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Case Report

Aberrant Expression of B-Cell Markers in T-Cell Lymphoblastic Lymphoma in Pleural Fluid

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- FCM: Flowcytometry; IPT: Immuno phenotype; T-cell LBL: T cell lymphoblastic lymphoma; PE: Pleural effusion; NHL: Non Hodgkin's lymphoma; ALL: Acute lymphoblastic lymphoma

Abstract

T-cell lymphoblastic lymphoma is an aggressive malignancy which accounts for 85% of all the lymphoblastic lymphomas. It has a male preponderance and manifests in young adulthood and adolescent age group. The patients typically present with pleural effusion, chest pain, and respiratory distress and in rare cases a vena cava syndrome can be encountered. We present the case of an 11-year-old female patient who presented with fever, cough, weight loss, chest pain and breathing difficulty for a month prior to admission. On examination, the patient had unilateral pleural effusion (PE). A work up of tuberculosis was started and pleural fluid analysis was done. The cytology however, showed the presence of lymphoblasts on smears. Flow cytometric analysis revealed T-cell lymphoblasts with aberrant expression of B-cell markers. A thoracic computed tomography (CT) scan was performed later and showed the presence of an anterior mediastinal mass measuring 7x10x3 cms. The patient also had un resolving pericardial effusion. A cardiocentesis was performed which showed similar findings. The patient was then shifted to the hemato-oncology ward for induction chemotherapy. T-cell lymphoblastic lymphomas are usually hard to diagnose considering the fact that the symptoms are often vague. The expression of aberrant B-cell markers made the diagnosis a challenge. It is essential to establish the diagnosis without delay and start appropriate chemotherapeutic treatment.

INTRODUCTION

Lymphoblastic lymphoma (LBL) is a rare malignancy accounting for less than 2% of non-Hodgkin's lymphomas (NHL). T-cell lymphoblastic lymphoma (T-LBL) accounts for 85 to 90% of all LBL and occurs most frequently in late childhood, adolescence, and young adulthood, with a male predominance of 2:1 [1]. Clinically majority of the cases of T-cell ALL present with a rapidly progressing mediastinal mass lesion and pleural effusions [2]. The accurate diagnosis is often a challenge, because of the low positivity of malignant cells by cytological examination of Pleural effusions, or as the malignant cells may be difficult to distinguish from the reactive lymphoid cell population and hence it requires a multimodal approach [3]. Traditionally histopathology and biopsy were considered the cornerstones of the diagnosis of lymphoma. Biopsy although accurate have a disadvantage of crush artifacts, limited availability of diagnostic material and requiring significant time for processing and immunohistochemistry. Fine Needle Aspiration followed by immunophenotyping on Flowcytometry (FC) offers many advantages in terms of its application in body cavity fluids, and it has proven to be very useful both in the setting of a known disease and for the diagnosis of new lymphomas [4]. We describe a case with pleural effusions, which was diagnosed as cortical T-LBL with aberrant B-cell expression on pleural fluid by flowcytometry. To the best of our knowledge this is the first case of T-cell LBL with aberrant expression B cell markers diagnosed on flowcytometry of pleural fluid.

CASE PRESENTATION

An 11-year-young female presented in the pediatric outpatient department of Kalawati Hospital, with fever, cough, weight loss, chest pain and shortness of breath for one month. The fever was low grade, intermittent and was relieved on medication. Cough was mildly productive. She complained of chest pain and shortness of breath that had progressively worsened in the past one week. General physical examination was within normal limit. No peripheral lymphadenopathy was seen. However, chest examination revealed significantly decreased breath sounds over the right hemi thorax with a dull percussion note. Liver was enlarged 2.5 cm below the costal margin, however there was no splenomegaly. Laboratory results included a complete blood count, liver function tests, kidney function test, Acid blood gas analysis (ABG). The leukocyte count was decreased to 2.37x 10^9/L; hemoglobin was 13.9 g/dl (normal); platelet count, 302 x 10^9/L (normal). A peripheral blood smear examination revealed leucopenia with no abnormal lymphoid cells. Serum creatinine, blood urea nitrogen, serum electrolytes, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) were all within normal limits. The

