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Original contribution

Bone marrow involvement in patients with posttransplant lymphoproliferative disorders: incidence and prognostic factors

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Summary Posttransplant lymphoproliferative disorders are classified as monomorphic, polymorphic, early lesions, or Hodgkin lymphoma type. Staging bone marrow examination is recommended in posttransplant lymphoproliferative disorder patients; however, information regarding bone marrow involvement in these disorders, especially as related to the posttransplant lymphoproliferative disorder subtype, is scarce. We reviewed the clinicopathologic features of 72 posttransplant lymphoproliferative disorder cases to determine the frequency of bone marrow involvement by various subtypes of posttransplant lymphoproliferative disorder, the clinical features of patients with and without bone marrow involvement, and their outcome. We also compared the incidence of bone marrow involvement of monomorphic posttransplant lymphoproliferative disorder (diffuse large B-cell lymphoma) with de novo diffuse large B-cell lymphoma (in both immunocompetent and HIV+ patients), and assessed the utility of various hematologic and serologic parameters as predictors of bone marrow involvement. Bone marrow involvement was seen in 23.5% of monomorphic posttransplant lymphoproliferative disorders and 15.7% of polymorphic posttransplant lymphoproliferative disorders, and the detection of bone marrow involvement on staging bone marrow biopsy upstaged 42% of monomorphic posttransplant lymphoproliferative disorders and 100% of polymorphic posttransplant lymphoproliferative disorders. Although bone marrow involvement appeared independent of patient age, organ transplanted, Epstein-Barr virus status, interval from transplantation to posttransplant lymphoproliferative disorder, or involvement of the grafted organ, it was significantly more frequent in cases without extranodal involvement; and it was associated with a significantly shorter survival. The incidence of bone marrow involvement in monomorphic posttransplant lymphoproliferative disorder (diffuse large B-cell lymphoma) was similar to that in HIV-associated diffuse large B-cell lymphoma, but higher than that in immunocompetent diffuse large B-cell lymphoma cases. No individual hematologic and serologic

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parameter was predictive of bone marrow involvement; however, the combination of elevated lactate dehydrogenase (>225 U/L) and decreased hemoglobin (<10 g/DL) can be used as a sensitive screening tool in determining which patients should proceed to bone marrow staging biopsy.

1. Introduction

Posttransplant lymphoproliferative disorders (PTLDs) represent a spectrum of lymphoid or plasma cell proliferations arising after solid organ or hematopoietic stem cell transplantation. The majority of PTLDs are Epstein-Barr virus (EBV) positive B-cell proliferations; however, PTLDs of T- and/or NK-cell lineage have been documented [1-3]. According to the present World Health Organization (WHO) classification system, PTLDs are classified as early lesions, polymorphic (p-PTLD), monomorphic (m-PTLD), or Hodgkin lymphoma type (HL). The m-PTLDs have been further subclassified, based on morphologic, immunophenotypic, genetic, and clinical features, into diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), plasma cell myeloma and plasmacytoma-like lesions, and various subtypes of T- and NK-cell lymphomas [4].

Currently, recommendations for staging PTLD are based on Ann Arbor clinical staging criteria [1,2]. Bone marrow (BM) examination is an integral part of the Ann Arbor staging system for all lymphoproliferative malignancies [1,2,5]. In non-Hodgkin lymphoma (NHL), Ann Arbor stage III to IV disease is an adverse prognostic feature in the International Prognostic Index [5-8]. BM involvement by PTLD defines stage IV disease; and similar to immunocompetent patients with NHL, patients with advanced-stage PTLD are known to have inferior prognosis and shorter overall survival [9-12]. While BM involvement by m-PTLD is believed to be uncommon, there have been remarkably few studies documenting the frequency of BM involvement in this patient population. Although some studies have shown that up to 40% of patients with PTLD have BM involvement at staging [9-14], most of these studies have not specifically addressed this issue in the context of the different subtypes of PTLD.

A previous study in immunocompetent patients with early-stage DLBCL questioned the necessity of staging BM biopsies in these patients because de novo DLBCL rarely presents with BM involvement [15]. Because of the potential prognostic significance of BM involvement, elimination of routine BM biopsies in newly diagnosed patients would require a sensitive surrogate predictive of BM infiltration. Hematologic parameters have been proposed as predictors of BM involvement in immunocompetent patients with both HL and NHL, with variable results [7,15-17].

In this study, we analyzed the clinicopathologic characteristics of a large series of patients with PTLD evaluated and treated at our institute, focusing on the frequency of BM involvement by different subtypes of PTLD, the clinical differences observed between patients with or without BM involvement, and the impact of BM biopsy in altering the stage of disease and the outcome. Considering the pathological similarities between m-PTLD (DLBCL) and de novo DLBCL in the nontransplant setting, we also compared the incidence of BM involvement by DLBCL in immunocompetent individuals and those infected by HIV. In addition, because there have not been any formal studies using hematologic parameters as predictors of BM involvement in PTLD, we also assessed the utility of various hematologic parameters and lactate dehydrogenase (LDH) levels as predictors of BM involvement in patients with PTLD.

2. Materials and methods

2.1. Case selection and clinical characteristics

After approval from our Internal Review Board, we searched our electronic data capture system (eResearch; Velos, Fremont, CA) to identify all patients diagnosed with lymphoid malignancies post solid organ transplantation at our institute over a 19-year period (January 1990 through February 2009) with an available staging BM biopsy. The cases were classified according to the WHO classification system as p-PTLD, m-PTLD, and HL with appropriate subclassification based on morphologic and phenotypic analysis [4]. For comparison with m-PTLD (DLBCL), cases of de novo DLBCL in nontransplant patients, including a subset of HIV-associated DLBCL, diagnosed over the same period were also identified.

The staging BM biopsy was performed before therapeutic intervention. A clinical and radiographic staging approach was performed in conjunction with BM assessment, all in accordance with the American Joint Committee on Cancer NHL staging system (*AJCC Staging Manual, Sixth Edition*). Morphologic features were assessed using hematoxylin and eosin (H and E)–stained sections of Bouin or formalin-fixed, paraffin-embedded BM biopsies. All staging BM biopsies considered positive for lymphomatous involvement showed morphologic evidence of disease on review of H and E–stained sections and/or after immunohistochemical staining (Figs. 1 and 2). There were no consistent or specific patterns of BM involvement by m-PTLD. Some cases showed subtle interstitial lymphomatous infiltrates detectable on H and E morphology, but better highlighted on immunohistochemical staining. Others showed overt infiltrates on H and E morphology in a