Differences in cerebrospinal fluid inflammatory cell reaction of patients with leptomeningeal involvement by lymphoma and carcinoma

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Dissemination of neoplastic cells into the cerebrospinal fluid (CSF) and leptomeninges is a devastating complication in patients with epithelial cell neoplasia (leptomeningeal carcinomatosis (LC)) and lymphomas (lymphomatous meningitis (LyM)). Information about the surrounding inflammatory cell populations is scarce. In this study, flow cytometry immunophenotyping was used to describe the distribution of the main leukocyte populations in the CSF of 83 patients diagnosed with neoplastic meningitis (LC, n = 65; LyM, n = 18). These data were compared with those obtained in the CSF from 55 patients diagnosed with the same groups of neoplasia without meningeal involvement (solid tumors, n = 36; high-grade lymphoma, n = 19). Median (interquartile) rates of lymphocytes, monocytes, and polymorphonuclear (PMN) cells were 59.7% (range, 35–76.6%), 24% (range, 16–53%), and 1.5% (range, 0–7.6%) in LC, respectively, and 98.5% (range, 70.8–100%), 1.5% (range, 0–29.3%), and 0% in LyM, respectively ($P < 0.001$). No difference was observed between patients with breast adenocarcinoma (n = 30) and lung adenocarcinoma (n = 21), nor with different rates of malignant CSF involvement. Patients with lymphoma (with or without LyM) had a similar CSF leukocyte distribution, but cancer patients with LC and without LC had a distinctive PMN cell rate ($P = 0.002$). These data show that CSF samples from patients with LC have a greater number of inflammatory cells and a different leukocyte distribution than seen in the CSF from patients with LyM. Description of PMN cells is a distinctive parameter of patients with LC, compared with the CSF from patients with LyM and patients with cancer but without LC. (Translational Research 2014;164:460–467)

Abbreviations: CNS = central nervous system; CSF = cerebrospinal fluid; FCI = flow cytometry immunophenotyping; FSC = forward scatter; LC = leptomeningeal carcinomatosis; LyM = lymphomatous meningitis; mAb = monoclonal antibody; neg = negative; PMN = polymorphonuclear; pos = positive; SSC = side scatter

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AT A GLANCE COMMENTARY

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Background

The inflammatory cell infiltrate surrounding tumors is progressively gaining importance, but at the moment, no information has been provided in patients with leptomeningeal involvement, a devastating complication that may develop in patients diagnosed with epithelial cell neoplasia and lymphoma.

Translational Significance

A description of the inflammatory cell distribution in the cerebrospinal fluid from patients with lymphomatous meningitis and leptomeningeal carcinomatosis could provide information for a better understanding of the pathophysiology of the disease and also for future possible design of immune-based cancer therapies. Currently, these data may add information for diagnostic purposes.

Leptomeningeal tumor involvement defines the dissemination of neoplastic cells into the cerebrospinal fluid (CSF) and infiltration of the leptomeninges. It is usually found in the context of epithelial cell solid tumors and melanoma (leptomeningeal carcinomatosis [LC]) and hematologic malignancies (leukemic or lymphomatous meningitis [LyM]), and less frequently in primary central nervous system (CNS) tumors.[1-3] Unfortunately, this neoplastic complication still leads to a very bad prognosis for the patient.

In recent years, several studies have shown that flow cytometry immunophenotyping (FCI) improves the sensitivity of classic cytologic examinations of the CSF. These studies highlight the importance of CSF FCI studies for early diagnosis of neoplastic CNS involvement in patients with aggressive lymphomas,[4-8] and there are also promising results in epithelial cell neoplasms.[9]

Currently, there is an increasing interest in the immunologic response to cancer.[10-13] Immune cells could develop cytotoxic activity that helps eliminate neoplastic cells. However, tumor cells also secrete cytokines, chemokines, and growth factors that—throughout their interaction with different cells in the tumor microenvironment—might contribute to angiogenesis and metastases.[11] Most of the studies focus on solid tumors from different cell lines,[11,14-17] and although many of them can spread into the CSF and meninges, information about the inflammatory populations in these loci is scarce.[18] The aim of our study was to perform an exploratory analysis of the CSF leukocyte populations in the CSF of patients diagnosed with leptomeningeal infiltration by solid tumors and lymphomas. We did not find similar studies during the period of this research.

METHODS

Study design. Two different populations of patients were included in our study. CSF samples from patients suspicious of having LC were provided by a prospective collection performed by 18 Spanish hospitals between 2010 and 2012 in the context of another study related to LC prognostic factors.[19] The CSF samples from patients with lymphoma were studied at diagnosis or relapse as part of the staging of patients with high risk for CNS involvement, although they might not have any suggestive symptomatology.

The diagnosis of LC was based on CSF cytology or on suitable clinical symptoms together with magnetic resonance imaging and/or biochemical CSF abnormalities.[20] Patients with melanoma, medulloblastoma, mesothelioma, acute leukemia, low-grade lymphoma, and primary brain tumors were not considered for this study. Immunodeficient patients (human immunodeficiency virus or transplant recipients) were also excluded.

This research was carried out according to the principles of the Declaration of Helsinki. Informed consent was obtained from each participant before their enrollment, and local ethics committees of participating centers approved the study.

Patients and samples. A total of 252 CSF samples from patients diagnosed with epithelial cell solid tumors (n = 207) and high-grade B-cell lymphoma (n = 45) were evaluated. The final number of samples included in the study was 138, after excluding CSF samples with macroscopic blood contamination and samples that showed erythrocytes in the cell pellet after centrifugation. Eighty-three CSF samples were from patients who were diagnosed finally with leptomeningeal involvement: 65 had LC and 18 had LyM. The localization of the primary epithelial cell tumor was as follows: breast, n = 30; lung, n = 23; gastrointestinal tract, n = 4; ovary, n = 4; bladder, n = 1; prostate, n = 1; and kidney, n = 2. Adenocarcinoma was confirmed histologically for 60 of 65 patients (92.3%). Histologic diagnoses of patients with lymphoma included diffuse large B-cell non-Hodgkin lymphoma (n = 14), Burkitt cell lymphoma (n = 3), and CNS primary lymphoma (n = 1).

A group of 55 patients from this series in whom the diagnosis of neoplastic involvement was excluded, and did not develop LC or LyM during the 12 months after the CSF study, were used for comparison of their