Clinical Case Reports

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CASE REPORT

Primary pleural precursor B-Cell lymphoblastic lymphoma

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Key Clinical Message

Intrathoracic lymphoblastic lymphoma (LBL) is classically of T-cell lineage, but these cases of pleural B-cell LBL suggest that this is not always the case. Despite the clinical challenges involved every attempt should be made to secure a biopsy and histological diagnosis, as we move into an era of lineage-directed therapies.

Keywords

Extramedullary, lymphoblastic lymphoma, pleura, precursor B-cell.

Introduction

B-cell acute lymphoblastic leukemia (pB-ALL) is a cancer of precursor B cells, involving the bone marrow (BM) and peripheral blood and is the most common childhood cancer. B-cell lymphoblastic lymphoma (pB-LBL) represents a rare form of this disease in which the lymphoblasts are confined to mass lesions with little or no BM involvement (<25% BM lymphoblasts). In contrast to the more common T-cell lymphoblastic lymphoma (T-LBL) where mediastinal disease predominates, pB-LBL can present a variety of extranodal sites. A review of such cases from three trials spanning nearly twenty years reported heterogeneous presentations with bone, skin, subcutaneous tissue, and mediastinum as the most common sites of disease [1]. Infiltration of the kidney, gastrointestinal tract, cervix, middle ear, and testicle has also been reported [1–4]. While malignant pleural effusions associated with pB-LBL have been noted previously [1,5], we report the first cases of pleural disease at presentation. Case 1 had B-LBL with pleural lesions as the only site of disease, whereas Case 2 also had bone marrow infiltration meeting the criteria for B-ALL, both responded well to conventional therapy.

Case Report 1

A 9-year-old boy was referred to our service with a six-week history of lethargy, loss of appetite, chest tightness, and progressive breathlessness. Clinical examination and chest radiography revealed a large right-sided pleural effusion with mediastinal displacement. Computer tomography (CT) of the chest, abdomen, and pelvis demonstrated a tense right hydrothorax with lobular thickening of the parietal pleura, collapsed right lung, and marked mass effect on the mediastinum and diaphragm (Fig. 1A). Prominent soft tissue was noted in the paratracheal, pretracheal, and subcarinal areas suggestive of lymphadenopathy, but this was not a particularly marked feature. There were no enlarged lymph nodes elsewhere and bony appearances were normal. The full blood count was normal at presentation and serum lactate dehydrogenase was mildly elevated. Thoracoscopy was performed with drainage of 2.5 L of hemoserous fluid; multiple masses covered with thickened pleura were observed across large parts of the parietal surface. The pleural fluid showed no evidence of malignancy on cytological inspection but pleural biopsy revealed diffuse sheets of medium to large lymphoblasts, some of which displayed vesicular

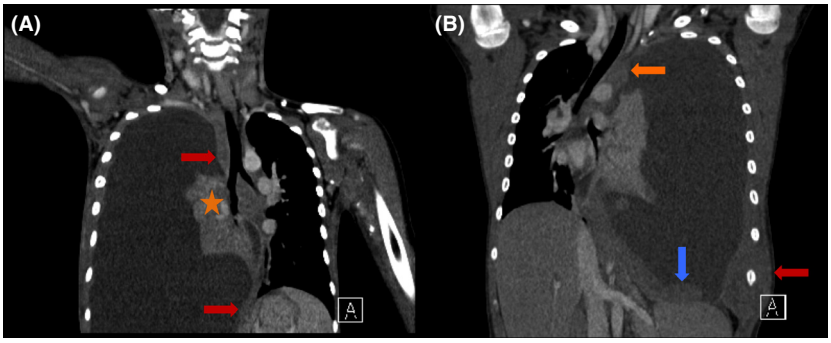

Figure 1. (A) Case 1: Coronal reconstructions of a contrast-enhanced computer tomography (CT) demonstrating a tense right hydrothorax with associated lobulated pleural thickening (arrows), collapsed right lung (asterisk) and marked mass effect on the mediastinum and diaphragm. (B) Case 2: Coronal reconstruction of contrast-enhanced CT showing a left-sided tension hydrothorax with surrounding lobular thickening of the pleura. The left lung is collapsed and there is marked mass effect on the left hemi-diaphragm and the mediastinum. Note involvement of the mediastinal pleura (orange arrow), diaphragmatic pleura (blue arrow) and associated chest wall mass encasing the left 8th, 9th and 10th ribs (red arrow).

