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ALK Positive Large B-Cell Lymphoma Masquerading as a T-Cell Lymphoma: A Histopathological Con

Smita SINGH[1], Rushali SAXENA[1], Mukesh DHANKAR[2]

Department of [1]Pathology and [2]Pediatrics, Lady Hardinge Medical College, NEW DELHI, INDIA

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ABSTRACT

Objective: ALK-positive large B-cell lymphoma is an aggressive form of lymphoma characterized by the expression of the ALK protein alongside the loss of pan-B-cell and pan-T-cell markers. Unfortunately, there is no established standard treatment for this subtype, resulting in a poor prognosis. Understanding the expression of aberrant markers is essential for accurate diagnosis and improved patient management.

Case Report: A 13-year-old male presented with intestinal obstruction to pediatric surgery and subsequently underwent exploratory laparotomy. Histopathological examination of the specimen revealed the presence of monomorphic tumor cells with plasmablastic morphology, which expressed CD45, CD79a, and CD3. Considering the patient's age and the tumor's morphology, further analysis showed the loss of other B-cell and T-cell markers, along with the expression of ALK, CD138, CD38 and lambda light chain restriction. Thus, the current case emphasizes the necessity of a comprehensive immunohistochemical analysis to accurately diagnose ALK-positive large B-cell lymphoma with aberrant CD3 expression, thus preventing misdiagnosis as T-cell lymphoma.

Conclusion: It is crucial to recognize the uncommon ALK-positive large B-cell lymphoma that exhibits aberrantly expressed CD3 to prevent misdiagnosis. Identifying this condition may allow for the incorporation of ALK inhibitors, potentially improving patient outcomes.

Keywords: ALK, CD-138, CD3, LBCL, Non-Hodgkin lymphoma, Immunohistochemistry

INTRODUCTION

ALK-positive large B-cell lymphoma is an exceptionally rare form of non-Hodgkin lymphoma, notable for its monomorphic plasmablastic morphology and a highly distinctive immunophenotype. This unique subtype of B-cell non-Hodgkin lymphoma is defined by the presence of anaplastic lymphoma kinase (ALK) in concurrence with the loss of pan-B-cell and T-cell markers. Its strong commitment to a terminally differentiated B-cell lineage is evidenced exclusively by the expression of plasmacytic markers CD138 and CD38 (1-3). Recognising this rare condition is crucial due to its highly aggressive clinical behaviour, making early diagnosis vital for improved patient management (4). This case report discusses a diagnostic challenge presented by this exceedingly rare entity, particularly due to the aberrant expression of CD3.

CASE REPORT

A 13-year-old male adolescent was referred to the pediatric surgery department due to abdominal pain and distention that had persisted for two months. Upon examination, a lump was detected in the right iliac fossa. CT imaging raised the suspicion of primary small bowel lymphoma with metastatic deposits in the liver. Laboratory tests, including a hemogram, peripheral smear, bone marrow aspiration, and bone marrow biopsy, showed unremarkable results. The patient's HIV status was negative.

Subsequently, the patient underwent an exploratory laparotomy. During the procedure, a specimen of the mass involving the ileocecal junction and ascending colon was resected. Additional specimens, including parts of the transverse colon, descending colon, a portion of the sigmoid colon, and thickened peritoneum, were collected in separate containers for histopathological examination.

The ileocecal region and ascending colon, measuring 41 cm in length, revealed a large mass that measured 16.5 x 12 x 12 cm and had a bosselated outer surface. Upon dissection, a grey-white tumor protruding into the lumen was observed, along with overlying thinned-out and partially ulcerated mucosa (Figure 1A). The adjacent mucosa appeared pale and flattened. Additionally, two other grey-white tumors measuring 2.8 x 1.8 cm and 2 x 1 cm were noted, indicating multifocal involvement of the small intestine and ascend-

Correspondence: Rushali SAXENA
Department of Pathology, Lady Hardinge Medical College,
NEW DELHI, INDIA
E-mail: rushali0928@gmail.com Phone: +91 954 073 20 07

