



An unusual case of de novo CD5-positive brain diffuse large B-cell lymphoma coexpressing MYC and BCL2

Un caso inusual de Linfoma B difuso de células grandes CD5 positivo primario cerebral con coexpresión de c-MYC y BCL2

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Conflict of Interest

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ABSTRACT

Diffuse large B-cell lymphoma is a rare neoplasm of the central nervous system with aggressive behavior and poor outcome. CD5 expression in nodal or extranodal in this neoplasm is infrequent. These cases tend to be more aggressive than the CD5 negative cases. Herein, we report a case of primary brain CD5-positive diffuse large B-cell lymphoma presenting in an immunocompetent 64-year-old woman. She presented with intensity frontoparietal headache, nausea, vomiting, generalized seizures and confusional symptoms. Nuclear magnetic resonance showed characteristics of malignant lymphoma. The patient received treatment with corticoids with good response. Two years after the initial condition, she presented symptoms again. Brain images studies showed bifrontal neoplasm. No tumors were found in other sites. On the basis of morphology and immunohistochemistry, the diagnosis was CD5-positive diffuse large B-cell lymphoma. The present case confirms in this neoplasm multiple pathways are altered. Its identification can be used as therapeutic targets.

Keywords: female, Humans, Middle Aged, Immunohistochemistry, Headache Seizures, Magnetic Resonance Imaging, Confusion, Magnetic Resonance Spectroscopy, Lymphoma, Brain, Neoplasms, Nausea, Vomiting, Adrenal Cortex Hormones, Lymphoma, B-Cell (Source: MeSH-MedLine).

RESUMEN

El linfoma difuso de células b grande es una rara neoplasia del sistema nervioso central con un comportamiento agresivo y un mal resultado. La expresión de CD5 en nodal o extranodal en esta neoplasia es poco frecuente. Estos casos tienden a ser más agresivos que los casos cd5 negativo. Aquí reportamos un caso de linfoma cerebral primario de células b grandes difusas CD5-positivas que se presentan en una mujer inmunocompetente de 64 años. Se presentó con intenso dolor de cabeza frontoparietal, náuseas, vómitos, convulsiones generalizadas y síntomas confusos. La resonancia magnética nuclear mostro características de un linfoma maligno. El paciente recibió tratamiento con corticoides con buena respuesta. Dos años después de la condición inicial, presentó síntomas otra vez. Los estudios de imágenes cerebrales mostraron una neoplasia bifrontal. No se encontraron tumores en otros sitios. Sobre la base de la morfología y la inmunohistoquímica, el diagnóstico fue linfoma difuso de células b grandes CD5-positivo. El presente caso confirma que en esta neoplasia se alteran múltiples vías. Su identificación pueden ser usados como blancos terapéuticos.

Palabras clave: mujer, Humanos, Inmunohistoquímica de mediana edad, Dolor de cabeza, Convulsiones, Imagen de resonancia magnética, Confusión, Espectroscopía de resonancia magnética, Linfoma, Cerebro, Neoplasias, Náusea, Vómitos, Hormonas de la corteza suprarrenal, Linfoma de células B (Fuente: DeCS-Bireme).



INTRODUCTION

The primary central nervous system (PCNS) lymphoma is an extranodal non-Hodgkin lymphoma (NHL), usually diffuse large B-cell lymphoma (DLBCL); it confines to the brain, leptomeninges, eyes, spinal cord, with no evidence of spreading outside the CNS, excluding lymphomas originated in the dura mater, intravascular large B-cell lymphoma, extranodal NK/T-cell lymphoma, nasal type, and immunodeficiency-associated lymphomas. Most cases are sporadic, and incidence increases with age. In a subgroup of patients, disease progression is caused by a state of immunosuppression, including HIV infection. This tumor represents 2,4 % - 3 % of all brain tumors and 4 % - 6 % of all extranodal lymphomas ^(1,2).

Approximately, 5 % - 10 % of nodal and extranodal DLBCL are CD5 positive (de novo CD5+ DLBCL). CD5+ DLBCL is a clinicopathological variant of DLBCL with an aggressive clinical course and a poor prognosis; it mostly affects elderly patients who present B symptoms, elevated LDH level, extranodal involvement, higher incidence of CNS involvement and advanced clinical stage. Rituximab-based chemotherapy regimens have improved the overall survival of CD5+ DLBCL patients, but it has failed to decrease the rate of CNS involvement ^(3,6).

CLINICAL HISTORY

A 64-year-old woman presented in our hospital with mild-moderate intensity frontoparietal headache, nausea, vomiting, generalized tonic-clonic seizures and confusional symptoms, with no significant findings on physical examination. A Brain NMR, revealed lesions with intense and homogeneous contrast enhancement at right sagittal section associated with marked vasogenic edema. Laboratory tests showed no abnormalities. Two years after the

initial condition, she presented a new confusional episode. Laboratory tests showed no abnormalities. Brain NMR showed extensive bifrontal neoformation crossing the midline, with signs of infiltration of the rostrum of corpus callosum, and subfalcine herniation, (see figure 1A).

Other images exams revealed no neoplasms in other sites. A stereotactic brain biopsy was performed. Patient's clinical evolution was unfavorable, and showed progressive neurological deterioration. Finally, the patient died.

METHODS

The histological examination with H&E stain was performed with a DAKO coverstainer machine (DAKO, Carpinteria, CA, USA). The immunohistochemical analysis was performed with a DAKO autostainer link48 machine (DAKO, Carpinteria, CA, USA). For the analysis of Chromogenic in situ hybridization (CISH), the incubation was performed with histosonda EBER (CENBIMO, Spain), which detects EBER1 and EBER2 of the EBV.