nuclei with prominent nucleoli. The background contained scattered macrophages (CD68 positive) imparting a focal starry sky pattern. The tumor cells showed nuclear positivity for TdT and strong membranous positivity for CD79a (Fig. 2A–C). The lymphoblasts also expressed CD10, CD20, CD34, CD45, and BCL2, with a Ki67 proliferative index of 80%. Pleural tissue was also used for florescent in situ hybridization (FISH) studies, using Vysis (Abbott Laboratories, Illinois, U.S.A) ETV6/RUNX1, MLL, and BCR-ABL1 probes, multiple tissue areas were examined and no evidence of these gene rearrangements were found. Bone marrow and cerebrospinal fluid examination was normal. He was treated with schedule B of the UKALL2003 trial, a repeat scan at day 28 of treatment revealed near-complete resolution of the pleural lesions and effusion [6]. Three years on, he has completed maintenance therapy and remains in remission.

Case Report 2

A 10-year-old boy presented with a one-week history of breathlessness, cough, fatigue, and a left inferolateral chest-wall swelling. On initial assessment, he was found to have a large left pleural effusion, a leucoerythroblastic blood film and mild thrombocytopenia. Contrast-enhanced chest CT revealed a left-sided tension hydrothorax with surrounding lobular thickening of the pleura involving both mediastinal and diaphragmatic surfaces. The left lung was collapsed and there was marked mass effect on the left hemidiaphragm and mediastinum. An associated chest wall mass encasing the left 8th, 9th, and 10th ribs was also noted (Fig. 1B). There was no mediastinal lymphadenopathy and the observed bones were otherwise unremarkable. Thoracocentesis was performed and cytological examination of the fluid revealed a mixed population of cells with occasional groups of abnormal cells resembling lymphoblasts. Peripheral blood and bone marrow flow cytometry identified a population of lymphoblasts-expressing CD 10, CD19, CD34, CD79a, and TdT. Bone marrow histology revealed subtotal replacement with a dense infiltrate of medium to large blasts with minimal residual hematopoiesis. Blasts were positive for expression of CD79a and TdT (Fig. 2D–E). Chromosome analysis demonstrated a hyperdiploid karyotype with a gain of 1q. FISH for MLL, BCR-ABL, ETV6/RUNX1, and TLX rearrangements were negative. Induction treatment was given in accordance with schedule B of the UKALL2011 trial [6], after two years of follow-up he remains in remission.

Discussion

The presentation of B-LBL may involve numerous extranodal sites and we report the first primary pleural presentation. Primary pleural lymphomas are extremely rare with the majority occurring in the context of chronic pyothorax or significant immunocompromise [7]. Occasional cases of pleural diffuse large B-cell lymphoma and marginal zone lymphoma in otherwise healthy subjects have been reported. In contrast, pleural infiltration by systemic lymphoma, usually in the form of an effusion, occurs in approximately 20–30% of patients with non-Hodgkin lymphoma (NHL)[8]. Lymphoblastic lymphoma accounts for 30% of childhood NHL; T-LBL represents approximately 85% of these and commonly presents with a mediastinal mass leading to respiratory compromise. Pleural effusions in this condition are common, reported in 70% in some series; indeed it has been proposed that pleural cytology could allow rapid diagnosis in this situation [9]. Pleural effusions associated with pB-ALL/pB-LBL