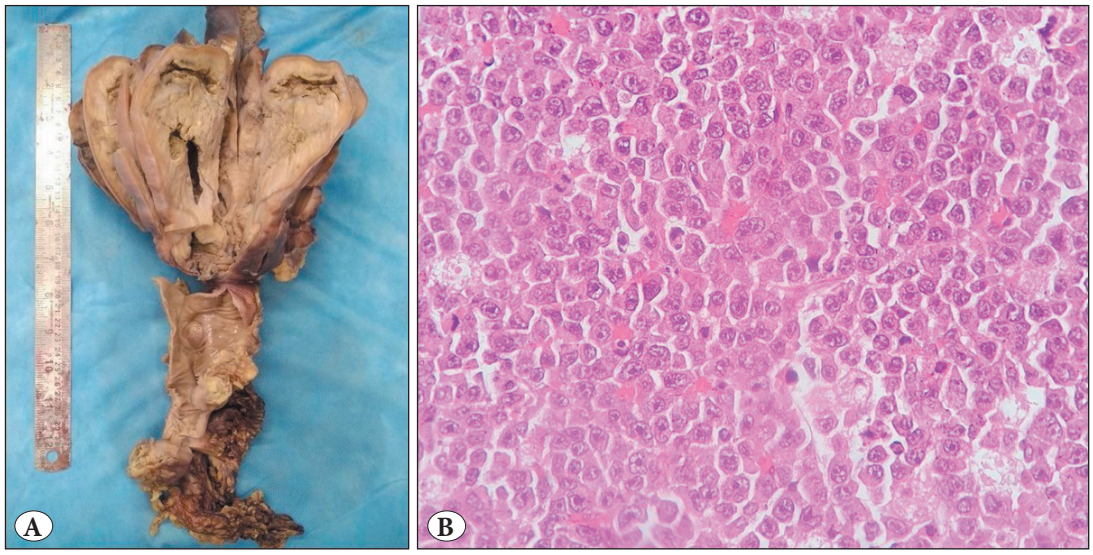

Figure 1: A) A large mass measuring 16.5 x 12 x 12 cm with a bosselated outer surface involving ileocecal junction and ascending colon. **B)** Haematoxylin and eosin stain, 400x shows monomorphic atypical lymphoid cells with plasmablastic morphology.

ing colon. A 6 cm length of transverse colon, along with its attached mesentery, was largely unremarkable, apart from some areas of focally ulcerated mucosa. At one end of the descending colon, a tumor mass measuring 3.8 x 0.8 x 0.3 cm was identified, along with another cut end that displayed a thickened area measuring 9 x 3 cm. In total, 16 lymph nodes were isolated during the examination.

Multiple haematoxylin and eosin sections from various tumor masses demonstrated diffuse infiltration of the intestine by monomorphic atypical lymphoid cells exhibiting plasmablastic morphology. These atypical cells were 2 to 3.5 times larger than a small mature lymphocyte nucleus, possessing a scant to moderate amount of agranular cytoplasm. They featured a round, central to eccentric nucleus, with some displaying irregularities in the nuclear membrane, vesicular chromatin, and prominent nucleoli (Figure 1B). In the initial panel of immunohistochemistry (IHC), these atypical cells showed focal positivity for CD45, as well as positivity for CD79a and CD3 (Figure 2A-C). They were negative for Pan-CK, CD19, CD20, PAX5, CD5, and CD10. The Ki67 proliferation index was 90% (Figure 2D). Given that the morphology and the age of the patient were inconsistent with T-cell lymphoma, further IHC panels were performed. The subsequent IHC analysis revealed that these cells expressed ALK, EMA, CD138, CD38 (Figure 3A-D). Additional markers such as OCT2, MUM1, BOB1, lambda, and kappa light chains (Figure 4A-E) supported the identification of these atypical lymphoid cells as belonging to the B-lineage. While these cells were found to be negative for CD5, CD4, CD8, CD30, BCL6, and BCL2. A lambda restriction was noted. All isolated lymph nodes were involved.

Based on the patient's age, histomorphology, and IHC findings, a diagnosis of non-Hodgkin lymphoma- ALK positive large B cell lymphoma with aberrant CD3 expression, Stage IV (Ann Arbor staging) was rendered.

DISCUSSION

Originally described as a rare subtype of diffuse large B-cell lymphoma by Desol et al. in 1997, this entity was later recognised as a distinct category by the World Health Organization classification of lymphoid neoplasms in 2017 (5). It is characterized by a male predominance and can occur in any age group (6).

In terms of morphology, immunoblastic variant of diffuse large b-cell lymphoma, ALK-positive large B-cell lymphoma, plasmablastic lymphoma, and poorly differentiated carcinoma were considered as differential diagnoses. In the present case, immunonegativity for Pan-CK and positivity for lymphoid markers helped rule out poorly differentiated carcinoma. Immunonegativity for CD20 and PAX5 excluded the possibility of diffuse large B-cell lymphoma. While plasmablastic lymphoma shares similar morphology and immunophenotypic expression (notably, loss or weak expression of CD45, CD20, and PAX5), it typically does not exhibit ALK expression (6,7).

