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Clinicopathological Features of Primary Bone Marrow Mature T and NK Cell Neoplasms

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Abstract

Primary bone marrow mature T and NK cell neoplasms are relatively uncommon, but could be the underlying etiology for anemia, neutropenia and thrombocytopenia. At our institution from 2003 to 2016, seventeen patients with primary bone marrow mature T and NK cell neoplasms were retrospectively studied, including 12 males and 5 females, with median age of 66 years (43 to 85). Nine patients had T cell large granular lymphocytic leukemia (T-LGL), 6 T cell neoplasm of undetermined significance (TNUS), and 2 chronic lymphoproliferative disorders of NK cells (CLPD-NK). The diagnosis of T cell neoplasm was confirmed by flow cytometry and immunohistochemical studies, as well as T cell receptor (TCR) gene rearrangement in the questionable samples. All patients had peripheral blood abnormalities as the clinical indication for bone marrow biopsy. Anemia was present in 12 patients, neutropenia 10, lymphocytosis 6 and thrombocytopenia 5. Positive EBER staining was seen in 3 samples. Two patients with TLGL showed abnormal karyotype at diagnosis, trisomy 22 in one, and del (6q) and del (7p) in another. There was no documented specific therapy targeted at the primary bone marrow mature T and NK cell neoplasm, except for 1 patient with T-LGL who received chemotherapy. Supportive treatment with occasional red blood cell transfusions was the principle management strategy for most patients. No death was documented directly from T and NK cell neoplasm in these 17 patients. The clinical presentation and peripheral blood findings of primary bone marrow mature T and NK cell neoplasm are often nonspecific, and TNUS usually is not expected clinically at the initial evaluation. Unlike T-LGL which is typically a disorder of CD8+ T cells, most primary bone marrow TNUS in this study are composed of CD4+ T cells. To our knowledge, this is the first study focusing on the clinicopathological features of primary bone marrow mature T and NK cell neoplasms as a collective group of diseases. Bone marrow biopsy is necessary for definitive diagnosis. Supportive and conservative management is the treatment of choice in most patients with overall favorable prognosis.

Keywords: T Cell Large Granular Lymphocytic Leukemia; Chronic Lymphoproliferative Disorders of NK Cells; T Cell Neoplasm of Undetermined Significance; Bone Marrow Biopsy; Anemia

Abbreviations

T-LGL: T Cell Large Granular Lymphocytic Leukemia;

CLPD-NK: Chronic Lymphoproliferative Disorders of NK Cells;

TNUS: T Cell Neoplasm of Undetermined Significance;

EBER: Epstein-Barr Virus Encoded RNA;

MDS: Myelodysplastic Syndrome;

TCR-V beta: T Cell Receptor-V beta;

CBC: Complete Blood Count;

MBL: Monoclonal B Lymphocytosis;

MGUS: Monoclonal Gammopathy of Undetermined Significance;

FISH: Fluorescence In Situ Hybridization

Introduction

Mature T and NK cell neoplasms are relatively uncommon, and many of them are still poorly characterized [1-3]. About 6.4% of the lymphomas found in bone marrow are mature T and NK cell lymphomas [4], and nearly 40% of them are secondary involvement by the previously diagnosed extramedullary T cell lymphomas [5]. Primary bone marrow T and NK cell neoplasm may be the underlying etiology for anemia, leukopenia, and thrombocytopenia. However, very few publications have focused on the pathological and clinical features of these lesions as a group of diseases [6,7]. This study is to evaluate the pathological features of primary bone marrow T and NK cell neoplasm and correlate with clinical features and patient management to better understand this rare, but important disease category.

Materials and Methods

Patient selection and related medical data collection

Bone marrow biopsy pathological reports filed at the Department of Pathology, William Beaumont Hospital - Troy from 2003 to 2014 were reviewed. In total, 17 patients were identified positive for primary bone marrow mature T and NK cell neoplasm. Retrospective review of the medical charts of these patients was performed and the clinical data was collected, including clinical presentation and indications for bone marrow biopsy, previous medical history and pathological studies, imaging evaluations, treatment received and clinical follow up for at least 6 months after the diagnosis was made.

