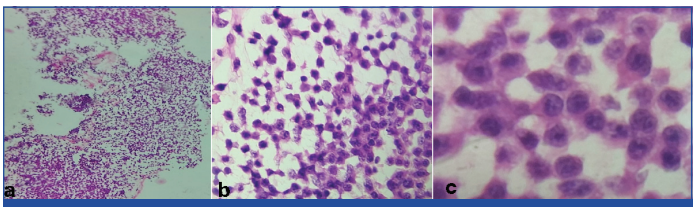


[Table/Fig-1]: a) Gross picture showing node with a grey white; b) Photomicrograph showing node with complete effacement of architecture (H&E stain, 40X); c) Photomicrograph showing large and medium-sized lymphoid cells traversed by prominent blood vessels (H&E stain, 100X); d) Photomicrograph showing immunoblast like cells with vesicular chromatin and prominent nucleoli (H&E stain, 400X); e) Photomicrograph showing diffuse positivity for CD3 (IHC, 400X).

Case 2

A 55-year-old male presented with breathlessness and distension of the stomach for one month. On examination, there was a bilateral

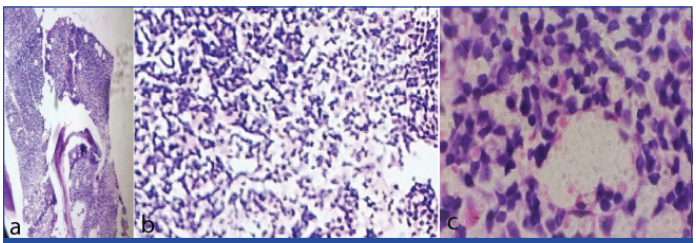
reduction in breath sounds and free fluid in the abdomen, with no palpable lymphadenopathy. Computed tomography lung showed bilateral pleural effusion and abdomen revealed jejunal thickening and ascites. His peripheral smear picture showed neutrophilic leuckocytosis. Pleural and ascitic fluid total count was around 2500 cells/cumm and cytological smears showed sheets of large cells with a moderate amount of cytoplasm and pleomorphic, hyperchromatic and convoluted nuclei [Table/Fig-2a,b,c]. The smear was reported as positive for lymphoproliferative disorder subsequently the cell block preparation also showed cells of similar morphology and a provisional diagnosis of non-Hodgkin's lymphoma was given. Flow cytometry revealed a 74% viability of all cells with CD7, CD56, CD38, Human Leucocyte Antigen (HLA) DR, and negative for CD2 and CD3. The final diagnosis was NHL-Natura Killer (NK) cell type. The patient was lost to follow-up.



[Table/Fig-2]: a) Photomicrograph showing a monotonous population of cells (H&E stain, 40X); b) Photomicrograph shows sheets of medium to large-sized cells (H&E stain, 100X); c) Photomicrograph showing large cells with a moderate amount of cytoplasm, pleomorphic nuclei and prominent nucleoli (H&E stain, 400X).

Case 3

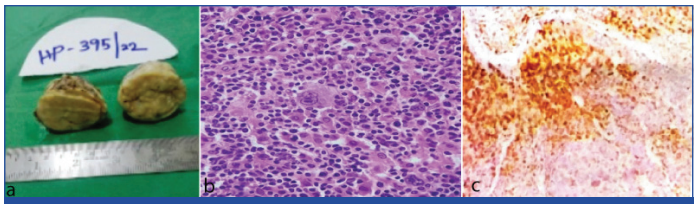
A 42-year-old male presented with an on and off fever for one month and generalised weakness. On physical examination, he was febrile, pale and had hepatosplenomegaly. No lymphadenopathy was noted. Complete haemogram report showed anaemia with haemoglobin of 8.0 g/dL and, haemotocrit of 24.0%, thrombocytopenia with platelet count of 0.60×10^9/L and leukopenia with white blood cell count of 0.15×10^9/L. His peripheral smear showed pancytopenia and bone marrow smear showed abnormal, immature dark blue cells with dispersed chromatin and inconspicuous nucleoli. These were thought to be lymphoblasts and bone marrow biopsy was advised, which showed erythroid series with normocytic maturation and diffuse sheets of blue cells suppressing the myeloid series. Megakaryocytes appeared reduced in number [Table/Fig-3]. Immunohistochemistry findings confirmed the diagnosis as acute B lymphoblastic leukaemia with positivity for CD10 HLA DR, CD34, Terminal deoxynucleotidyl transferase (TdT), CD79a, Ki67-intermediate index. The tumour cells were negative for CD15 and CD68. Patient was lost to follow-up.