The unique immunophenotype of non-Hodgkin lymphoma includes the expression of ALK along with CD138, CD38 and a loss of pan B-cell markers, T cell markers, cyto-

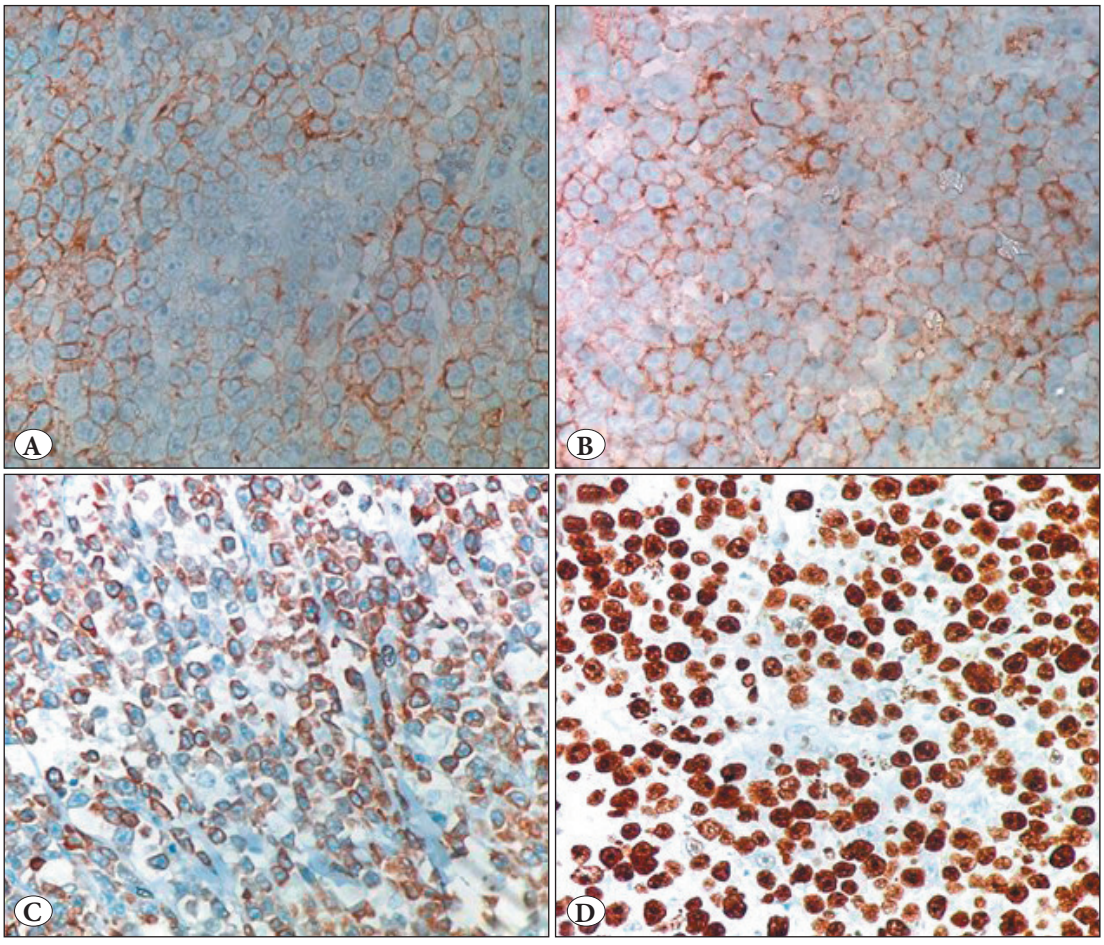

Figure 2: A-D) Initial Immunohistochemistry panel, 400x. The tumor cells were immunopositive for **A)** CD45, **B)** 79a **C)** CD3, **D)** Ki67.

toxic granular protein, and CD30. The presence of CD138 and CD38 is the only evidence indicating a commitment to a terminally differentiated B-cell lineage (1-3). Most documented cases have reported monotypic IgA lambda expression. However, select studies noted monotypic kappa expression (3,8). In the present case, we observed lambda light chain restriction.

While aberrant CD4 expression is well-established in the literature (1,2,5,6,9), it was absent in this particular case.

