INTRODUCTION

Natural killer (NK) cell neoplasms are a group of rare but highly malignant tumors with a broad spectrum of morphologic, immunophenotypes and clinical features. The WHO classification of NK cell neoplasms encompasses 3 distinct entities: 1) aggressive NK cell leukemia, 2) extranodal NK/T-cell lymphoma, nasal type [1], and 3) blastic NK cell lymphoma [2]. NK cell tumors are prevalent in Asia and Central and South America.

NK cells were originally described as large granular lymphocytes with natural cytotoxicity against tumor cells. NK cells were later recognized as a separate lymphocyte lineage [3]. NK cells represent a lineage of non-T lymphocytes and non-B lymphocytes that mediate a major histocompatibility complex–nonrestricted cytotoxicity against tumor cells and bacterial or viral infected cells [4]. They constitute 10 to 15% of human peripheral blood lymphocytes and express CD2, cytoplasmic CD3ε and...
A Case of Natural Killer Cell Leukemia Case

CD56 without T cell receptor (TCR) gene rearrangement [5, 6]. The CD56 antigen is regarded as a marker of NK cell leukemia because it is consistently expressed although not specific for NK cells [7]. The etiology of NK cell neoplasm is not well understood but is considered to be strongly associated with Epstein–Barr virus (EBV). We report here the clinical, laboratory, and immunophenotypic findings of NK cell leukemia of a 54-yr-old woman.

CASE REPORT

A 54-yr-old woman presented with a 2-month history of progressive left neck mass. One month later, right neck and scalp masses were observed. Fine needle aspiration of supraclavicular nodes performed at that time showed findings consistent with tuberculosis and tissue PCR for M. tuberculosis was positive. Impression was then tuberculous lymphadenopathy. Two weeks later, she developed febrile and chilling sensation accompanied by cough and sputum. Because of the persistence and progression of the symptoms, she was referred to a pulmonologist for further evaluation and management. On physical examination, there were generalized palpable lymphadenopathy and hepatosplenomegaly. There were palpable masses on both mandibular angles, which were hard and movable. Hemoglobin was 9.1 g/dL, white blood cell count was 20.2 × 10^9/L with 89.5% lymphocytes and 5.2% neutrophils, and platelet count was 76 × 10^9/L. Peripheral blood smear showed leukoerythroblastic features with 31% atypical blastoid cells (Fig. 1). Aspartate aminotransferase was elevated to 63 IU/L and lactate dehydrogenase was elevated to 2,939 IU/L. Gram stain and acid fast bacilli (AFB) stain were negative. Culture of sputum for M. tuberculosis was negative after examinations for 8 weeks. Chest x-ray showed bronchiectasis of the left lower lobe. Computed tomography scan of the chest, abdomen and pelvis showed multiple enlarged lymph nodes in the lower neck, both supraclavicular, right paratracheal, paraaortic, subcarinal, both hilar, both axillary, portocaval, both common iliac and both inguinal areas, probably consistent with malignant lymphoma.

Bone marrow aspiration showed 80% to 90% cellularity, hypercellular for her age, with adequate megakaryocytes. M:E ratio was 1.3:1. Approximately 90% of hematopoietic cells were blastoid cells (mononuclear cells). These cells were irregular in size and shape with ovoid to irregular nuclei, irregular nuclear membrane, reticular pattern chromatin, inconspicuous nucleoli, and scanty agranular cytoplasm, compatible with L2 morphology by Frech–American–British classification (Fig. 2). The cytochemistry was positive only for periodic acid–Schiff (PAS) (Fig. 3). Immunophenotyping of the blastoid cells of bone marrow aspirates was positive for CD45 and HLA–DR but negative for other T cells, B cells, and myeloid markers: CD3, CD5, CD7, CD10, CD13, CD14, CD19, CD20, CD22, CD33, CD34, and CD61. We added CD16/56 for the immunophenotyping because blasts of this case were not positive for any lymphoid or myeloid antigen marker in our routine immunophenotyping panel for leukemia. Blasts were positive (94%) with mean fluorescence intensity of 11.0. There were no EBV–encoded RNAs by RNA in situ hybridization. The PCR for TCR gene rearrangement was not done. The histologic appearance of the biopsied lymph node showed a diffuse infiltrate of polymorphous tumor cells. Immunohistochemical staining of this specimen revealed that the tumor cells were only positive for CD56, and negative for CD3, CD20, and terminal deoxynucleotidyl transferase (TdT) (Fig. 4). The cytogenetic finding was 46, XX normal karyotype. With these findings, she was diagnosed with blastoid NK cell lymphoma/leukemia involving bone marrow, and lymph node. For further management, she was transferred to a community cancer center.