ABG however revealed a decrease in the oxygen saturation to 60mmhg (normal 83-108), and a decrease in the carbon dioxide saturation to 26mmhg (normal 32-45). Serum test results were negative for hepatitis B virus (HBV), human immunodeficiency virus (HIV). Sputum cultures were negative for bacteria, fungus, and Mycobacterium tuberculosis.

Chest X-ray demonstrated a right sided pleural effusion of depth 14mm with thick septae within along with pleural thickening suggestive of an empyema. The left sided costophrenic (CP) angle was clear. There was also associated pericardial effusion of depth 7mm at the apex in systole (Figure 1). Chest ultrasonography revealed massive right sided pleural effusion of depth 9 mm, pleural thickening with underlying collapse. A pericardial effusion of 12 mm was also present. USG abdomen showed an enlargement in the liver size to 13 cm with no intra hepatic biliary radical dilatation or space occupying lesion. No splenomegaly was noted. Pancreas, kidneys, urinary bladder were also within normal limit. No free fluid was detected. No lymphadenopathy was detected. Thoracocentesis was performed. Pleural fluid was grossly straw colored and the routine biochemical examination showed a sugar content of 10mg/dl (low) and proteins 4200 mg/dl (normal). The total leukocyte count was $50x10^9$/L. The cytologic examination of the effusion smears revealed massive number of atypical lymphoid cells. These cells were predominantly small to intermediate in size, with a high nucleo cytoplasmic ratio, thin rim of cytoplasm. Nuclear chromatin was condensed with many of the cells showing indentations and clefting. Nucleoli were inconspicuous. Mitotic count was high ranged from 10 to 12 per 10 high power field (Figure 2). Pleural fluid cultures were negative for M. tuberculosis. A cytological diagnosis of Non-Hodgkin Lymphoma was given.

A flowcytometry analysis of the pleural fluid was also performed. The total cell count of the fluid was $50x10^9$/L. The panel initially comprised of limited markers including CD45, CD19, CD10, CD3, CD34 and MPO. The gating strategy used was CD45 vs. Side Scatter. The flow depicted a tight cluster which was low side scatter and dim to moderate CD45 positive, no other cells were present in the entire population. This population depicted

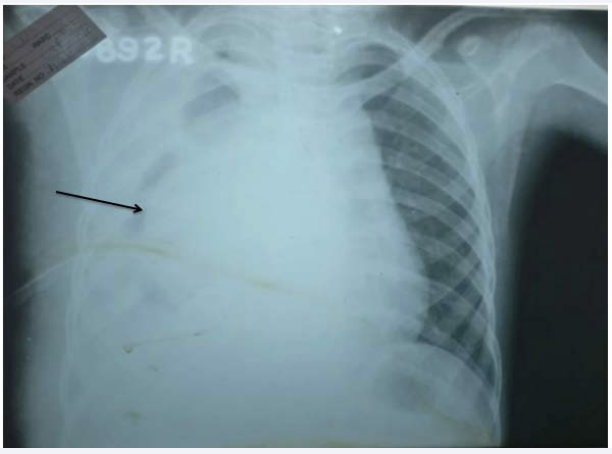

Figure 1 Right sided pleural effusion of depth 14mm with thick septa within along with pleural thickening suggestive of an empyema.

