The immunophenotype of pre-TALL/LBL revisited

Robert E. Lewis, Julius M. Cruse⁎, Catherine M. Sanders, Rachel N. Webb, Benjamin F. Tillman, Kevin L. Beason, John Lam, Jonathan Koehler

Department of Pathology, University of Mississippi Medical Center, 2500 North State Street, Jackson, Mississippi 39216, USA

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Abstract

Flow cytometric analysis of cluster of differentiation (CD) markers in abnormal lymphocyte populations is crucial in the diagnosis of precursor T cell acute lymphoblastic leukemia (T-ALL)/lymphoblastic lymphoma (LBL). The World Health Organization (WHO) suggested immunophenotype for pre-T ALL/LBL typically includes the expression of TdT, cCD3, and CD7, while CD2, CD3, CD4, CD5, CD8, and CD10 are variably expressed. The myeloid antigens CD13 and CD33 are usually positive, whereas CD117 and cCD79a are infrequently expressed. Furthermore, there is frequent dual expression of CD4 and CD8. In the present investigation, 19 cases of pre-TALL/LBL were analyzed for selected CD marker expression. Fifteen of 19 cases studied were evaluated for TdT, cCD3, and cCD79a expression. Eleven (73.3%) positively expressed TdT, 15 (100%) positively expressed cCD3, and 9 (60%) positively expressed cCD79a. Of the 17 cases analyzed for CD7, CD5, and CD10 expression, CD7 and CD5 were positive in all 17 (100%) cases, whereas CD10 was positive in 8 (47.1%) cases. Of the 18 cases evaluated for CD2, CD3, CD4, CD8, and dual expression of CD4 and CD8, CD2 was expressed in 14 (77.8%), while CD3 was expressed in 7 (38.9%) cases. CD4 was positive in 11 (61.1%), and CD8 was expressed in 9 (50%) cases. Dual expression of CD4 and CD8 occurred in only 4 (22.2%) of the cases. Of the 16 analyzed for CD13, CD33, and CD117, only 1 case (6.3%) expressed CD13, while 2 (12.5%) cases expressed CD33 and CD117. Thus, these data point to the need for a more extensive study to reevaluate the current WHO defined immunophenotype used in the diagnosis of pre-TALL/LBL.

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Introduction

Precursor T cell acute lymphoblastic leukemia (T-ALL)/lymphoblastic lymphoma (T-LBL) is a disease involving the presence of neoplastic T cell lymphoblasts in both the blood and the bone marrow. When there is extensive involvement in both the bone marrow and the blood, the preferred term is leukemia. However, if a mass lesion is present with minimal blood and bone marrow involvement, the appropriate term is lymphoma (Jaffe et al., 2001). As cells mature, they undergo antigenic transformation or the gain and loss of specific cluster of differentiation (CD) markers. In addition, cells also undergo antigenic transformation as they become malignant. The CD markers are analyzed using flow cytometry in order to distinguish different types of leukemias and lymphomas.

Normal T lymphoblasts usually express TdT, CD2, CD5, CD7, and lack CD3 while cCD3 is typically expressed. CD4 and CD8 are usually coexpressed (Cruse et al., 2004). The World Health Organization (WHO) suggested immunophenotype for pre-T ALL/LBL typically includes the expression of TdT, cCD3, and CD7, while CD2, CD3, CD4, CD5, CD8, and CD10 are variably expressed. The myeloid antigens CD13 and CD33 are usually positive, whereas CD117 and cCD79a are infrequently expressed. Furthermore, there is frequent dual expression of CD4 and CD8 (Jaffe et al., 2001).

Materials and methods

Nineteen cases of precursor T cell acute lymphoblastic leukemia/lymphoma were diagnosed based on immunophenotype, clinical assessment, and morphology over the course of four years in the Department of Pathology at the University of Mississippi Medical Center in Jackson. Immunophenotyping was performed by analysis of peripheral blood samples collected in EDTA, bone marrow aspirates, and lymph node cell preparations by flow cytometry (Epics XL and FC500, Beckman and Coulter, Miami, FL) using standard techniques.
Results

Of the 19 cases studied, a subpopulation of 15 was evaluated for TdT, cCD3, and cCD79a expression. TdT was positively expressed in 11 (73.3%) cases, cCD3 was expressed in 15 (100%), and cCD79a was positively expressed in 9 (60%). Of the 17 cases analyzed for CD7, CD5, and CD10 expression, CD7 and CD5 were positive in all 17 (100%) cases, whereas CD10 was positive in 8 (47.1%) cases. Of the 18 cases evaluated for CD2, CD3, CD4, CD8, and dual expression of CD4 and CD8, CD2 was expressed in 14 (77.8%), while CD3 was expressed in 7 (38.9%) cases. CD4 was positive in 11 (61.1%), and CD8 was expressed in 9 (50%). Dual expression of CD4 and CD8 occurred in only 4 (22.2%) of the cases. Of the 16 analyzed for CD13, CD33, and CD117, only 1 case (6.3%) expressed CD13, while 2 (12.5%) cases expressed CD33 and CD117 (Fig. 1).

Discussion

Normal T lymphoblasts typically express TdT, CD2, CD5, CD7, and lack CD3 surface expression while cCD3 is typically expressed. CD4 and CD8 are usually coexpressed (Cruse et al., 2004). As T cells become malignant, they undergo antigenic transformation or a change in immunophenotype. The WHO suggested immunophenotype of pre-TALL/LBL typically includes the expression of TdT, cCD3, and CD7, while CD2, CD3, CD4, CD5, CD8, and CD10 are variably expressed. CD13 and CD33 are usually positive, whereas CD117 and cCD79a are infrequently expressed. Furthermore, CD4 and CD8 are frequently coexpressed (Jaffe et al., 2001).

