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Cytogenetic abnormalities precede morphological abnormalities in developing malignant conditions: Report of 2 cases

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ABSTRACT

We previously hypothesized that cytogenetic abnormalities precede morphological abnormalities in developing malignant conditions. In this context we evaluated additional cases to further confirm that hypothesis. We report on 2 additional cases in which clonal cytogenetic abnormalities were observed in otherwise morphologically normal samples. Case 1 is a bone marrow from a 73 year old male with transformed follicular lymphoma (FL), while case 2 is a lymph node from a 53-year-old with lymphadenopathy, both referred to the cytogenetics laboratory for evaluation. A 73-year-old male presented with an enlarging left inguinal mass surrounding and obliterating the left iliac vein. A tissue core biopsy of the mass revealed recurrent high grade FL with diffuse large B-cell lymphoma (DLBCL). Examination of a random bone marrow biopsy of the adjacent left posterior iliac crest showed only mild hypercellularity (50%) and no evidence of malignancy, and the results were confirmed by flow cytometry. Cytogenetic evaluation revealed an interstitial deletion, del (9)(q13q32). In case 2, morphologically the lymph node showed extensive paracortical hyperplasia with numerous eosinophils and no clear indication of a neoplastic process with no abnormal lymphoid population observed by flow. PCR studies for *TCR gamma* and *IgH* gene rearrangements were negative for clonality. Chromosome analysis demonstrated 47, XY,+add(1)(p22),t(3;14)(q27;q11.2)[13]/46,XY[7]. FISH studies showed a *BCL6* gene rearrangement but no *TCRAD* rearrangement. A subsequent inguinal lymph node biopsy showed DLBCL. These cases along with the other cases in the literature provide further evidence of genetic abnormalities preceding morphological abnormalities in developing malignant conditions.

Introduction

Although there is no gold standard by which all tumors are defined in WHO classification, morphology is considered most important while additional features such immunophenotype and genetic abnormalities help arrive at consensus in defining a particular neoplasm. As more and more novel genetic abnormalities are detected due to improved technology, the importance of genetic abnormalities in defining neoplasms is becoming more evident even in the absence of atypical morphological and immunological features. There are a few previously reported cases which have shown that cytogenetic abnormalities often precede morphological evidence in a developing neoplasm and that critical information needed for patient care may be incomplete or inaccurate if such cytogenetic investigations are overlooked (Hain et al., 2003; Hudnall et al., 2007; Northup et al., 2007; Steensma et al., 2003). Here, we present two additional cases with clonal cytogenetic abnormalities, lacking morphologic and immunophenotypic evidence of malignancy.

Case report

Case 1

A 73-year-old male presented with enlargement of his left inguinal region with mild, intermittent pain and 1+ pitting edema in his lower left leg. The patient had a history of B-cell non-Hodgkin lymphoma (NHL) initially diagnosed in December 1976, with recurrent NHL in 1977 and 1983, followed by transformation to DLBCL in 1985. The patient remained in remission from 1985 until 1998 at which he relapsed and received chemotherapy and radiation treatment. After which, the patient was again disease free until June 2010. CT scans demonstrated a left inguinal mass measuring 9.6 cm × 7.1 cm, encasing the left external iliac artery and obliterating the lumen of left external iliac vein. A complete blood count revealed a mild macrocytic anemia (hemoglobin 12.1 g/dL, hematocrit 36%, MCV 100.0 fL, MCH 33 pg), mild thrombocytopenia (136 × 10e9/L), and a normal WBC (7.11 × 10e9/L). A complete metabolic panel revealed elevated serum lactate dehydrogenase (236 U/L). A fine needle aspiration

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and biopsy of the inguinal mass and a bone marrow biopsy with immunohistochemistry, flow cytometry, and cytogenetics studies were performed for staging and to rule out an early myelodysplastic syndrome (MDS). The patient underwent four cycles of rituximab followed by external radiation treatment (XRT) of the left inguinal mass, with a complete response.

The left inguinal mass biopsy was diagnosed as with FL with large cell transformation. Histological sections displayed a diffuse lymphocytic infiltrate in a sclerotic background with focal areas of necrosis and increased number of large centroblasts. The lymphocytes showed diffuse reactivity to CD20, CD10, and BCL6 with the large cells displaying increased Ki-67 staining (focally up to 50%) (Fig. 1). Examination of the left iliac bone marrow biopsy revealed a mild increase in cellularity (50% hypercellular) with no evidence of lymphoma. No lymphoid aggregates or large cell lymphoma were identified. Flow immunophenotypic analysis of the core biopsy of the left inguinal mass revealed CD19 positive B-cells with clonal expression of surface lambda light chain immunoglobulin. Immunophenotypic analysis of the bone marrow revealed the marrow to be normal, with no abnormal clonal populations detected.

