sis of the CSF showed neoplastic cells with a frequency of 92.0% (Fig. 2C) and positivity for both CD56 and CD123 on immunocytochemical staining (Fig. 2D). He was diagnosed with leptomeningeal involvement of BPDCN. He was treated with intrathecal injections of high-dose cytarabine (40 mg) and methotrexate (15 mg) for 3 months, and he has been in complete remission for 4 months without evidence of residual disease.

DISCUSSION

Because markers are useful for confirming BPDCN, a recently performed multicenter study recommends immunohistochemical staining using 6 antigens, such as CD4 (positive in 94.6% of cases), CD56 (positive in 96.5% of cases), CD123 (positive in 95.3% of cases), TCL1 (positive in 89.3% of cases), CD2AP (positive in 80.5% of cases), and BDCA2/CD303 (positive in 75.0% of cases) [1]. As a single antigen does not exhibit positivity in all cases of BPDCN, immunohistochemical staining using at least the 3 antigens mentioned previously (CD4, CD56, and CD123), all of which possess higher positivity rates compared with other antigens, should be performed to confirm BPDCN to provide maximum sensitivity. Our 2 cases demonstrated positivity for all these 3 antigens, which is adequate evidence of BPDCN involvement. Given that leptomeningeal involvement in BPDCN is a rare phenomenon, our second patient, who developed simultaneous leukemic manifestation and leptomeningeal involvement of BPDCN, is a very rare case and worth being reported.

In conclusion, we report 2 cases of BPDCN exhibiting leukemic manifestation (1 with simultaneous leptomeningeal involvement) confirmed with positive CD4, CD56, and CD123 expression on immunohistochemical staining and flow cytometry. Immunohistochemical staining for CD4, CD56, and CD123 can confirm the BPDCN diagnosis, and it should be performed in all cases suspected of having BM involvement in BPDCN.

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Received on Apr. 15, 2014; Revised on May 25, 2014; Accepted on Aug. 25, 2014

http://dx.doi.org/10.5045/br.2014.49.3.198

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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Bone marrow hypoplasia, isochromosome 8q and deletion of chromosome 6q preceding B-cell lymphoma

TO THE EDITOR: Abnormalities of chromosome 6q involving deletion of the regions 6q16-q27 have been reported in a variety of hematologic malignancies, most frequently in multiple myeloma [1-3]. The 8q isochromosome is also an uncommon clonal abnormality found primarily in T-prolymphocytic leukemia [4, 5]. Concurrent chromosome 6q- and i(8) are extremely rare in patients with hematologic malignancies and have never been reported as chromosomal abnormalities preceding evidence of malignancy.

Several case reports suggested that chromosomal abnormalities can provide evidence for hematologic malignancies before they develop [1-3]. We describe a patient with bone marrow hypoplasia and persistent unexplained chromosomal abnormalities of del(6)(q16) and i(8)(q10) who subsequently developed B-cell lymphoma 8 months after his initial presentation.

CASE

A 50-year-old man was admitted to our hospital in December 2009 with persistent fever. Peripheral blood counts showed hemoglobin 9.0 g/dL, white blood cell (WBC) count 6.2×10^9/L (65% neutrophils, 15% lymphocytes, 10%