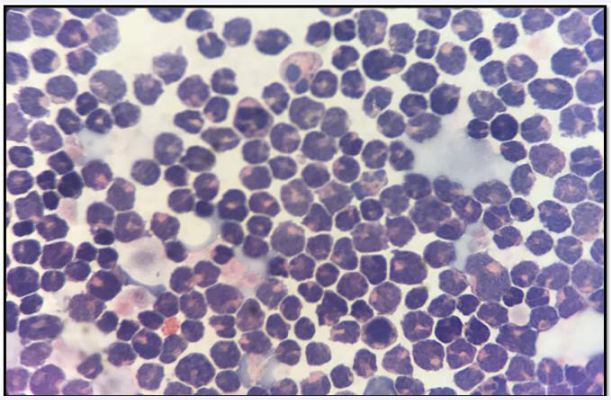

Figure 2 Pleural effusion cytology, Pap (1000x): Small to intermediate in size, Scant cytoplasm, High nucleo-cytoplasmic ratio, condensed nuclear chromatin, indentations and cleft, Inconspicuous nucleoli.

blasts which were positive for both CD10 and CD3, hence arriving at a diagnostic dilemma. Cells were then further analysed with an extensive panel and showed the presence of all the T-cell markers including CD3, CD4, CD5, CD7, cytoplasmic CD3, CD8, CD99 and immaturity markers including Tdt and CD1a. These cells also showed a positivity of B-cell markers like CD79a and CD10. However they were negative for CD19, HLA-DR and other myeloid markers. Hence, a diagnosis of Cortical T-cell LBL with aberrant expression of B-cell Marker (Figure 3). In addition, bone marrow aspirate was performed and was negative for malignant cells. A cardiocentesis was performed thereafter and the fluid was sent again for cytology. The pericardial fluid showed a similar picture as the pleural fluid with a total cell count of $42x10^9$/L. The cytospin smears revealed the presence of atypical lymphoid cell population which was similar to the pleural fluid smears. A CECT chest was performed thereafter, which showed the evidence of a heterogeneously enhancing soft tissue density mass measuring 7.5x8.9x10.4 seen in the anterior mediastinum involving and infiltrating the anterior chest wall (Figure 4).

DISCUSSION

T-LBL is a rare type of non-Hodgkin's lymphoma, with an overall incidence of 0.1 per 100 inhabitants which predominantly occurs in male adolescents or young adults [5]. Most of these patients present with pleural and pericardial effusion [6]. To the best of our knowledge this is the first case of T-cell LBL with aberrant B-cell expression in a pleural fluid. Here we reported an 11-year-old female with a unilateral pleural and pericardial effusion. The initial cytologic examination of pleural fluid was worked up for tuberculosis; however the pleural fluid cytology revealed massive lymphocytosis. A lymphoma/leukemia was suspected but the definitive diagnosis was unclear then. The cyto morphological analysis was uncertain to distinguish between a reactive lymphoid population from lymphoma including T-LBL. Based on morphology alone these neoplasms cannot b ruled out. T-cell Lymphoblastic Lymphomas exhibit a varied immunophenotype profile based on maturation. According to the World Health Organization (WHO) 2016 classification, it can be divided as Pro (early) which is cCD3 positive, CD7 positive, CD2 negative, CD1a, CD4, CD8 negative and CD34 positive or negative.