Terminal deoxynucleotidyl transferase (TdT) is an early lymphocyte marker involved in the rearrangement of T cell receptor genes and immunoglobulin (Cruse et al., 2004). According to Jaffe et al. (2001), TdT is expressed on all lymphoblasts in pre-TALL/LBL. Additionally, Bain et al. (2001) states that TdT is expressed in more than 90% of patients with pre-TALL/LBL. Also, according to Cruse et al. (2004), TdT can be detected in 90% of acute lymphoblastic leukemia cases. However, in this study only 11/15 (73.3%) confirmed pre-TALL/LBL cases were positive for TdT expression conflicting with the immunophenotype proposed by WHO, Bain, and Cruse. These results suggest that the T lymphoblasts of pre-TALL/LBL may drop TdT expression.

CD2 which is expressed by T cells and NK cells functions as an adhesion molecule and is involved in signal transduction (Cruse et al., 2004). Additionally, CD2 inhibits T cell apoptosis and functions in mediating NK cell lysis (Abbas and Lichtman, 2005). According to Jaffe et al. (2001), CD2 is variably expressed on T lymphoblasts in pre-TALL/LBL. Bain et al. (2001) state that the expression of CD2 varies with the progression of the disease. Concurrently, CD2 was expressed in 14 of 18 (77.8%) cases in this investigation.

CD3, a T cell marker, is involved in signal transduction and the assembly of the T cell receptor complex (Cruse et al., 2004). CD3 is typically not expressed in T lymphoblasts; expression occurs after the cells mature. However, cCD3 is expressed by immature T cells. Jaffe et al. (2001) state that CD3 is variably expressed in pre-TALL/LBL, while Bain et al. (2001) state that CD3 is expressed in more than 50% of patients presenting with pre-TALL/LBL. Pui et al. (1990) analyzed 86 cases of pre-TALL for CD3 expression and found 33% of these cases positively expressed CD3. In the current investigation, 7/18 (38.9%) cases positively expressed CD3, and 15/15 (100%) cases expressed cCD3. These results along with the results obtained by Pui et al. (1990) agree with the WHO standard, but conflict with Bain’s diagnostic immunophenotype for pre-TALL/LBL.

CD4 functions in regulating T–B cell adhesion and as a coreceptor in antigen-induced T cell activation. CD4 also binds to MHC class II molecules and is involved in thymic differentiation (Cruse et al., 2004). It is expressed on monocytes, T cells, and granulocytes. CD8, expressed by T cells, is a coreceptor for MHC class I molecules (Cruse et al., 2004). In addition, CD8 is involved in thymocyte development (Abbas and Lichtman, 2005). According to WHO, CD4 and CD8 are often coexpressed on T lymphocytes in pre-TALL/LBL (Jaffe et al., 2001). In the present investigation, CD4 and CD8 were only coexpressed in 4/18 (22.2%) cases conflicting with the diagnostic immunophenotype published by WHO. These data suggest that the malignant T lymphoblasts of pre-TALL/LBL may lose CD4/8 dual expression as the disease progresses.

CD5 is a costimulatory molecule found on T cells and B cells and is a key regulator of immune tolerance (Cruse et al., 2004). Greater than 50% of cases of pre-TALL/LBL are expected to express CD5 (Bain et al., 2001). The WHO states that CD5 is variably expressed by lymphoblasts in TALL/LBL (Jaffe et al., 2001). In a study of 86 cases of pre-TALL conducted by Pui et al. (1990), 94% of the cases exhibited positive expression of CD5. Concurrently, in this study 17/17 (100%) cases positively expressed CD5. The results of this study and the study conducted by Pui et al. (1990) imply that CD5 may be positive in more cases of pre-TALL than the established immunophenotype suggests.

CD7 which is expressed on T cells, dendritic cells, and NK cells is a costimulatory and adhesion molecule (Cruse et al., 2004). According to WHO, CD7 is usually positive in pre-TALL/LBL (Jaffe et al., 2001). In the current study, 17/17 (100%) cases positively expressed CD7 agreeing with the established WHO immunophenotype for pre-TALL/LBL.

CD13 and CD33 are pan myeloid markers. CD13 is an immunopeptidase involved in the alteration of target cell specificity and cleavage of peptides bound to MHC II molecules (Abbas and Lichtman, 2005). CD33 is involved in negative selection for human self-regenerating hematopoietic stem cells (Cruse et al., 2004). Jaffe et al. (2001) state that CD13 and CD33 are frequently expressed in pre-TALL. Conversely, in this investigation, CD13 was present in only 1/16 (6.3%) confirmed case of pre-TALL, and CD33 was only positive in 2/16 (12.5%) cases.

Conclusion

The presence or absence of certain CD markers in nineteen confirmed cases of pre-TALL/LBL was compared to the existing suggested immunophenotype. The data collected in the current
investigation questions the inclusion of several immunophenotypic markers such as TdT, CD3, CD5, coexpression of CD4/8, CD13 and CD33 currently used to aid in the diagnosis of pre-TALL/LBL. Thus, these data point to the need for a more extensive study to reevaluate the current WHO defined immunophenotype used in the diagnosis of pre-TALL/LBL.

Fig. 1. Flow cytometry histograms representing pre-TALL/LBL cases used in this study: (A) absence of TdT expression and positive expression of cCD3, (B) absence of CD3 expression, (C) positive expression of CD5 and CD7, (D) absence of CD4/CD8 expression, (E) absence of CD13 expression, (F) absence of CD33 expression.
References