[Table/Fig-3]: a) Photomicrograph showing bone marrow biopsy with effaced architecture, (H&E stain, 40X); b) Photomicrograph showing small and medium-sized primitive cells, (H&E stain, 100X); c) Photomicrograph blast with indented nucleus, (H&E stain, 400X).

Case 4

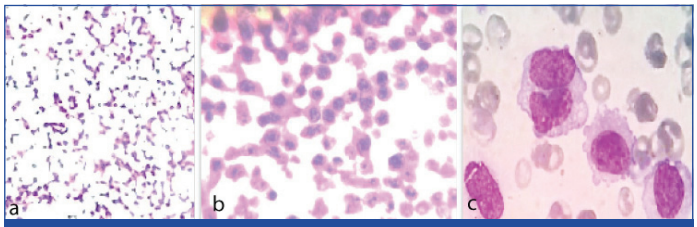
A 45-year-old female presented with complaints of swelling over the groin for four weeks with no significant fever, loss of weight. On examination, she was pale, and had a 6x5 cm hard swelling in the inguinal region. Haemogram showed anaemia with haemoglobin of 8.5 g/dL and, haematocrit of 25.5% and platelet count was 150.0×10^9/L.. An excision biopsy of the node was sent for examination. Grossly, the node measured 6x5 cm, the external surface was capsulated, and the cut surface was firm grey white [Table/Fig-4a]. Histomorphological picture showed a lymph node with completely effaced architecture and diffusely infiltrated by large and medium-sized lymphoid cells with vesicular chromatin and prominent single nucleoli (immunoblast). There were cells with 2-4 nucleoli (centroblast) [Table/Fig-4b]. Histomorphological features were suggestive of DLBCL. Immunohistochemistry confirmed the diagnosis. The cells were positive for CD20 [Table/Fig-4c], Paired box (PAX) 5, B-cell lymphoma (BcL) 6, and negative for CD3 and Anaplastic Lymphoma Kinase (ALK). Patient was lost to follow-up.



[Table/Fig-4]: a) Gross picture showing node with a fleshy tan cut surface; b) Photomicrograph showing diffuse infiltrate of large lymphoid cells (H&E stain, 400X); c) Photomicrograph showing CD 20 positive cells (IHC stain, 400X).

Case 5

A 45-year-old male presented with abdominal distension and weakness for one-month duration. On examination, free fluid was noted in the abdomen. Computed tomography findings revealed a peritoneal mass with a massive fluid collection. Ascitic tapping was done and sent for cytology and the ascitic fluid total count was approximately. 1500 cells/cumm. Cytospin smear and cell block cytological smear showed large cells with pleomorphic convoluted nuclei and prominent nucleoli. The provisional diagnosis of lymphoproliferative disorder with the possibility of NHL was given because of cellularity and nuclear features [Table/Fig-5]. Flow cytometry revealed an 80% viability of cells with positivity for CD7, CD56, CD38, HLA DR, and negative for CD2, and CD3. Thus, the disease was confirmed to be NHL-NK cell type. Patient was lost to follow-up.