In May 2011, the patient developed recurrent large cell lymphoma with multiple confluent masses seen on surveillance imaging, the largest mass located in the anterior mediastinum, measuring 7.8 cm × 4.1 cm × 6.9 cm, totally encasing the patient's coronary artery bypass grafts. Biopsy of this mass confirmed the diagnosis, with flow immunophenotypic analysis revealing an atypical, surface immunoglobulin negative, B cell population. Examination of the right iliac bone marrow biopsy revealed the marrow to be relatively normal, with only a mild hypocellularity (ranging from 5 to 30% cellularity). No lymphoid aggregates or large cell lymphoma were identified. Flow immunophenotypic analysis of the bone marrow aspirate was negative for a monoclonal B cell, aberrant T-cell, or increased blast population. The patient underwent six cycles of bendamustine and rituximab with a significant response and complete resolution of 3 out of 4 dominant masses, with a 4 centimeter residual retroperitoneal mass remaining. He continues on maintenance rituximab with stable disease since.

Chromosomal analysis

Cytogenetic studies of the bone marrow showed an interstitial deletion of chromosome 9(q13q32) (Fig. 2). The karyotype was interpreted as 46,XY,del(9)(q13q32)[7]/46,XY[13] (ISCN, 2009).

Repeat cytogenetic studies of the bone marrow performed in May 2011, showed a continued interstitial deletion of chromosome 9(q13q32). The karyotype was interpreted as 46,XY,del(9)(q13q32)[7]/46,XY[13], similar to the initial studies performed in 2010.

Case 2

A 53-year-old male presented with lymphadenopathy. The lymph node architecture was distorted by a polymorphous cellular infiltrate composed of lymphocytes, histiocytes and numerous eosinophils (Fig. 3A). It was unclear whether this process is neoplastic or reactive. Immunohistochemistry studies showed a mixture of small T-cells (CD2+, CD3+, CD5+, CD43+, and BCL2+) and small to intermediate-sized B-cells (CD20+ and PAX5+). Molecular studies showed no clonal *IgH* gene rearrangement or *TCR gamma* gene rearrangement. The histological pattern is not typical of any common lymphoma.

A subsequent lymph node biopsy six months later demonstrated that the lymph node was involved by a diffuse infiltrate of large lymphoid cells with anaplastic features (Fig. 3B) that marked as B-cells (CD45, CD20+, PAX5+, OCT-2+, BOB.1+) and coexpressed CD30. The neoplastic cells were negative for CD15 and ALK1. These findings are diagnostic for diffuse large B-cell lymphoma. The *IgH* and *TCR gamma* gene rearrangement studies were negative.

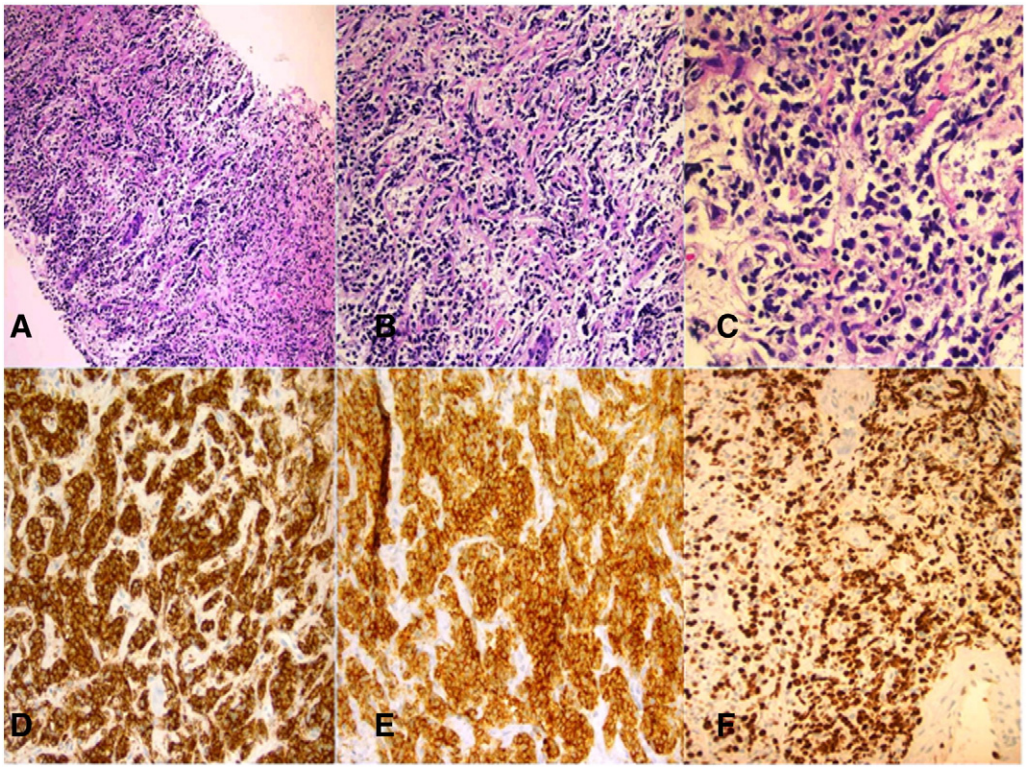

Fig. 1. Photomicrographs of the patient's (case 1) left inguinal mass demonstrating a dense lymphocytic infiltrate in a sclerotic background with focal areas of necrosis and increased large centroblasts. A. 10× magnification B. 20× magnification C. 40× magnification. D. Lymphocytic infiltrate staining positive for CD20. E. Infiltrate positive for CD10. F. Increased proliferation rate demonstrated by Ki-67 positive staining, focally up to 50%.