The expression of CD3 has rarely been reported, and it appears in only two cases (8,10). This is the first case, to our knowledge, from India, where aberrant CD3 immunohistochemical expression suggests the possibility of T cell lymphoma based on the initial immunohistochemical workup. However, given the monomorphic plasmablastic morphology of the tumor cells, there was also consideration for the rare possibility of ALK-positive large B-cell lymphoma and plasmablastic lymphoma. Subsequent testing revealed positivity for ALK, plasmacytic markers CD138 and CD38, as well as lambda light chain restriction, leading to the final diagnosis of ALK-positive large B-cell lymphoma with aberrant CD3 immunohistochemical expression.

The literature consistently reports primary lymph node involvement. Furthermore, extra-nodal involvement has been documented in various organs such as the stomach, duodenum, nasal cavity, ovaries, and brain (11-14). Xing et al. and McManus were among the first to report extra-nodal ALK positive large B-cell lymphoma manifesting as non-Hodgkin lymphoma in the duodenum and stomach, respectively (12,15).

The current case report describes extensive involvement of the large colon and ileum, along with regional lymph node involvement, indicating the highly aggressive nature of ALK- positive large B-cell lymphoma with a rare CD3 aberrant expression.

CONCLUSION

ALK-positive large B-cell lymphoma represents a very rare subtype of non-Hodgkin lymphoma that can often be misdiagnosed due to the absence of CD45 and pan B-cell and pan T-cell markers. Its CD20-negative status signifi-

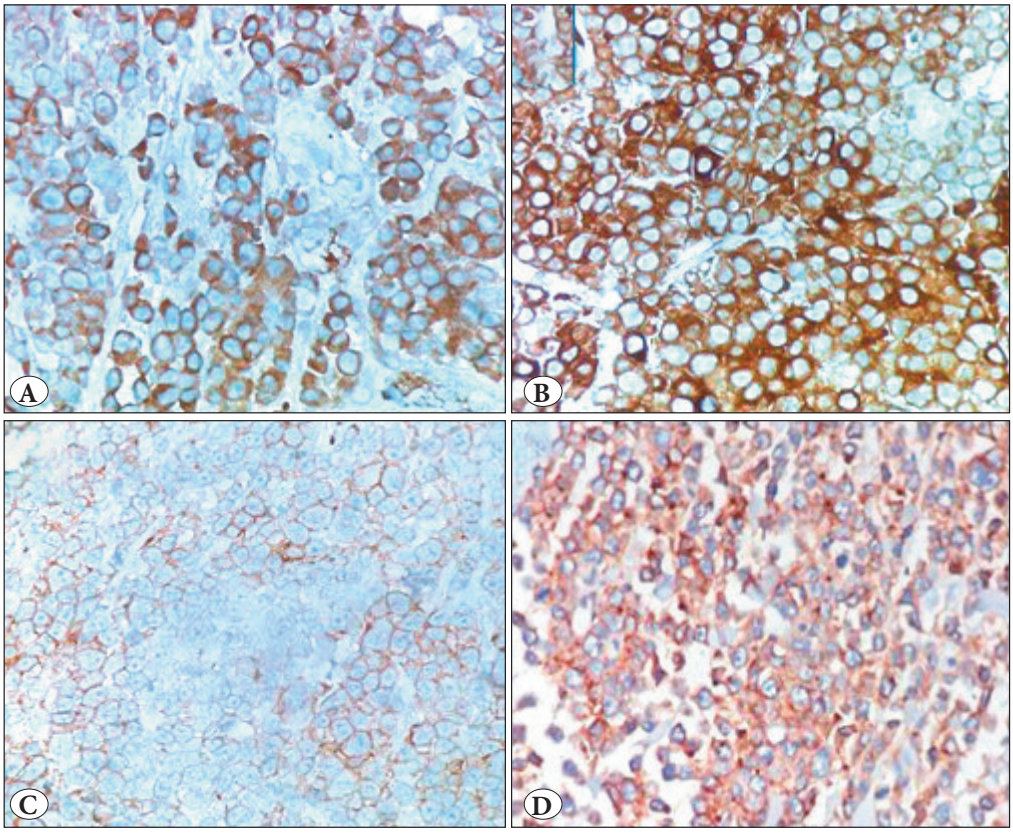

Figure 3: A-D) Further Immunohistochemistry panel, 400x. The tumor cells were immunopositive for, **A)** ALK, Cytoplasmic granular, **B)** EMA, **C)** CD138, **D)** CD38.