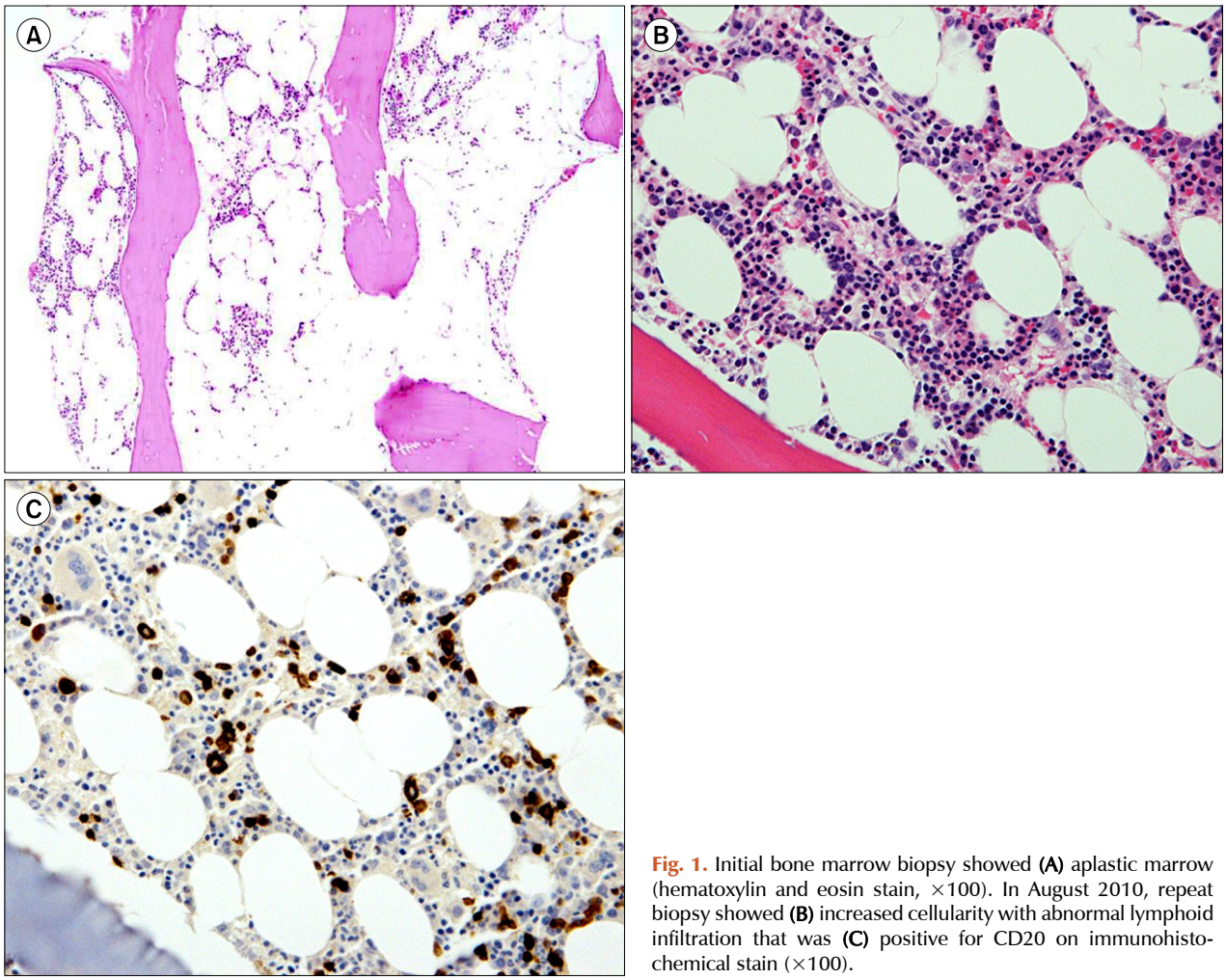

Fig. 1. Initial bone marrow biopsy showed **(A)** aplastic marrow (hematoxylin and eosin stain, ×100). In August 2010, repeat biopsy showed **(B)** increased cellularity with abnormal lymphoid infiltration that was **(C)** positive for CD20 on immunohistochemical stain (×100).

monocytes, 8% atypical lymphocytes, 2% eosinophils), and platelets 201×10^9/L. The reticulocyte count, iron, folate, and vitamin B12 levels were within the normal range.

The bone marrow showed a 1.2:1 myeloid:erythroid (M:E) ratio, no evident dysplasia and decreased cellularity (20%) (Fig. 1A). Cytogenetic analysis performed on bone marrow using a 24-hour unstimulated culture revealed the following distinct abnormal clone: 46,XY,del(6)(q16),i(8)(q10)[8]/46,XY[12] (Fig. 2). To evaluate his fever of unknown origin, brain magnetic resonance imaging (MRI), whole-body positron emission tomography/computerized tomography (PET/CT) and thoracic and abdominal CT were performed. These studies revealed only moderate hepatosplenomegaly with no evidence of malignancy. In addition, markers for viral infection and autoimmune disease showed negative results.

In August 2010, peripheral blood counts showed hemoglobin 9.1 g/dL, WBC count 4.45×10^9/L (73% neutrophils, 11% lymphocytes, 9% monocytes, 6% atypical lymphocytes, 1% eosinophils), and platelets 154×10^9/L. The bone marrow showed 1.7:1 M:E ratio, no evident infiltration of abnormal lymphoid cells, and hypocellular marrow. However, bone marrow biopsy showed relatively increased cellularity (40–60%) than before, with focal infiltration of atypical lymphoid cells that were positive for CD20 and CD79a, but