DISCUSSION

We reported one case of blastoid NK cell lymphoma/leukemia with clinical, morphological and immunophenotypic features. At first, it was diagnosed as tuberculous lymphadenopathy according to the positive result of tissue PCR for M. tuberculosis. PCR is a powerful and reliable technique for rapid diagnosis of M. tuberculosis with a reported sensitivity of 55–95% in culture positives, and 100% in both smear– and culture–positive clinical specimens [8, 9]. In a previous study, tissue PCR was found to be highly sensi–

There can be problems in the PCR technique. PCR may be influenced by the processing technique. PCR may be false positive due to contamination. In addition, positive PCR results of *M. tuberculosis* have been reported from sarcoidosis lesions, which may not have clinical relevance [12]. In our case, Gram stain and AFB stain were negative. Culture was examined weekly for 8 weeks and there were no visible colonies. Therefore, this tissue–PCR result may be false positive.

NK cell tumors are a heterogeneous group of disorders. These are classified into three groups: 1) aggressive NK cell leukemia, 2) extranodal NK/T-cell lymphoma, nasal type and 3) blastic NK cell lymphoma [2]. Among these, extranodal NK/T-cell lymphoma, nasal type is the most common type and is characterized by extranodal presentation, pleomorphic cells with angioinvasion and angiodestruction, azurophilic granules, and a strong association with EBV. Extranodal NK/T-cell lymphomas are considered to originate from mature NK cells and express CD56, CD2, and cytoplasmic CD3ε, but not surface CD3, CD5, CD16 or CD57 [2,7].

Imamura et al. characterized aggressive NK cell leukemia first as a catastrophic, systemic disease and more prevalent in Asians than in Caucasians [6]. It is highly malignant and rapidly progressive. Clinical features are fever, systemic symptoms, liver dysfunction, hepatosplenomegaly, and systemic lymphadenopathy. Cutaneous lesions are un-
common. The neoplastic cells are slightly larger than normal large granular lymphocytes (LGLs). The cytoplasm is pale or slightly basophilic with fine or coarse azurophilic granules. The nuclei have inconspicuous or distinct nucleoli with slightly immature chromatin.

Chronic NK cell lymphocytosis is a chronic expansion of mature looking NK cells (≥600/μL) in the peripheral blood for ≥6 months. This is characterized by a chronic, indolent course. In rare cases, the disease is transformed into aggressive NK cell leukemia [13].

Precursor lymphoblastic lymphoma/leukemia (LBL) expressing NK-cell associated antigens is a rare entity [14]. In a study by Sheibani et al., six tumors that expressed CD16 and CD57 in addition to terminal deoxynucleotidyl transferase (TdT), CD2, and CD4 were identified among 38 patients who were screened for LBL. These tumors, were grouped as “NK-LBL” [14]. Subsequently, CD56 has been recognized as a sensitive marker for NK cells. The patients frequently presented with leukemia and lymphadenopathy without skin involvement. These tumors were negative for EBV [12].

Our case was diagnosed with blastic NK cell lymphoma/leukemia. In our case, the leukemic cells expressed CD56 in the absence of the markers of T-cell, B-cell, and myeloid lineage–specific antigens. These cells involved bone marrow, peripheral blood and lymph node. There was no involvement of skin or nasal cavity. Morphologically, these cells were blasts rather than large granular lymphocytes. Intracytoplasmic azurophilic granules were absent. EBV was negative. These findings are unusual in aggressive NK cell leukemia. Aggressive NK cell leukemia is associated with EBV, whereas blastic NK cell lymphoma is not related to EBV. Azurophilic granules in the cytoplasm are present in aggressive NK cell leukemia, whereas they are absent in blastic NK cell lymphoma. Consequently, this case was classified as blastic NK cell lymphoma/leukemia.

Although NK cell neoplasm is a very rare entity, clinicians should always recognize this disease. NK cell neoplasms show overlapping clinical and pathologic features with other lymphomas. When morphology of tumor cells is blastic, and immunophenotyping of these cells has no myeloid or lymphoid lineage specific markers, it is necessary to add NK cell specific marker for immunophenotyping. CD56 is not lineage–specific and can be expressed by other neoplasms. However, specific markers for NK cells, such as CD161, CD117, and CD94 [15] are not routinely tested in clinical hematology laboratory. These markers will be useful for clarifying blastic NK cell leukemia.

REFERENCES

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