[Table/Fig-5]: a) Photomicrograph showing sheets of monomorphic cells4 (H&E stain, 40X); b) Photomicrograph showing sheets of large cells with a moderate amount of cytoplasm and hyperchromatic nuclei (H&E stain, 400X); c) Photomicrograph showing large lymphocyte with convoluted nuclei (H&E stain, 1000X).

DISCUSSION

The NHLs have distinct morphological, immunophenotypical and clinical features. Aggressive lymphoma is of non-Hodgkin's type, the most common being DLBCL, angioimmunoblastic T cell lymphoma, and NK cell lymphoma. Immunosuppressed conditions increase the risk of NHL. It is unusual for both aggressive B cell and T cell non-Hodgkin's lymphomas to present with defined symptomatology. DLBCL, angioimmunoblastic lymphoma and NK cell lymphoma usually present with nodal or extranodal lesions. Lymph node involvement is more often noted in adults than in children. Rarely, patients may present with leukaemia with bone marrow and Central Nervous System (CNS) involvement [1].

The primary effusion lymphoma of the B cell type, occurred in Human Immunodeficiency Virus (HIV) infected patients with HHV-8 coinfection [1]. In this series, two cases presented with serous effusion of peritoneal and pleural spaces, but with any underlying immunosuppression. A diagnosis of NHL was made, which was later confirmed to be of NK cell type by flow cytometric analysis. In another case series, there was emphasis on algorithmic approach to diagnosing haematolymphoid neoplasms in effusion by combining Morphological, Immunohistochemical and Molecular Cytogenetics (MICM) [4]. The majority were DLBCL (15 cases),

followed by 12 cases of plasma cell myeloma. An earlier study also laid emphasis on the MICM combined technique for diagnosis [5]. In this series also, two cases reported were NK/T cell lymphoma and one case reported as DLBCL presented only with inguinal lymphadenopathy.

A study on 22 cases of NK/T cell lymphoma in children and adolescents found that the nasal site was the most involved region followed by the non nasal site (27.3%) of all cases [6]. The neoplastic cells were positive for CD3 in all cases and 19 cases were positive for CD56. All patients were Epstein-Barr Virus (EBV) positive. But in this series, the two reported cases of NK cell lymphoma were positive for CD56 and were non nasal type with EBV negativity.

In another case series by Bahri R et al., it was found that EBV was mostly latent and clonal in Angioimmunoblastic Lymphoma (AIL) [7]. Also found that AIL was associated with poor prognosis in 90% of patients. But in this case series, a case of angioimmunoblastic lymphoma was diagnosed by the histomorphological and immunohistochemical study of an inguinal lymph node, was EBV Negative.

In another case series by Dorfman DM and Sadigh S the author found six cases of NHL presenting with leukaemia like picture [8]. While some cases in the series presented with high cell counts, some had pancytopenia [8]. In the present series, one patient with acute B cell leukaemia presented with pantocytopenia.

A literature search was done in PubMed, Google Scholar and Scopus to find reports of NHL presenting with atypical features and finally diagnosed as DLBCL, angioimmunoblastic lymphoma, acute B cell leukaemia or NK cell lymphoma. As with the present case series, male preponderance was noted in Wang G-N et al., Elis A et al., studies [6,9]. In a case series by Chandramohan J et al., the clinical presentation was jejunal thickening and pleural effusion which was also found in the present study [10]. In the present case series, hypoglycaemia was a presenting complaint in one patient which was also present in a study done by Hamada T et al., [1]. The summary of the case studies, clinical findings, site, and diagnosis are presented in [Table/Fig-6] [1-3,6,8-13].