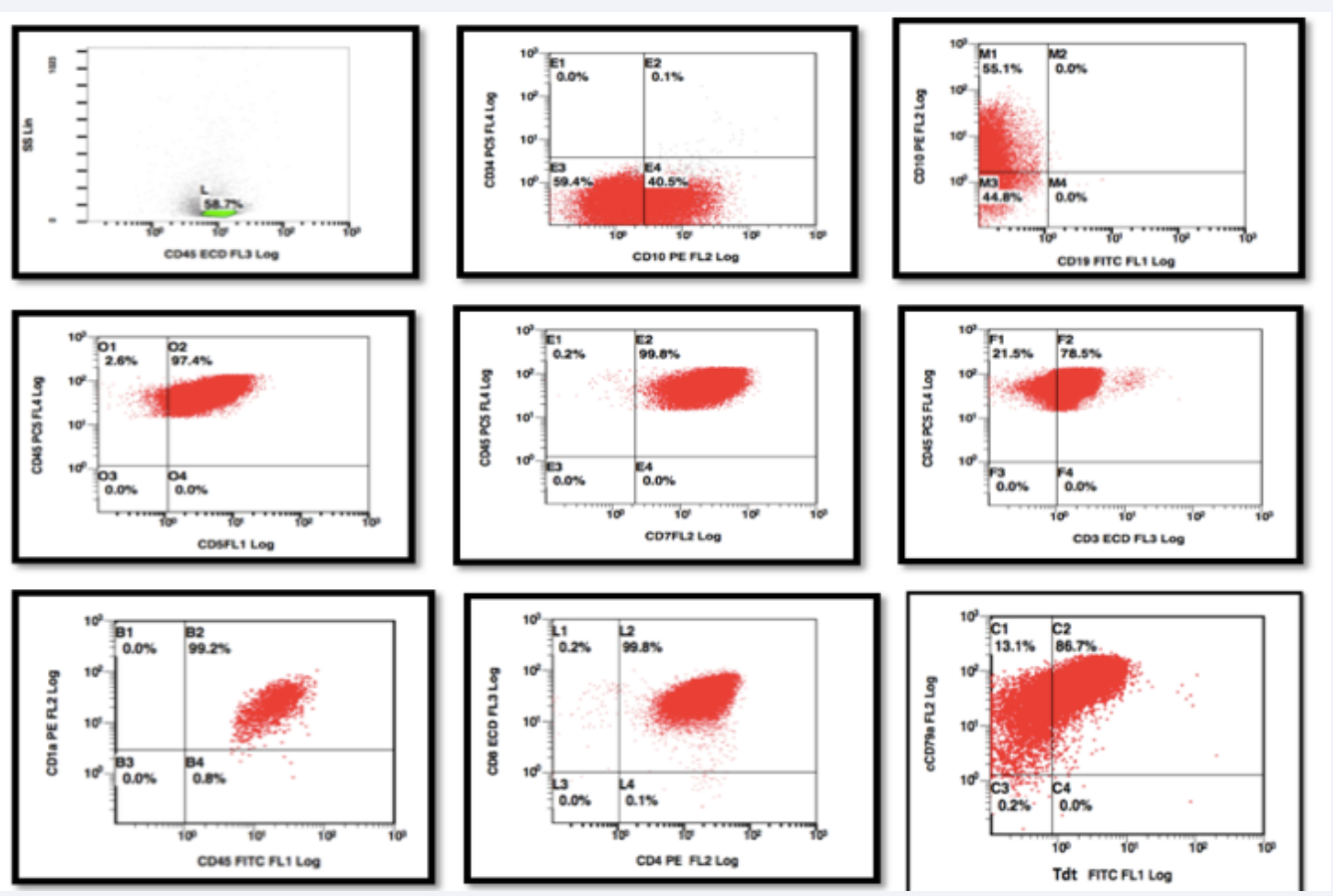

Figure 3 FCM-IPT (pleural fluid) Beckman Coulter FC500.

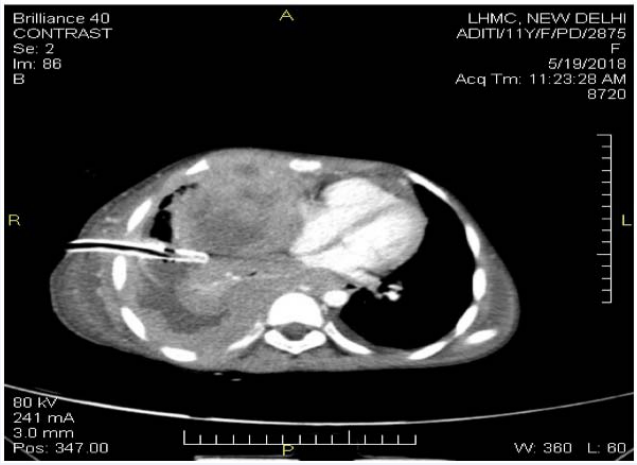

Figure 4 CECT Chest: Heterogeneously enhancing soft tissue density mass measuring 7.5x8.9x10.4 seen in the anterior mediastinum involving and infiltrating the anterior chest wall.

