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ScienceDirect
Annals of Diagnostic Pathology 11 (2007) 55–60
Annals of DIAGNOSTIC PATHOLOGY

Unusual expression of CD94 on CD8$^+$ TCR-$\alpha\beta$ T cells in infectious mononucleosis

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Abstract Infectious mononucleosis, caused by primary Epstein-Barr virus (EBV) infection, is usually a benign, self-limited lymphoproliferative disorder. We report a case of a 21-year-old woman who presented with fever, sore throat, severe neutropenia, and absolute lymphocytosis with atypical lymphocytes. In situ hybridization for EBV-encoded small RNA performed on the marrow aspirate clot specimen demonstrated scattered positive cells. EBV serology was compatible with primary infection. Flow cytometry immunophenotypic studies performed on aspirate material revealed a profoundly expanded population of CD8$^+$ T-cell receptor (TCR)-$\alpha\beta$ T cells with uniform expression of CD94. No evidence of a monoclonal T-cell population was found as assessed by V_β use with flow cytometry and by TCR γ-chain gene rearrangement using a polymerase chain reaction method. Uniform expression of CD94 in an exuberant reactive proliferation of CD8$^+$ TCR-$\alpha\beta$ T cells in infectious mononucleosis has not been reported previously, and combined with atypical morphology might be misinterpreted as a malignant neoplasm.

Keywords: CD94; NK cell receptors; Immunophenotype; Infectious mononucleosis

1. Introduction

CD94 is a type II transmembrane glycoprotein with a C-type lectin domain in its extracellular portion and a very short cytoplasmic domain. It is expressed as a disulfide-linked heterodimer with a variety of natural killer (NK) cell receptor subfamily G2 (NKG2) molecules [1,2] CD94/NKG2 receptors belong to a group of proteins known as NK cell receptors (NKRs). This group also includes killer cell immunoglobulin-like receptors (KIRs, CD158). Natural killer cell receptors play a role in recognition of major histocompatibility complex class I molecules and in inducing NK-cell self-tolerance. Initially thought to be restricted to NK cells, CD94/NKG2 and CD158 are also expressed by small populations of T cells, mainly T-cell receptor (TCR)-$\gamma\delta$ T cells and CD8$^+$ TCR-$\alpha\beta$ T cells [3,4].

Expression of NKRs in these small subsets of T cells in healthy subjects is heterogenous and diverse. This diversity results from variable proportions of T cells expressing individual NKRs as well as different levels of intensity of NKR expression [5-7]. In contrast, neoplastic T cells in patients with lymphoproliferative disorders would be expected to display NKR repertoires in a uniform clonal manner, with respect both to proportion of NKR$^+$ cells and to levels of cell surface expression. Indeed, uniform expression of CD158 or CD94 or both has been found in T-cell large granular lymphocyte (LGL) leukemia [5-7] and hepatosplenic T-cell lymphoma (HSTL) [8]. A clonal pattern of CD158 expression was observed in 50% to 70% of T-cell LGL leukemia cases and in all HSTL cases. Uniform/abnormal expression of CD94 was also observed in 40% to 95% of T-cell LGL leukemia and in all HSTL cases. These studies, therefore, support the notion that uniform clonal expression of NKRs can serve as markers for detecting a neoplastic T-cell proliferation.

However, other conditions, such as viral infections, can clinically mimic T-cell LGL leukemia by causing neutropenia and increased LGL levels with abnormal expression of CD94/NKG2 [9-11]. In infectious mononucleosis, Poon et

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1092-9134/$ – see front matter © 2007 Published by Elsevier Inc.
doi:10.1016/j.anndiagpath.2006.06.005

al [12] reported CD94/NKG2 being expressed by a small subset of $CD8^+$ T cells. Another group reported that CD94/NKG2 was down-regulated in $CD8^+$ TCR-$\alpha\beta$ T cells and expressed in up to 85% of $CD8^+$ TCR-$\gamma\delta$ T cells [13].

Here we describe a patient with infectious mononucleosis presenting with severe neutropenia and lymphocytosis with atypical lymphocytes. Flow cytometry immunophenotypic studies showed uniform expression of CD94 in a profoundly expanded population of $CD8^+$ TCR-$\alpha\beta$ T cells. This unusual pattern of CD94 expression could lead to misdiagnosis without knowledge of its occurrence in infectious mononucleosis.

2. Case presentation

A 21-year-old white woman with a 1-month history of an enlarged right cervical lymph node was referred to a hematologist. She also reported enlarged lymph nodes in the neck and groin, fever, sore throat, headache, fatigue, and nausea, but denied any abdominal pain, night sweats, or chills. The patient had previously received clindamycin for her sore throat from her family physician and this seemed to be helpful. Her past medical history was notable for a 1-week hospitalization at the age of 8 years because of a viral infection, anemia diagnosed 5 years ago and treated with vitamin B_{12} for 1 year, and possible infectious mononucleosis 5 years ago.