CONCLUSION(S)

The present case series highlights that lymphoma can present with varied clinical and radiological manifestations. It should always be suspected in patients with massive serous effusion and unexplained bowel thickening in CT imaging with or without lymphadenopathy and immunosuppression. These cases emphasise the importance of

Author and year of the study	Age/Sex	Clinical features	Site	Diagnosis
Elis A et al., 1998 [9]	Range: 21-82 years	Pleural effusion	Pleural effusion	Non-Hodgkin's Lymphoma: 4 cases: Low grade; 10 cases: Intermediate grade and 3 cases: High grade
Vallianou N et al., 2016 [13]	60 years/male	Fever, generalised lymphadenopathy, hepatosplenomegaly, anaemia, hypergammaglobulinemia and autoimmune like manifestations	Generalised lymphadenopathy	Angioimmunoblastic T-cell lymphoma
Soutelo J et al., 2017 [11]	59 years/male	Stage IV chronic kidney disease, asthenia, dehydration, hypoglycaemia, and hypercalcaemia	Inguinal lymph node	T-cell histiocyte-rich large B-cell lymphoma
Brüggen MC et al., 2018 [3]	Range: 51-87 years	Painful oral aphthous stomatitis and gingival bleeding, skin nodule, generalised ulcerations, and pruritus, disseminated ulcerating skin nodules, oral necrotic ulcerations, and axillary and cervical lymphadenopathy	Nasal, extranasal and cutaneous	Aggressive T/NK cell lymphoma
Wang G-N et al., 2019 [6]	Range: 15-18 years	Anaemia and leucopenia	Nasal cavity, nasopharynx and maxillary sinus. Non nasal sites: Skin, lymph nodes and testis	NKTCL and all the cases were Epstein-Barr Virus (EBV) positive
Hamada T et al., 2020 [1]	73 years/female	Hypoglycaemia, lactic acidosis, hypothyroidism and hypertension	Gastric	DLBCL
Al Maqrashi Z et al., 2021 [2]	65 years/male	Loss of weight and appetite, generalised fatigue, persistent hypoglycaemia	Mediastinal	DLBCL
Dorfman DM and Sadigh S, 2022 [8]	Mean age: 70 years/male	Leukocytosis with circulating neoplastic cells, which mimicked leukaemic blasts, thrombocytopenia, and anaemia	Cervical lymphadenopathy/bone marrow	Peripheral T-cell lymphoma, Not Otherwise Specified (NOS) Burkitt lymphoma High-grade B cell lymphoma, Aggressive B cell lymphoma DLBCL B-prolymphocytic leukaemia
Zhu M et al., 2022 [12]	18 years/male	Abdominal distension and epigastric pain, accompanied by anorexia, nausea, vomiting, dyspnoea, palpitations, as well as low fever and night sweats	Diffuse thickening of the peritoneum and omentum and abdominopelvic effusion	Diffuse large B-cell lymphoma, germinal center B-cell type, stage IV.
Chandramohan J et al., 2022 [10]	Range: 20-60 years	Low backache, headache, fever and fatigue	Anterior abdominal wall nodules Skin nodule Lymphadenopathy Jejunal thickening-(1) Massive pleural effusion	ALK positive diffuse large cell lymphoma
Present study case:1, 2021	55 years/male	Fever, abdominal distension, and generalised weakness	Ascites, and inguinal lymphadenopathy.	Angioimmunoblastic lymphoma
Present study case: 2, 2021	55 years/male	Breathlessness and distension of the stomach	Bilateral pleural effusion and abdomen revealed jejunal thickening and ascites.	NHL-NK cell type
Present study case: 3, 2021	42 years/male	Intermittent fever and generalised weakness	Hepatosplenomegaly./bone marrow findings	Acute B cell leukaemia
Present study case: 4, 2021	45 years/female	Complaints of swelling over the groin	Lymphadenopathy	Diffuse Large B Cell Lymphoma (DLBCL)
Present study case: 5, 2021	45 years/male	Abdominal distension and weakness	Peritoneal mass with a massive fluid collection	NHL-NK cell type

[Table/Fig-6]: Summary of the previous and present case studies, clinical features, site and diagnosis.

early pathological diagnosis and immunohistochemical confirmation so that appropriate treatment can be started at the right time.

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