The Cortical T-cell LBL is generally cCD3, CD7, CD2, CD1a, CD4, CD8 positive and CD34 negative. Medullary T-cell LBL is generally cCD3, sCD3, CD7, CD2 positive, CD4, CD8 positive or negative, CD34 and CD1a negative. In the current study, the flowcytometry analysis conducted on the pleural fluid was positive for CD3, 5, 7, TdT, CD1a, CD4, CD8 along with B cell markers CD79a and CD10. This extensive panel confirmed the lymphoma to be of a T-cell type with aberrant expression of a B-cell marker.

In India, Tuberculosis is the most common inflammatory condition causing pleural effusion and should be distinguished from a lymphomatous effusion. Cytomorphological evidence of activated lymphocytes, with plasma cells points to a reactive etiology. The presence of nuclear clefting, hand mirror cells, mitotic figures favors a lymphomatous effusion. Flowcytometry is highly useful in these situations because a reactive T-cell population would be either CD4 or CD8 positive, but a dual positivity and a monoclonal population suggests malignancy.

The expression of this aberrant marker (CD79a) is of prognostic significance. A study done by Lai, et al. suggested that the expression of CD79a was confined to pediatric cases of T-cell Leukemia/lymphoma and high expression of CD79a was biased toward a certain immunophenotype- types and unusual cytogenetic abnormalities, as well as a poor response to treatment [7].

However, the expression of these aberrant markers can be used for developing targeted therapies as well as for monitoring minimal residual disease post induction chemotherapy.

Immunophenotyping by FC is a well-established diagnostic method for the detection and sub typing of hematolymphoid malignancies in blood, lymph nodes, bone marrow, and

other organs. The incorporation of this method into routine cytopathologic diagnostics appears to be less well established and varies among institutions. The application of FC by cytopathologists is feasible and rewarding in relation to the diagnostic yield. As the diagnostic criteria of hematologic diseases tend to incorporate more and more immunogenic and molecular features of the tumor cells instead of purely architectural attributes of the tissue, as defined in the current WHO classification, the spectrum of final diagnoses in hematopathology within the reach of cytopathology widens [8,9]. Very few case reports depicted the role of flowcytometry in diagnosis of T-cell LBL in pleural fluid Barnett, et al. also reported a case of Pro-T cell ALL presenting with dyspnea and pleural effusion by flowcytometry [10]. Czedu and Ali studied 32 lymphomatous effusions by flowcytometry but none of them was T-cell LBL. Bhaker et al. studied the spectrum of cytomorphology and FC immunophenotyping in 15 cases of T-LBL, including 10 FNA and 5 effusion (4 pleural and 1 pericardial) samples [11]. FC demonstrated positivity for all T-cell markers with presence of CD10 in 7 of 15 cases and human leukocyte antigen-D related in 1 of 15 cases. Dual CD4/CD8 positivity was observed in all cases forming a tight cluster, which is consistent with the cortical T-LBL subtype. The combination of cytomorphology and FC enables an accurate and rapid diagnosis of T-LBL on FNA and effusion cytology specimens, thereby obviating the need for a biopsy. We suggest the use of flowcytometry immunophenotyping as the preferred ancillary investigation in patients with such type of lymphoma.

CONCLUSION

In conclusion, we reported this case with pleural effusions, because of rarity of diagnosis of lymphoblastic lymphoma by flowcytometry analysis. This case points out the importance of early utilization of a minimally invasive method, for the undiagnosed pleural effusion for the physician to make diagnosis of pleural diseases. Cytomorphology complemented with IPT provides a reliable, fast and accurate diagnosis and typing of T-cell LBL enabling a prompt institution of therapy.

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