Case report

Primary bone marrow lymphoma: A case report and a review of the literature

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Introduction:

Bone marrow involvement by non-Hodgkin Lymphoma (NHL) has conventionally been considered as a systemic dissemination of a nodal malignancy. The most frequent type of non-Hodgkin lymphoma (NHL) is diffuse large B-cell lymphoma (DLBL). Extra nodal involvement including the bone marrow is mostly considered as stage IV, and portends a poorer prognosis. Recent literature has thrown light over few cases of NHLs arising primarily in the bone marrow. This had led to a better recognition of this rare entity. These NHLs have been termed Primary Bone Marrow Lymphoma (PBML). Thus far, around 32 cases have been reported in the English literature. (1-4). In all these cases, bone marrow biopsy revealed infiltration of abnormal lymphoid cells with a diffuse or interstitial pattern.

Morphologically, these were medium-to-large-sized lymphoid cells. Immunohistochemically, these cases were classified as lymphoma of B-cell or T-cell lineage. A majority of these cases were

of T-cell lymphoma, as only eight cases in 32 previous reports were DLBL in English literature (5-6). We report a case of PBML associated with thrombocytopenia and review the past literature on primary bone marrow lymphoma and discuss clinical and diagnostic challenges.

Case report:

A 41-year-old man was admitted for fever that had persisted for a month. He had a history of alcoholism, excessive fatigue and dyslipidemia. On physical examination, a petechial rash was seen all over the body; most pronounced over the lower abdomen and groin area. The clinical examination did not reveal organomegaly or lymphadenopathy. The other systemic and other general examination findings were within normal limits.

Laboratory findings on admission were as follows: Hemoglobin 11.4 g/dL; Hematocrit:33%, platelet count: $22.0 \times 10^9/L$; total leucocyte count: $3.7 \times 10^9/L$; ESR 90mm/hour. The peripheral smear confirmed the thrombocytopenia and showed a normocytic

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normochromic anemia with anisopoikilocytosis and nucleated RBCs. The manual differential leucocyte count showed 63% lymphocytes and 15% abnormal lymphoid cells (Fig.1).

Fig.1. The peripheral smear showing abnormal lymphoid cells (Leishman x100)

A bone marrow study was requested for evaluating the abnormal lymphoid cells. Meanwhile, the serological investigations showed negativity for antibodies to HIV-1&2, Hepatitis B surface antigen and Hepatitis C virus. The antiplatelet antibody test was also negative.

The bone marrow aspirate smears studied showed a dry tap with blood clots and markedly diluted cell trails. The imprint smear however showed preserved clusters of abnormal lymphoid cells. The cells were medium to large in size with scant cytoplasm, a high nuclear to cytoplasmic ratio and dense nuclear chromatin. A few cells had inconspicuous nucleoli. (Fig.2). The lymphoma cells were negative for Periodic Acid Schiff (PAS) stain.

A diagnosis of marrow infiltration by non-Hodgkin Lymphoma (NHL) was made and a flow cytometry was performed on a repeat aspirate

Fig.2. Bone marrow imprint smear showing an abnormal lymphoid cell (Leishman x 200)

for sub-classification. A CT scan of the abdomen confirmed the absence of organomegaly and enlarged lymph nodes, hence the presence of a primary malignancy could not be established.

The bone marrow trephine biopsy showed hypercellular marrow spaces. The normal hematopoietic elements were replaced by an interstitial infiltrate of abnormal lymphoid cells (Fig.3a). The biopsy also revealed areas of coagulative necrosis (Fig.3b). The cells were predominantly large with scant cytoplasm, a round nucleus with a convoluted nuclear membrane and vesicular chromatin. Increased mitotic figures were also noted (Fig.3c).

The other hematopoietic elements were suppressed.

Fig.3. a) Trephine Biopsy showing diffuse infiltration by lymphoma cells. b) An area of necrosis (H & E;x100) c) Large cells with convoluted nuclear membrane and vesicular nuclear membrane (H & E x400)

Since a flow cytometry could not be performed, immunohistochemistry (IHC) on the bone marrow biopsy was performed. The IHC profile (Fig.4) of the lymphoma cells were as follows: CD20+, BCL-2+, CD10+; CD34-, BCL6- and CD99- .

Considering all the clinical and morphological data available, we gave a diagnosis of Diffuse Large B Cell Lymphoma arising as a primary in the bone marrow. After a search through the available literature, we rephrased this entity as a primary bone marrow lymphoma.

Fig 4: Immunohistochemistry (IHC) showing positive antibodies against CD20 BCL-2 and CD10 & negativity for CD34, BCL-6 and CD99

Discussion

Primary Bone Marrow Lymphoma (PBML) is a rare entity with only 32 fully documented cases in the English-language literature (1-4). The first reports of this entity were noted in 1980s (1-2). However, in both these reports, the diagnosis was based only on physical examination and chest X-ray without CT scan; thus leaving a possibility of lymphadenopathy undetectable by these methods. Ponzoni et al reported four cases of lymphoma confined to bone marrow in 1994(3). Chachashvili et al also reported two cases of PBML, where the bone marrow was infiltrated by small lymphoid cells, which were derived from B-cell origin according to the analysis of immunophenotypes (4).