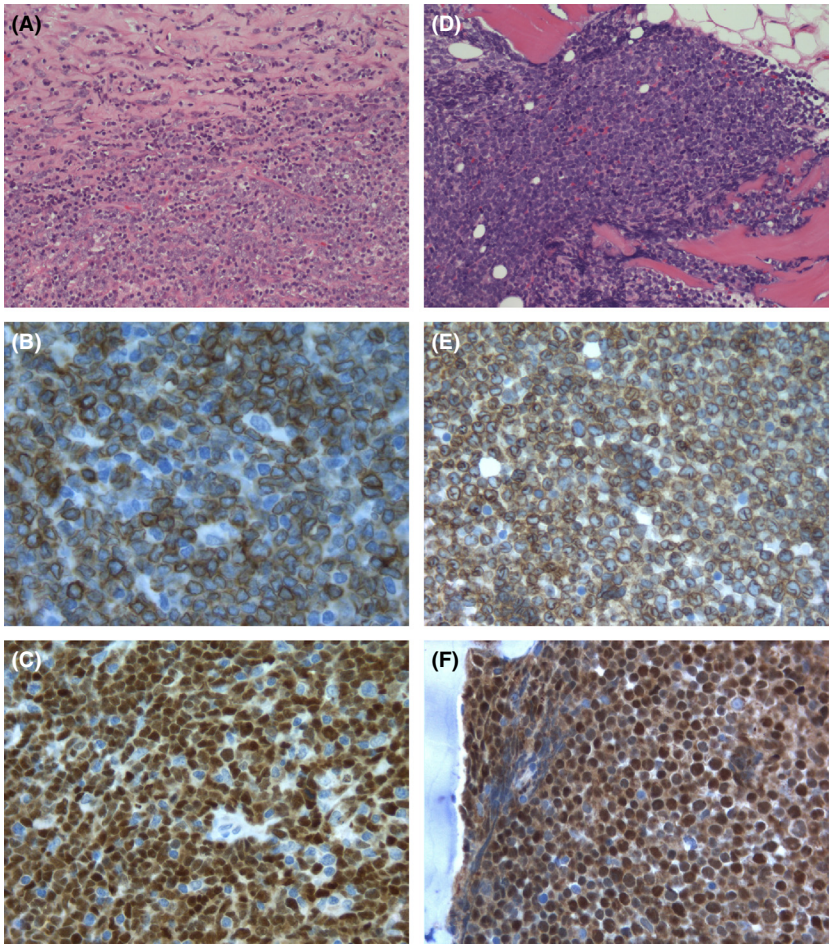

Figure 2. (A) Case 1: Pleural biopsy showing infiltration with medium to large immature lymphoid blasts. Some nuclei appear vesicular and contain prominent nucleoli, the background contains scattered plasma cells, small lymphocytes and occasional macrophages. The tumors cells show strong membranous positivity for CD79a (B) and nuclear positivity for TdT (C). (D) Case 2: Bone marrow trephine showing subtotal replacement with a monomorphic infiltrate of immature lymphoid cells. The infiltrating cells demonstrate strong and diffuse membranous positivity for CD79a (E) and nuclear positivity for TdT (F).

are much less common, but cases of diagnosis, using pleural cytology have also been reported [5]. Our experience of pleural cytology in this condition was less positive with one case having normal cytology despite impressive pleural disease and the second patient having only scant abnormal cells, insufficient for cytometric evaluation.

A reviewer has suggested that these cases may simply represent lateral extension of mediastinal disease to the external surface of the pleura. However, the prominent mediastinal soft tissue observed in Case 1 was of borderline significance and for the second case there was no evidence of mediastinal disease at all. The pleural biopsy for Case 1 demonstrated diffuse and extensive infiltration consistent with the radiological evidence of a tumor arising from within the pleura.

While pB-ALL may involve extramedullary sites, this is more commonly a feature of relapse, indeed, pleural disease has already been reported in this context [10]. The finding of prominent pleural disease at presentation is noteworthy as the clinical picture we describe is much more common in T-LBL/T-ALL or Hodgkin disease. Many patients with intrathoracic LBL will present with severe respiratory compromise mandating urgent empirical therapy with corticosteroids. Rapid disease response and tissue necrosis means that subsequent biopsy will fail to provide a definitive histological diagnosis in a subset of these patients. Where biopsy has been impractical or nondiagnostic treatment is often continued under the presumption that the clinical picture is that of T-LBL. As we move into an era of increasingly targeted therapies, the distinction between lineages will become increasingly relevant. As such, it is important that a histological diagnosis is pursued wherever possible and assumptions about lineage are not made on the basis of clinical features

alone. Developments in the field of cytopathology may assist in this regard by improving the diagnostic yield from pleural fluid examination.

The number of patients with this presentation is too small to assess its prognostic impact, but both of our patients responded well to standard therapy and remain in remission after two years. All children with pB-LBL should be treated with intensified remission induction therapy as here, rather than NCI criteria-directed therapy, which is probably inadequate, although evidence from randomized studies is lacking in this rare disease.

Acknowledgments

There are no acknowledgements.

Conflict of Interest

There are no disclosures or conflicts of interest to declare.

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