RESULTS

The H&E stain showed brain tissue infiltrated by large pleomorphic cell sheets, with predominantly centroblastic morphology, a lower proportion of immunoblasts, a high mitotic index, and areas of necrosis. Areas of angiotropism and angiocentricity were also evidenced.

The immunophenotype of the neoplastic cells was CD20+, CD5+, BCL2+, MUM1+, C-MYC+, LMP1 (EBV)-, CD10-, CD23-, CD43-, CICLIN D1-, CD30-, BCL6- and CD3-, with Ki67 in approximately 70 % (Figures 1B, 1C, 1D, 1E, 1D). The case was diagnosed as de novo CD5 positive DLBCL coexpressing C-MYC and BCL2, non-germinal center (non-GC) type. The bone

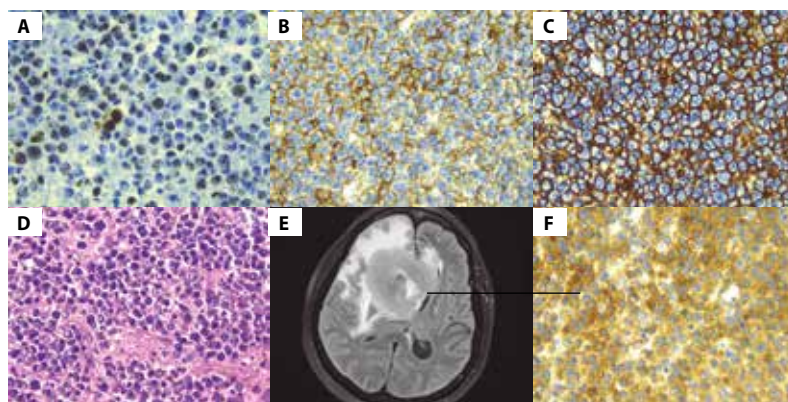


Figure 1. Brain NMR showing bifrontal neoformation crossing the midline with infiltration of the corpus callosum (A). The brain tissue show diffuse infiltration by large lymphoid tumor cells with both centroblastic and immunoblastic features (hematoxylin & eosin x 40; B). Tumor cells are strongly positive for CD20 (C), CD5 (D), and BCL-2 (E). Immunostaining for Ki-67 shows high proliferative index (F)

marrow biopsy showed no evidence of neoplastic cell infiltration. The EBER was negative.

According to the updated WHO classification, the characteristics of the present case were consistent with PCNS DLBCL.

DISCUSSION

The PCNS DLBCL is an infiltrative neoplasm, whose fundamental histological features are angiocentricity and angiotropism. The migration of lymphocytes within the CNS depends on a selective interaction of adhesion molecules with the vascular endothelium of the CNS. Other factors that are related to the pathogenesis of these neoplasms are the JAK/STAT signaling pathway, deregulation of the B-cell receptor (BCR), the NFκB pathway and the Toll-like receptor signaling pathway. In some of these cases, it has been proposed that the sentinel inflammatory lesions may be the first immunological response to the development of this neoplasia^(2,8,9,10).

CD5 is a surface glycoprotein typically expressed on normal and neoplastic T- cells, as well as in normal virgin B cells and some B lymphoma cells such as chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL / SLL) and mantle cell lymphoma (MCL).

In Japan, a frequency of 5-22% of CD5 expression has been reported in all DLBCL cases^(3,5). These neoplasms are more aggressive than the CD5- and correspond to elderly patients, mostly female, who have >1 ECOG performance status, elevated LDH level, advanced stage disease, high IPI, >1 extranodal sites involved, and B-symptoms^(3,10) and frequent bone marrow involvement. CD5+ DLBCL in Western countries had lower prevalence, although they share common findings such as performance status, non-GCB subtype, BCL2 overexpression, bone marrow involvement and recurrence. Nevertheless, they are more common in men, where extranodal involvement, higher and advanced LDH stages are less frequent^(3,10). Four histological variants have been described: the common or monomorphic/centroblastic variant; with monomorphic proliferation of centroblasts and some giant cells; giant cell rich variant with multiple nucleoli and presence of immunoblasts and centroblasts; the polymorphic variant, and finally, the immunoblastic variant. A total of 38 % of the cases are associated with intravascular/sinusoidal pattern⁽⁵⁾. They often express pan-B markers such as CD19, CD20; most cases are positive for MUM1 and negative for Cyclin D1. Some cases express CD10, and they rarely are CD23+. The more frequently expressed Immunoglobulin isotype is IgM, having been observed CD30 expression in some

cases of giant cell rich variant^(3,5). They are usually non-GCB type and overexpress BCL2^(5,10).

Recently have been reported two de novo CD5 DLBCL coexpressing MYC and BCL2, and MYC and BCL6^(11,12). First of them describe a primary cardiac DLBCL and the latter a primary gastric DLBCL. The question arises if there are DLBCL quadruple-hit, de novo CD5 positive, MYC positive, BCL2 positive, BCL6 positive. This could have an adverse prognostic impact as described in cases where lymphoma-specific genetic events in parallel have been identified (MYC, BCL2, BCL6 and CCND1)^(13,14).

The case described is quite unusual, but reaffirms the heterogeneous nature of DLBCL. The identification of certain molecular pathways in DLBCL could be used more frequently in the future as a therapeutic target. CD5 determination should be part of the DLBCL diagnosis panel.

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