Of the 32 cases of reported PBML, a majority were typed as T-cell lymphoma and only eight cases were DLBL in English literature (5,6). These eight patients consisted of four men and four women with an age range from 42 to 86 years. The most frequent clinical findings in these patients with DLBL were weakness, fatigue, and B symptoms of NHL according to the Ann Arbor staging system. In the present case, the demographics and clinical features concurred with the above.

The haemogram findings in our case revealed an isolated thrombocytopenia. This mode of presentation has been described in the literature of PBML as well. The bone marrow suppression of megakaryocytes due to infiltration of lymphoma cells was implicated in these cases. Sporadic cases of immunologic abnormalities

including autoimmune thrombocytopenia have been reported in patients with PBML (7). Hauswirth et al. (8) reported that the prevalence of autoimmune thrombocytopenia in NHL was 0.72%. In our case, the antiplatelet antibody test was negative, thus ruling out an immune mediated suppression. Other forms of presentation of PBML included a leukoerythroblastic blood picture and pancytopenia (5). Rarely, a hemolytic anemia has also been associated with PBML (9).

The present classification of NHL subtypes consists of a combination of morphologic, immunophenotypic and genetic characteristics. Criteria to diagnose PBML encompass isolated bone marrow infiltration, with no evidence of nodal or extra nodal involvement, including the bone, and the exclusion of leukemia/lymphomas that are considered to primarily involve the bone marrow (10). In our present case, the clinical examination and radiological investigations ruled out organomegaly and lymphadenopathy. The abnormal cells in the peripheral smear did lead to a consideration of leukemia but the morphology of the cells suggested otherwise. Moreover, Martinez et al in their review of 21 PBMLs have described a single case of DLBL with leukaemic involvement (10).

In the recent retrospective case review of 21 PBMLs reviewed by the International Extra nodal Lymphoma Study Group from 12 institutions in 7 different countries over a 25-year period; 15 cases were typed as DLBL (10). Of these, 9 cases had a diffuse pattern of infiltration in the marrow. In our case, the morphology of

the abnormal lymphoid cells characterized by medium to large cells with scant cytoplasm and dense chromatin was suggestive of a DLBL. A diffuse infiltration pattern was observed in the trephine biopsy as well. This was in concordance with the above mentioned study.

Immunohistochemistry is a valuable tool in sub classification of PBML. Of the 21 cases reviewed in a recent study, 4 cases were typed as follicular lymphomas, 15 cases as DLBL and 2 cases as Peripheral T- cell lymphoma, not otherwise specified (10). Among the DLBL, 9 cases showed bcl-2 positivity. In our present case, the lymphoma cells were strongly positive for BCL-2, CD10 and CD20; thus substantiating their B-cell lineage and origins from follicular center cells (Fig.4). The cells were negative for CD34 and CD99, thus ruling out a lymphoblastic nature of the neoplastic cells (Fig. 4).

Genetic characteristics of PBMLs are characterized by BCL-2 and IRF4 (Interferon regulatory factor 4) gene rearrangement (10). In our case, we did not have a provision for genetic analysis.

Various chemotherapeutic protocols were used in the eight patients with DLBL in previous reports of PBML (5,6). Except for one patient, all patients manifested with initial transient improvement or complete remission. Five of them showed a good response to CHOP or CHOP with Rituximab, but no standard protocol seems to offer a definitive treatment for PBML. In our case, the patient was treated with CHOP plus Rituximab for six cycles.

The prognosis of PBML is generally poor. Among the previously reported eight patients of PBML with DLBL, four died either of complications of chemotherapy or of relapse after treatment. Their survival after diagnosis ranged from 10 days to 17 months (5, 6). Two younger patients, survived for more than 4 years (one received bone marrow transplantation). In the case review by Martinez and colleagues, the median overall survival of PBML cases having a DLBL was 1.8 years (10). In our case, the subsequent bone marrow examination showed that the marrow was not in remission. The patient also developed co-morbidities such as chronic otitis media, headache and facial nerve palsy. The cerebrospinal fluid examination showed infiltration by large lymphoma cells. At the time of submission of this article, the patient had developed backache due to lymphomatous spread to the C 6-8 vertebra.

Primary bone marrow lymphoma (PBML) is a rare entity whose real morphological boundaries and clinical significance are not well defined. As the data regarding PBML is being scrutinized and debated, an awareness of this neoplasm is of significance. In the current scenario, it can be easily overshadowed by its more recognized hematolymphoid counterparts. The recognition of this rare, yet ever-increasing entity is important to establish accurate diagnosis and adequate therapy.

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