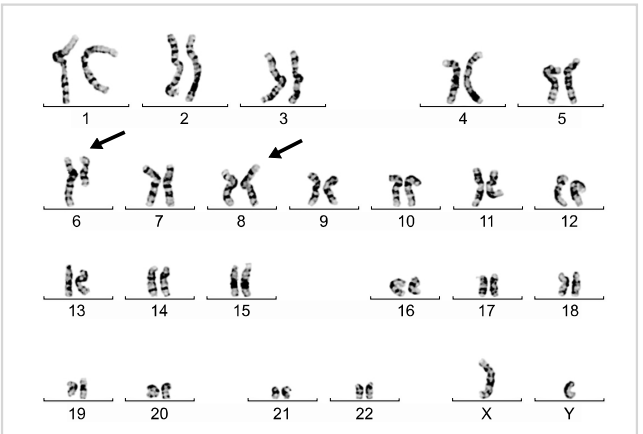

Fig. 2. Giemsa-banded karyotype showing 46,XY,del(6)(q16),i(8)(q10) 9 months before evidence of B-cell lymphoma in the bone marrow. The abnormal chromosomes are marked by arrows.

negative for CD3, myeloperoxidase (MPO) and terminal deoxynucleotidyl transferase (TdT) on immunohistochemical stain (Fig. 1B and 1C). The results of chromosomal analysis were 46,XY,del(6)(q16),i(8)(q10)[7]/46,XY[5], showing the same abnormal clone as 8 months previously. Repeat brain MRI showed focal enhancements in the frontal and parietal skull bones suggestive of hematologic malignancy such as lymphoma or myeloma. Repeat whole-body PET/CT showed increased patchy uptake in multiple levels of the thoracic and lumbar spine suspicious of bone marrow infiltration. Cerebrospinal fluid analysis showed many atypical lymphoid cells. Together, these findings were consistent with lymphoma involving the central nervous system (CNS) and the patient was diagnosed as having B-cell lymphoma confined to the bone marrow and CNS (stage IV).

There were no accessible lymph nodes to perform a diagnostic biopsy. Treatment was immediately initiated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Bone marrow analysis showed complete hematologic remission after 2 cycles of CHOP and the bone marrow karyotype after chemotherapy was normal (46,XY[20]). In May 2011, he underwent autologous peripheral blood stem cell transplantation (PBSCT). Two years after PBSCT, in October 2013, the patient showed no morphologic evidence of residual lymphoma and no suspicious findings on follow-up whole-body PET/CT.

DISCUSSION

Deletion of 6q is frequently described in lymphoid malignancies. In lymphoid malignancies, a range of deleted sub-regions has been identified within the chromosomal region 6q14-q21. Interestingly, the most proximal region has been identified in adult T-cell leukemia, whereas the more distal regions have been linked to childhood B-ALL and, rarely, chronic lymphocytic leukemia [6]. The detection of a 6q deletion in several malignancies suggests that this region contains an unidentified tumor-suppressor gene that deserves further investigation of its role in the malignant process [7]. Del(6q) has been shown to be a prognostic factor associated with longer event-free survival in adult T-ALL [5]. In our case, the patient had a favorable clinical course without relapse during 4 years of follow-up, even with CNS involvement. Accordingly, this case supports an association between del(6q) and favorable prognosis.

There have been 182 cases of i(8)(q10) in hematologic malignancies published, with the majority (166 cases, 91.2%) exhibiting complex karyotypes [5], suggesting that i(8)(q10) is a secondary chromosomal abnormality. However, reports of i(8)(q10) in acute B-cell lymphoblastic leukemia/lymphoma have rarely been reported with only 5 cases published to date [5]. Several reports have suggested that the gain of 8q, but not the loss of 8p, is important in leukemogenesis [4, 8].

It can be difficult to distinguish bone marrow hypoplasia preceding lymphoma from aplastic anemia. In our case, persistent anemia and bone marrow hypoplasia were prominent, although neutropenia or thrombocytopenia was not evident. In adults, the major causes of pancytopenia involving bone marrow are clonal disorders such as acute myeloid leukemia (26%), myelodysplastic syndrome (17%) and non-Hodgkin lymphoma (NHL, 6%) [9]. In this case, persistent bone marrow hypoplasia was suspected as a rare manifestation of NHL. The most likely cause for the patient's bone marrow hypoplasia was a clonal disorder that suppressed hematopoietic stem cell proliferation and eventually resulted in lymphoma by selection of an abnormal clone [10, 11]. We suspected that the patient had lymphoma at the initial presentation, with the aplastic phase caused by the clonal cells' direct inhibition of normal bone marrow stem cells.