Routine histologic examination of bone marrow biopsy and peripheral blood

Each bone marrow biopsy sample submitted for pathological study had bone marrow core biopsy, bone marrow aspirate and peripheral blood. The core biopsy samples were processed and Hematoxylin and Eosin (H&E) stained slides were prepared for routine microscopic examination. Giemsa stained smears from the bone marrow aspirate and Wright stained smears from peripheral blood samples were prepared for cytological evaluation.

Flow cytometry and immunohistochemistry

Portions of the bone marrow aspirate were sent for flow cytometry and cytogenetic studies. Multicolor flow cytometry evaluation was focused on identifying evidence of lymphoma, leukemia and myelodysplasia. A more sensitive and specific T cell receptor-V beta (TCR-V beta) panel was added since 2010. Immunohistochemical studies were performed on some of the bone marrow core biopsy samples as needed with adequate controls.

FISH and Cytogenetic studies

All bone marrow aspirate samples were submitted for conventional cytogenetic analysis and most samples also had MDS FISH panel for the evaluation of myelodysplasia as clinically indicated.

T cell receptor (TCR) gene rearrangement and Epstein Barr virus (EBV) RNA detection by in-situ hybridization [8]

TCR gene rearrangement studies were performed on bone marrow core biopsy samples in some patients to confirm the diagnosis of T cell neoplasms, including all patients with TNUS. Three in-house validated multiplexed primer sets spanning the variable and joining regions of the T-cell receptor gamma (TCR-gamma) chain gene were used. EBV infection was determined by EBER in situ hybridization on paraffin sections by using the Leica Microsystems (Leica Microsystems, Bannockburn, IL 60015) fluorescein labeled EBER probe (ISH5687-A) and the Bond Polymer refine detection kit (DS9800) detecting latent EBV infection.

Results

General information and pathological features

The patients were from 43 to 85 year old, with the median age of 66. Male patients were predominant, with a male/female ratio of 12/5. The primary bone marrow mature T and NK cell neoplasms in this study (table 1) included 9 T cell large granular lymphocytic leukemia (T-LGL), 6 T cell neoplasm of undetermined significance (TNUS), and 2 chronic lymphoproliferative disorders of NK cells (CLPD-NK).

Diagnosis	Number of cases
T-LGL	9
CLPD-NK	2
TNUS	6

T-LGL: T cell large granular lymphocytic leukemia
CLPD-NK: Chronic lymphoproliferative disorders of NK cells
TNUS: T cell neoplasm of undetermined significance

Table 1. Summary of Primary Bone Marrow Mature T and NK Cell Neoplasms

Bone marrow core biopsy, aspirate and peripheral blood examination

Mild interstitial lymphocytic infiltrate and small lymphoid aggregates were seen in the core biopsy sections from patients with T-LGL (Figures 1 and 2). The lymphocytes were small to medium in size on the aspirate smears. Normal hematopoiesis was generally preserved. Active hemophagocytic activity was seen in one patient. Peripheral blood lymphocytosis was seen in patients with T-LGL and CLPD-NK, with many large granular lymphocytes.

