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CASE REPORT
ΕΝΔΙΑΦΕΡΟΥΣΑ ΠΕΡΙΠΤΩΣΗ

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The use of immunocytochemistry in the diagnosis of secondary central nervous system lymphoma

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Ανοσοϊστοχημεία για τη διάγνωση δευτεροπαθούς λεμφώματος σταδίου ΙΙ του κεντρικού νευρικού συστήματος

Περίληψη στο τέλος του άρθρου

Central nervous system involvement, a well recognized complication of aggressive non-Hodgkin's lymphoma (NHL), has been rarely reported in indolent lymphomas. The case is reported of a 67 year-old male patient with follicular lymphoma (grade II) who presented with fever, night sweats, generalized lymphadenopathy and bone marrow involvement. Excellent initial clinical regression of the lymphoma was achieved with fludarabin and cyclophosphamide chemotherapy. However, during the fifth cycle of chemotherapy, progressive neurological symptomatology with respiratory depression appeared. A diagnosis of lep tomeningeal lymphoma was made by immunohistochemical analysis of cytospin slides of the cerebrospinal fluid (CSF), with the finding that 90% of CSF mononuclear cells were CD20$^+$, kappa$^+$, lamda$^-$. Systemic and intrathecal chemotherapy were ineffective, and ten days later the patient died.

Key words

Cerebrospinal fluid
CNS involvement
Differential diagnosis
Indolent non-Hodgkin's lymphoma
Immunohistochemical analysis

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The central nervous system (CNS) is frequently involved in non-Hodgkin's lymphoma (NHL). It may be one of multiple localisations of the disease or the initial or only site of disease. CNS involvement can manifest as lymphomatous meningitis or parenchymal involvement.[1] The diagnosis of CNS lymphoma is established by neuroimaging and laboratory analysis of cerebrospinal fluid (CSF).[1] High-grade NHL carries a 39% risk of CNS relapse, the majority of relapses occurring in the first 14 months after the initial diagnosis.[2] The prognosis after CNS relapse in patients with high and intermediate grade NHL is poor. The median survival is reported to be ~4 months among patients with aggressive histology.[3] Conversely, patients with low-grade NHL have a 7% risk of CNS relapse, but in all these patients, the low malignancy grade had been transformed into a higher malignancy grade at the time of relapse.[2]

CASE REPORT

A 67 year-old man presented in April 2005 with fever, night sweats and generalized lymphadenopathy. On physical examination, firm lymph nodes measuring up to 7 cm were palpable in all regions, and the spleen was palpable 3 cm below the left costal margin. Laboratory blood tests showed an accelerated erythrocyte sedimentation rate (ESR) of 55 mm/hour, and elevated levels of C-reactive protein (CRP) (9 mg/L), and β_2-microglobulin (3.25 mg/L). Computed tomography (CT) scan revealed mediastinal and retroperitoneal lymph node enlargement (2 cm and 7 cm, respectively), and splenomegaly (14 cm). Bone marrow biopsy showed multiple paratrabecular and centromedular nodular lymphoid infiltrates, with 6–15 centroblasts per high power field (histological grade II). Lymphoid infiltration constituted approximately 80% of the bone marrow surface area, with the following immunophenotype: CD79α$^+$, CD20$^+$, Bcl-2$^+$, bcl-6$^+$, CD10$^+$. Cyclin D1 was positive in 5% and Ki-67+ in 8% of lymphoid cells, respectively.

Treatment was started with fludarabin and cyclophosphamide chemotherapy, with an excellent and prompt response: after only two cycles of chemotherapy, the adenopathy completely disappeared and the laboratory tests became normal. Suddenly, during the fifth cycle of chemotherapy, the patient complained of fatigue, headache, vomiting and nausea, and presented repeated seizures. Neurological examination showed weakness, somnolence, lowered right eyelid, mild central paresis of the facial nerve and positive meningeal signs. The patient was transferred to the Institute of Infective Diseases because respiratory failure developed and mechanical ventilation was necessary. Laboratory blood tests showed only elevated creatine kinase (2240 U/L), with normal ESR (4 mm/hour), fibrinogen (3.2 g/L) and CRP (5 mg/L). Chest X-ray was normal and abdominal ultrasound revealed no enlarged lymph nodes or splenomegaly. Nuclear magnetic reso-

nance of the brain revealed bilateral, periventricular, probably postischemic, lesions. Biochemical analysis of the CSF showed a decrease in the glucose level, while the levels of protein and lactates were elevated. Examination of CSF cytospin slides demonstrated numerous lymphocytes. Microbiological and serological analysis from multiple CSF samples was negative, including for *Listeria monocytogenes*, *Cryptococcus*, Rubella and herpes simplex virus-1. Polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* was negative. The immunohistochemical CSF lymphocyte profile showed CD20 expression in the majority of cells (>90%) and light chain restriction (kappa$^+$, lamda$^-$) (fig. 1). Thus, a diagnosis of CNS lymphoma was established. The patient was treated with methotrexate 1800 mg iv on day 1, Dexason 40 mg iv on days 1–6 and methotrexate 12 mg intrathecally on days 1, 3, 5. However, there was no response to treatment, and the patient died 10 days after initiation of therapy due to septic schock.