Hematologic malignancies preceded by chromosomal abnormalities have rarely been reported [1, 3]. However, in these cases the preceding chromosomal abnormalities may have signaled disease progression rather than the hematologic malignancy itself. This report describes the first case of B-cell lymphoma preceded by bone marrow hypoplasia with del(6)(q16) and i(8)(q10) prior to morphologic evidence of hematologic malignancy, followed by a favorable and persistent complete remission for nearly 4 years from the initial detection of the chromosomal abnormalities. Close follow-up in patients with abnormal karyotypes, even without morphologic evidence of hematologic malignancy, could uncover hidden hematologic malignancies and allow initiation of early and proper treatment.

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Received on Apr. 8, 2014; Revised on May 26, 2014; Accepted on Aug. 22, 2014

http://dx.doi.org/10.5045/br.2014.49.3.200

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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T-cell large granular lymphocytic leukemia: 4 cases

TO THE EDITOR: T-cell large granular lymphocytic leukemia (T-LGL) is a rare clonal hematological disorder characterized by peripheral blood and bone marrow lymphocytic infiltration with large granular lymphocytes (LGLs), splenomegaly, and cytopenia, of which neutropenia is most common [1]. T-LGL is characterized by persistent increases in LGLs ranging from 2×10^9/L to 20×10^9/L on peripheral blood in the absence of a reactive cause [2]. The exact pathogenesis is unknown, but is believed to result from clonal expansion of mature postthymic T cells [3]. T-LGL typically presents in the sixth decade of life, with an equal male to female ratio [4]. Approximately 40% of patients have an associated autoimmune disorder, most commonly rheumatoid arthritis (RA), pure red cell aplasia, or immune thrombocytopenia [5]. Approximately one third of patients are asymptomatic when routine blood counts reveal cytopenia and LGL, which leads to diagnosis. The symptoms, if present, are related to cytopenia [6].

Bone marrow aspirate may be required to confirm the diagnosis, especially in those with low absolute numbers of circulating LGLs. Patients with T-LGL have a median survival of more than 10 years [7]. The most common indications for treatment are cytopenia, recurrent infection, pure red cell aplasia, progressive splenomegaly, and B symptoms [8]. The reported incidence of T-LGL is 2–5% of the chronic lymphoproliferative disorders (LPDs) in North America and about 6% in Asia [9]. The incidence and prevalence is not known in Pakistan. In this case series, we describe the laboratory findings and clinical courses of 4 patients diagnosed with T-LGL in a tertiary care hospital.

CASES

The first case was a 24-year-old man who presented with lymphocytosis in November 2010. His physical examination was unremarkable and showed no hepatosplenomegaly or lymphadenopathy. A complete blood cell (CBC) count revealed lymphocytosis with the presence of LGLs (Table 1). Based on bone marrow morphological and immunophenotypic assessments, the patient was diagnosed with T-LGL (Table 1). His follow-up visits showed persistent lymphocytosis with a declining platelet count. On his follow-up in December 2013, CBC revealed hemoglobin (Hb), 13.5 g/dL; white blood cell (WBC) count, 17.9×10^9/L with an absolute lymphocyte count (ALC) of 11.4×10^9/L; and platelets, 93×10^9/L.

The second case was a 61-year-old man who was referred in November 2010 for assessment of persistent lymphocytosis lasting for about 7 months. His physical examination was unremarkable. CBC showed lymphocytosis, whereas blood smear, bone marrow morphology, and immunophenotyping were consistent with T-LGL (Table 1). He remained asymptomatic throughout the disease course without any treatment. His CBC in August 2013 revealed Hb, 14 g/dL; WBC, 7.6×10^9/L with an ALC of 5.3×10^9/L; and platelets, 100×10^9/L.

The third case was a 61-year-old man who was diagnosed with hairy cell leukemia (HCL) in 1992 after morphological findings from peripheral smear/bone marrow and underwent splenectomy as the sole treatment for HCL. He was then lost to follow-up until 1998, when he presented with recurrent chest infections. His physical examination was unremarkable, whereas CBC revealed lymphocytosis and LGLs on peripheral smear (Table 1). Subsequent examination of bone marrow morphology and immunophenotyping was consistent with T-LGL (Table 1). During follow-up visits, he continued to have chest infections and was started on low-dose oral methotrexate 5 mg once daily for 7 days in a 4-week cycle. He responded well to treatment and the repeated infections resolved. He is still on the regimen and is asymptomatic. His most recent follow-up CBC revealed Hb, 12.5 g/dL; WBC, 19.5×10^9/L with an ALC of 12×10^9/L; and platelets, 181×10^9/L.