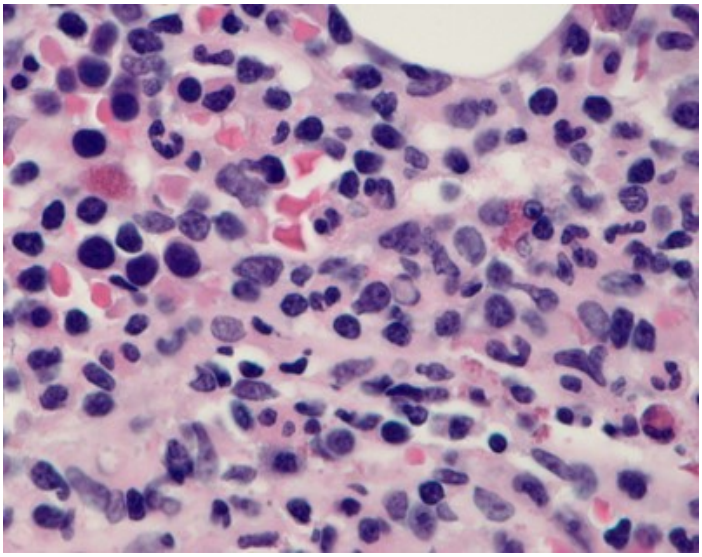

Figure 1. Bone marrow core biopsy section of T-LGL showed mild interstitial leukemic infiltrate (H&E, x1000). A few atypical lymphocytes (arrow) were seen among the normal hematopoietic elements.

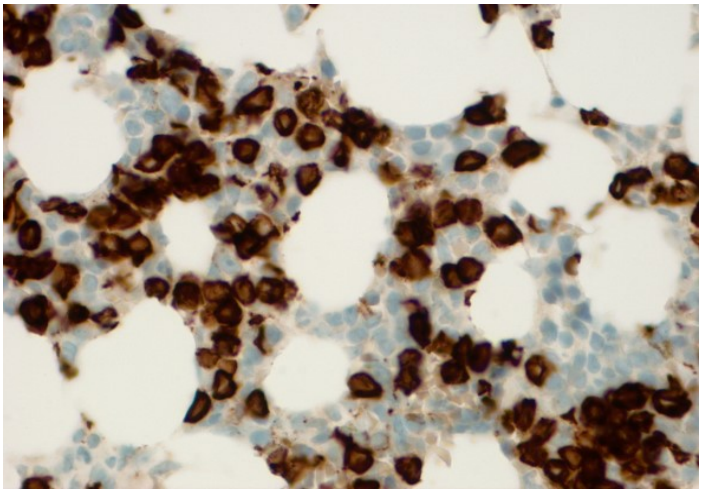

Figure 2. Bone marrow core biopsy section of T-LGL showed the infiltrating lymphocytes positive for CD3 (Immunohistochemistry, x1000)

In 6 patients, the bone marrow biopsy specimens showed unremarkable bone marrow hematopoietic tissue without histological evidence of lymphocytic infiltrate or lymphoma involvement (Figures 3 and 4). However, small clonal T cell populations were identified by immunophenotyping studies and the T cell clonality in these cases was further confirmed by TCR gene rearrangement. Since these disorders could not be further classified according to the current WHO criteria [1], and hence, were of undetermined significance, they were grouped as T cell neoplasm of undetermined significance (TNUS) or monoclonal T cell lymphocytosis of undetermined significance.

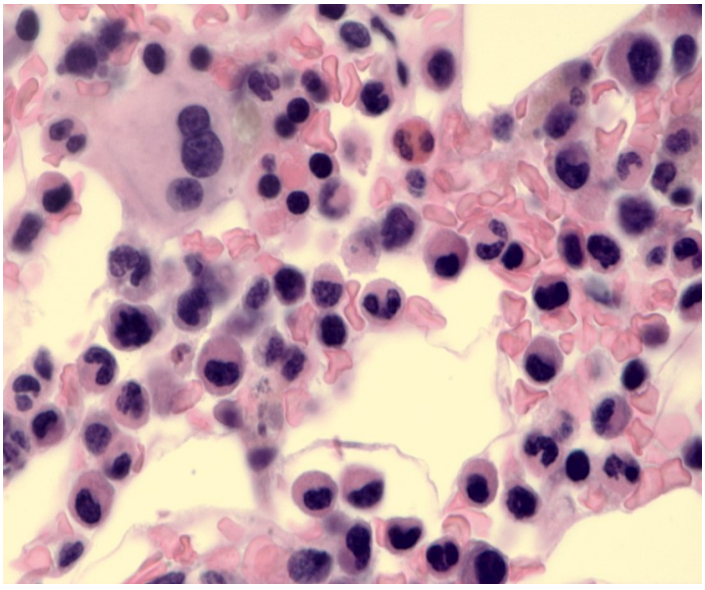

Figure 3. Bone marrow core biopsy section of TNUS showed unremarkable bone marrow tissue (H&E, x1000). No histological evidence of infiltrating lymphocytic lesion.