COMMENT

CNS involvement in malignant lymphoma can appear at the time of the original diagnosis, during treatment for systemic lymphoma, or later during the relapse of the disease. Secondary CNS lymphoma is defined as CNS involvement not obvious at the initiation of treatment for systemic lymphoma. Secondary CNS lymphoma may be solitary, but is frequently encountered in the context of poorly controlled disease elsewhere. Histologic evidence of aggressiveness, an advanced clinical stage, elevated serum lactate dehydrogenase levels, the involvement of more than one extranodal site, a high age-adjusted International Prognostic Index score at presentation, and specific anatomical sites of involvement, such as the testis, are important risk factors for secondary CNS lymphoma.[3]

Although CNS involvement is very rare in indolent lymphoma, this complication should be considered in the differential diagnosis of new neurological symptoms and signs in patients with indolent lymphoma, especially when disease transformation is obvious.[4] In the case reported, the patient developed neurological symptomatology during his fifth cycle of chemotherapy, after an excellent initial systemic response to treatment. During differential diagnostic evaluation, a CNS infection was considered first, because the patient was immunocompromised, both as a consequence of the malignancy and because of the well known immunosuppressive effect of fludarabine. As the tests for numerous infective agents were negative (including agents which can cause leptomeningitis with lymphocytosis in the CSF), the diagnostic confirmation was effected by immunohistochemical analysis of CSF cytospin slides, which showed the monoclonal origin of the CSF lymphocytes. It was demonstrated that immunohistochemical analysis of CSF is a reliable and quick technique for the detection of CSF seeding of leukemia/lymphoma, particularly in cases, such as this, of CNS disturbance accompanied by mononuclear cells in the CSF, when infectious etiology is an alternative diagnostic option. Recently, PCR and flow cytometry assays of CSF[5] have become available for the correct diagnosis of secondary CNS lymphoma. CNS involvement should be considered in cases with indolent NHL presenting with new neurological signs, even in the absence of evidence of active systemic lymphoma or signs of histological transformation.

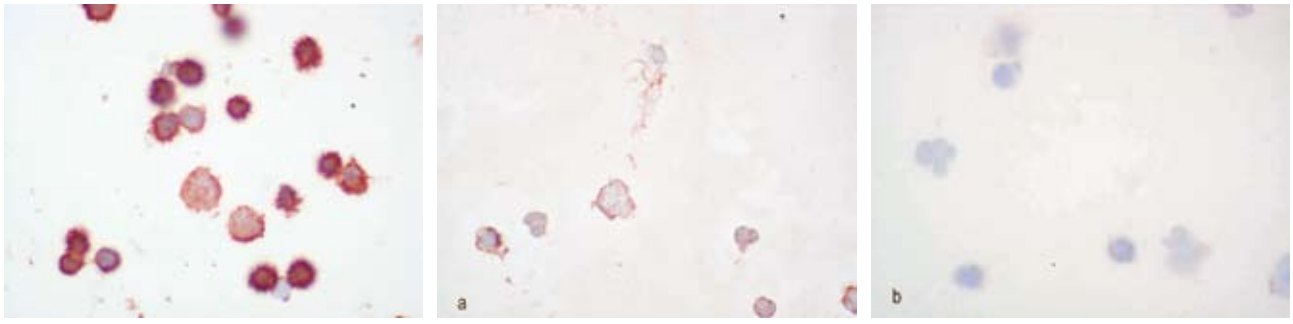

Figure 1. Immunohistochemical analysis of cerebrospinal fluid slides: Lymphocytes showing positivity for CD20 antigen (left) and light chain restriction (a-kappa$^+$, b-lamda$^-$) (right).

ΠΕΡΙΛΗΨΗ

Ανοσοϊστοχημεία για τη διάγνωση δευτεροπαθούς λεμφώματος σταδίου ΙΙ του κεντρικού νευρικού συστήματος

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Η προσβολή του κεντρικού νευρικού συστήματος αποτελεί μια γνωστή επιπλοκή του επιθετικού λεμφώματος non-Hodgkin, που εμφανίζεται σπανιότερα στα λεμφώματα χαμηλής κακοήθειας. Περιγράφεται η περίπτωση ενός άρρενα ασθενούς, ηλικίας 67 ετών με οζώδες λέμφωμα (σταδίου ΙΙ), το οποίο εκδηλώθηκε με εμφάνιση πυρετού, νυκτερινών ιδρώτων, γενικευμένηw διόγκωσηw λεμφαδένων και προσβολήw του μυελού των οστών. Αρχικά, υπήρξε πολύ καλή ανταπόκριση στη θεραπεία συνδυασμού με φλουνταραμπίνη και κυκλοφωσφαμίδη. Κατά τη διάρκεια του πέμπτου κύκλου της χημειοθεραπείας εμφανίστηκαν νευρολογικά συμπτώματα με εκδηλώσεις προσβολής του κέντρου της αναπνοής. Η ανοσοϊστοχημική ανάλυση των κυττάρων του εγκεφαλονωτιαίου υγρού έδειξε την ύπαρξη 90% κυττάρων θετικών στο CD20 και τις κ ελαφρές αλυσίδες, ενώ οι λ ελαφρές αλυσίδες ήταν αρνητικές. Η συστηματική και η ενδορραχιαία χημειοθεραπεία δεν ήταν αποτελεσματικές, με κακή κατάληξη του ασθενούς 10 ημέρες αργότερα.

Λέξεις ευρετηρίου: Ανοσοφαινότυπος, Διαφορική διάγνωση, Εγκεφαλονωτιαίο υγρό, Μη Hodgkin λέμφωμα χαμηλής κακοήθειας, Προσβολή κεντρικού νευρικού συστήματος

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