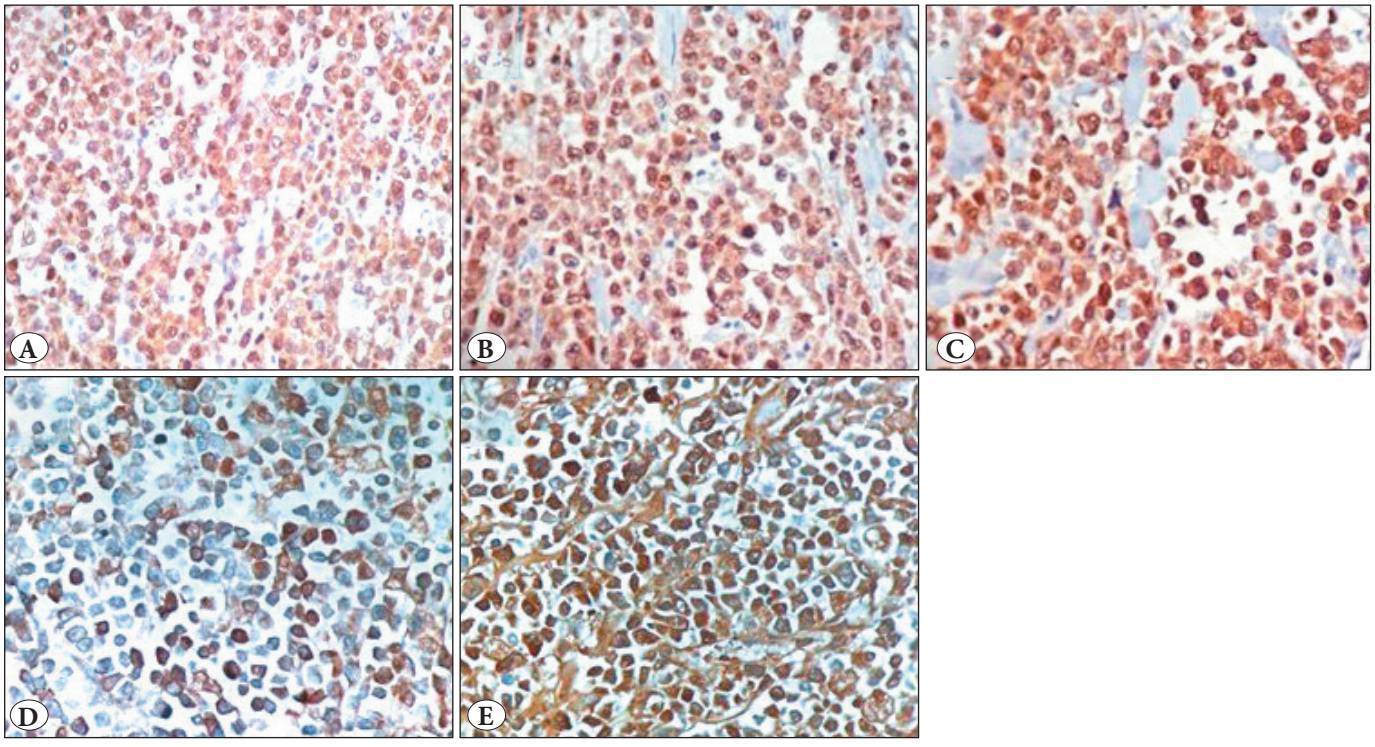

Figure 4: A-E) Immunohistochemistry panel depicting B- lineage, 400x. The tumor cells were immunopositive for, **A)** OCT2, **B)** MUM1, **C)** BOB1, **D)** Kappa, **E)** Lambda.

cantly limits treatment options, posing a major challenge to patient management. Additionally, in rare cases, it may express aberrant CD3, which can create diagnostic challenges. Therefore, any lymphoma exhibiting plasmablastic morphology with CD3 positivity on the initial immunohistochemistry panel must be subjected to a comprehensive diagnostic workup with an extensive panel that includes CD138, ALK, kappa, and lambda markers. This thorough approach is crucial for achieving an accurate diagnosis and may allow for the incorporation of ALK inhibitors, leading to improved outcomes for these patients.

Conflict of Interest

The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Authorship Contributions

Concept: **SS,** Design: **SS, RS,** Data collection and/or processing: **SS, RS, MD,** Analysis and/or interpretation: **SS, RS,** Literature search: **RS,** Writing: **RS,** Approval: **SS, MD.**

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