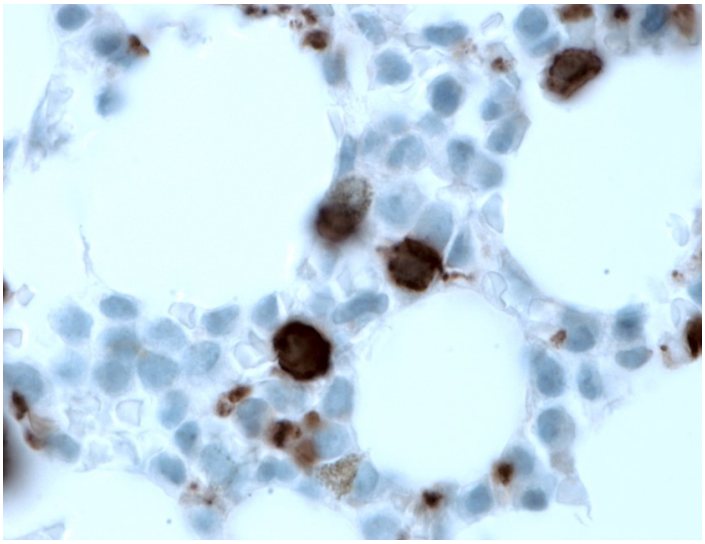

Figure 4. Bone marrow core biopsy section of TNUS showed occasional lymphocytes positive for CD3 (Immunohistochemistry, x1000)

Flow cytometry, Immunohistochemistry and TCR gene rearrangement studies

In 9 patients, aberrant T lymphocytes (CD3+, CD8+ and CD57+) were identified in the bone marrow by flow cytometry, consistent with T-LGL. Two patients had increased NK cells (CD3-, CD16+, CD57+) with aberrant phenotype by flow cytometry and that were negative for TCR gene rearrangement, consistent with CLPD-NK. The remaining 6 patients had aberrant T lymphocytes identified by flow cytometry or immunohistochemistry. Four of them showed a T cell phenotype (CD3+, CD4+, CD8-), and the other 2 showed CD3+ T cells with possible CD4/CD8 co-expression (incomplete immunophenotyping due to limited tissue available). In the questionable samples, the diagnosis of a T cell neoplasm was confirmed by positive TCR gene rearrangement studies.

Cytogenetic and FISH studies and EBER in situ hybridization

Two patient with T-LGL showed abnormal karyotype at diagnosis, one with trisomy 22 and another with del(6q) and del(7p). The findings were confirmed by FISH studies. Cytogenetic and FISH studies on bone marrow aspirate samples revealed normal karyotype in 15 patients.

Three bone marrow core biopsy samples were interpreted as positive for EBV by EBER in situ hybridization.

Clinical presentation, imaging studies and other laboratory findings

All patients had abnormal peripheral blood changes as the clinical indication for bone marrow biopsy. As summarized in table 2, anemia was the most common finding, followed by neutropenia, lymphocytosis, and thrombocytopenia. Splenomegaly was seen in 6 patients by imaging studies. No evidence of prior or current extramedullary T and NK cell lymphoma was identified in any of the patients. One patient was found to have B cell lymphoma in a lymph node biopsy and another patient with plasma cell neoplasm. The comorbidities included diabetes, hypertension, renal dysfunction and pneumonia in some patients.

Disorders	Number of patients
Anemia	12
Neutropenia	10
Lymphocytosis	6
Thrombocytopenia	5

Table 2. Summary of Abnormal Peripheral Blood Changes

Clinical management and follow up

There were no documented specific therapies targeted at the primary bone marrow mature T and NK cell neoplasm, except for 1 patient with T-LGL who received chemotherapy. Supportive treatment with regular follow up examinations including complete blood counting (CBC) was the principle management strategy for these patients with occasional red blood cell transfusions. Clinical management also included treatment for the comorbidities. Three patients died of renal failure, pneumonia, and sepsis respectively as the direct cause of death during the follow up period. There was no documented mortality directly related to bone marrow T and NK cell neoplasms in these patients at the end of this study.