Physical examination was remarkable for multiple 1- to 2-cm lymph nodes bilaterally in her neck, the left axilla, and bilateral groins. An abdominal ultrasound showed borderline splenomegaly, but there was no palpable spleen on physical examination. The patient's laboratory findings showed elevated levels of bilirubin (1.1 mg/dL; reference range [RF], 0.0-1.0), total protein (8.8 g/dL; RF, 6.0-8.2), alkaline phosphatase (457 IU/L; RF, 38-126), alanine aminotransferase (721 IU/L; RF, 7-56), aspartate aminotransferase (509 IU/L; RF, 15-46), lactic dehydrogenase (1914 IU/L; RF, 313-618), and immunoglobulin (Ig) G (2030 mg/dL; RF, 600-1600). Epstein-Barr virus (EBV) serology was most compatible with primary infection with increased IgM to viral capsid antigen (2.01 index, detected by enzyme-linked immunosorbent assay technique). There was serologic evidence of hepatitis C virus infection but no evidence of previous cytomegalovirus infection. Peripheral blood examination revealed severe neutropenia (0.16×10^9/L) and absolute lymphocytosis (7.2×10^9/L) with atypical lymphocytes. Bone marrow aspirate and biopsy specimens showed increased interstitial lymphocytes. Flow cytometry immunophenotyping demonstrated uniform expression of CD94 in a profoundly expanded population of $CD8^+$ cytotoxic T cells. Assessment of TCR V_β use showed no evidence of monoclonality. This was further confirmed by analysis of the TCR γ-chain gene that showed an oligoclonal amplification pattern.

The clinical, morphologic, serologic, flow cytometric, and molecular studies supported the diagnosis of infectious mononucleosis. No specific treatment was recommended except for the patient to complete the previously prescribed clindamycin treatment for her sore throat. Three weeks later, her absolute neutrophil count recovered to 1.59×10^9/L. Her fatigue was reduced and she then returned to school.

3. Materials and methods

The peripheral blood and bone marrow aspirate smears were stained with Wright-Giemsa. The bone marrow aspirate clot and trephine biopsy specimens were fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin.

Four-color flow cytometric immunophenotypic studies on bone marrow aspirate material were performed by using a FACSCalibur instrument with CellQuest Pro software as described previously (both from BD Biosciences, San Diego, CA) [14]. Data analysis was performed with Paint-a-Gate software (BD Biosciences). Distinct cell populations (clusters) were identified based on any combination of forward and orthogonal light scatter properties and fluorescence intensity with various antibody combinations. The assessment of dim or bright expression of an antigen in a population was qualitative, based on a definitive shift of that population cluster compared with internal control cluster. The panel of antibodies used to analyze the lymphocytes included CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD16, CD19, CD20, CD45, CD56, CD57, CD94, CD158a, CD158b, CD158e, TCR-$\alpha\beta$, and TCR-$\gamma\delta$. In addition, the specimen was analyzed with 24 antibodies against TCR β-chain variable

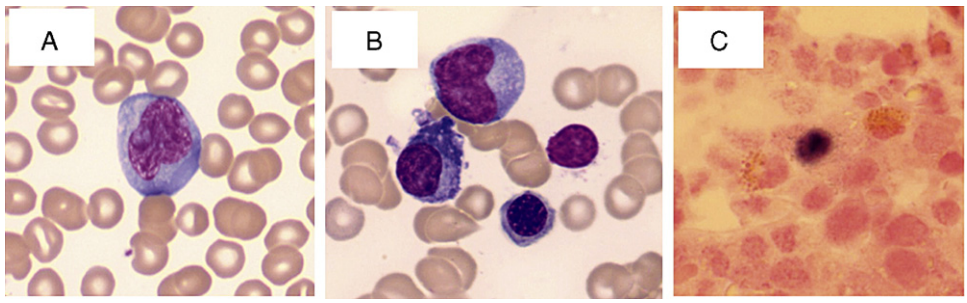

Fig. 1. Peripheral blood (A) and bone marrow aspirate smears (B) show numerous medium-sized to large lymphoid cells with abundant basophilic cytoplasm and variable peripheral basophilia, oval to irregular nuclear contours, slightly dispersed chromatin, and occasional nucleoli (original magnification, ×1,000). (C) Rare EBV positive cells in bone marrow (detected by in situ hybridization of EBV-encoded small RNA; original magnification, ×500).