Discussion

Anemia and other peripheral blood abnormalities are relatively common disorders especially in elderly patients [9-11]. Primary bone marrow mature T and NK cell neoplasm has rarely been considered as one of the causes unless a bone marrow biopsy had revealed the diagnosis. All patients in this study had unexplained anemia, neutropenia, thrombocytopenia or lymphocytosis, which were likely due to or partially related to the bone marrow involvement by mature T and NK cell neoplasm. The fact that no evidence of prior or concurrent extramedullary T and NK cell neoplasm was found in these patients during the follow up period support that these disorders were primary bone marrow mature T and NK cell neoplasms.

Primary bone marrow TNUS has not been previously well studied. Unlike T-LGL which is typically a disorder of CD8+ T cells [12,13], most of TNUS in this study are composed of CD4+ T cells. Histologic examination of the bone marrow tissue alone may miss this lesion, and ancillary testing including flow cytometry and/or TCR gene rearrangement is essential to establish the diagnosis. Similar disorders have already been documented in B cell and plasma cell disorders, such as monoclonal B lymphocytosis (MBL) [14] and monoclonal gammopathy of undetermined significance (MGUS) [15]. To our knowledge, this is the first study to document such T cell disorder involving the bone marrow. These clonal lesions are likely very early events in the pathogenesis of T cell, B cell and plasma cell neoplasms. Although these lesions are usually chronic and indolent and may even show regression, disease progression and transformation to a more aggressive lymphoma may occur [16,17].

In our series, only one patient received short term chemotherapy for T-LGL, most patients were managed conservatively for the diagnosed T and NK cell neoplasms with supportive treatment including occasional transfusions for anemia as needed. Another patient with TNUS received chemotherapy for extramedullary large B cell lymphoma. As commonly seen in senior population, hypertension and diabetes are present as co-morbidities in several patients and treated accordingly. No

death has been documented directly related to the primary bone marrow mature T and NK cell neoplasm during the study period from 6 months to more than 10 years. Overall, primary bone marrow mature T and NK cell neoplasm has been shown to be a chronic and indolent disease with favorable long term outcome without targeted or specific chemotherapy.

By histologic examination, T and NK cell infiltrates in the bone marrow was mild to moderate in patients with T-LGL and CLPD-NK, and minimal in other 6 patients. Normal hematopoiesis was generally preserved without significant architectural distortion. It is postulated that hematopoietic dysfunction caused by bone marrow T and NK cell neoplasm could be the mechanism for anemia and cytopenias in these patients. Hemophagocytic syndrome is seen relatively common in patients with systemic T and NK cell neoplasms, and patients may present with anemia, cytopenias, splenomegaly and fever [18]. Inflammatory cytokines released from macrophages and lymphocytes are believed to play a role in this life-threatening syndrome [19,20]. However, morphological evidence of active hemophagocytic activity was seen in only 1 patient in this study, and its significance in this disorder has yet to be determined.

Similar to other T and B cell neoplasms, the pathogenesis of primary bone marrow mature T and NK cell neoplasm is unclear. Epstein-Barr virus (EBV) infection has been documented in some T and NK cell lymphomas as a closely related etiologic factor [21,22]. Further studies on EBV status in these patients may be useful to investigate the etiology of this disorder.

Conclusion

To our knowledge, this is the first study focusing on the clinicopathological features of primary bone marrow mature T and NK cell neoplasms as a collective group of disease. Unlike T-LGL, primary bone marrow TNUS is a disorder of CD4+ T cells in most patients. Although relatively uncommon, this disorder may be the underlying cause for some unexplained anemia and peripheral blood cytopenias. Awareness of this disorder is important for both clinician and pathologists to examine the bone marrow specimen with proper tests to establish the diagnosis.

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