Eur J Cancer Clin Oncol, Vol. 23, No. 1, pp. 1–4, 1987.
Printed in Great Britain

0277–5379/87$3.00+0.00
Pergamon Journals Ltd.

Perspectives and Commentaries

Cerebrospinal Fluid Tumor Markers for the Diagnosis and Management of Leptomeningeal Metastases

MARK G. MALKIN and JEROME B. POSNER

Department of Neurology, Memorial Sloan-Kettering Cancer Center, 1275 *York Avenue, New York, New York* 10021, *U.S.A.*

(A COMMENT ON: Twijnstra A, van Zanten AP, Nooyen WJ, Hart AAM, Ongerboer de Visser BW. Cerebrospinal fluid beta$_2$-microglobulin: a study in controls and patients with metastatic and non-metastatic neurological diseases. *Eur J Cancer Clin Oncol* 1986, **22**, 387–392.)

THE DIAGNOSIS of leptomeningeal metastases (LM), either from solid tumor or hematologic malignancy, often presents a formidable problem. The diagnosis is considered established when malignant cells are found on cytologic examination of the cerebrospinal fluid (CSF). However, frequent false-negative and occasional false-positive results limit the reliability of that test. In an effort to circumvent this difficulty, investigators have looked for biochemical tumor markers in the CSF. Beta-2-microglobulin (β2m), an 11,800 D protein subunit of the histocompatibility antigens found on the surface of nucleated cells, is normally present in CSF. Lymphocytes and macrophages are particularly rich in β2m, hence the assumption that β2m would be useful in the diagnosis of LM from hematologic malignancies. β2m as a tumor marker has been the subject of several reports.

In this Journal, Twijnstra *et al.* [1] reported β2m levels in the CSF of almost 200 patients with a variety of illnesses, in order to define the usefulness of this marker for the diagnosis of LM. Each CSF specimen was also examined for protein, glucose, lactic dehydrogenase (LDH), and culture and cytology. The criterion for the diagnosis of LM was the presence by cytologic examination of tumor cells in the CSF. In 48 otherwise healthy patients with back pain of discogenic or musculoskeletal origin who served as controls, the logarithm of the β2m concentration was related to age. The β2m values were transformed logarithmically prior to final analysis, because the data distribution was both skewed (asymmetrical) and kurtotic (unusually shaped). Their age-standardized "normal" reference values of 0.65–2.20 mg/l at 50 years are consistent with those of other laboratories. No sex differences were noted.

β2m was increased when CSF contained malignant cells from either solid tumors (68%) or hematologic malignancies (89%), but minor elevations also occurred with epidural (21%) and parenchymal (80%) metastases from solid tumors. β2m was even slightly raised in a few patients with solid tumors (9%) and hematologic malignancies (25%) without central nervous system (CNS) metastases. The authors found a sensitivity of 70% for LM from solid tumors, and a sensitivity of 90% for LM from hematologic malignancies; overall specificity was 93%. Inspection of their raw data reveals an overall false-positive rate of 7% and a false-negative rate of 26%. They concluded that β2m was a sensitive marker for LM, especially in hemopoietic malignancies.

No correlation between serum and CSF β2m was found, surprisingly, since one might expect some crossing of the blood–brain barrier, particularly a barrier damaged by tumor when the serum level is very high. No serum levels are given in the paper. The authors conclude that there is autonomous production of β2m in the two compartments, and therefore no rationale for the use of the CSF/serum ratio. Comparison of the CSF β2m level with a reference range will suffice.

Accepted 10 July 1986.

Twijnstra *et al.* speculated that increased β2m levels in patients with cerebral and epidural metastases reflect ependymal or meningeal invasion, i.e. LM with a false-negative cytologic examination. One can imagine in such situations, and also in LM, that rapidly proliferating malignant cells cling to surrounding structures and are sequestered from cytologic scrutiny, whereas cell surface antigens break off and are detected by assay.

The strengths of the Twijnstra paper lie in the number of patients tested, and in the data transformation and statistical analysis. The study would have been enhanced by serial samples in individual patients to monitor the course of disease and to evaluate the response to therapy. The authors excluded patients with bacterial meningitis from the study, but it is important to remember that in such patients CSF β2m may be elevated and confuse the diagnosis, especially in a patient with a systemic hematologic malignancy and an opportunistic CNS infection.

Others have also measured β2m in CSF. Koch *et al.* [2] examined 23 patients with leukemia, lymphoma and small cell lung carcinoma to evaluate the usefulness of this test in the early detection of CNS metastases. Like Twijnstra et al., they found higher levels in patients with CNS metastases than in normal controls, or in patients without CNS disease. Serial measurements were performed on two patients; in both, β2m became elevated coincident with CNS relapse, and returned to normal as remission was achieved. No correlation with CSF glucose was found, which suggests that glucose and β2m abnormalities may reflect independent pathologic processes in LM. No correlation existed between serum and CSF β2m. The false-negative rate of 8% compared favorably with the 26% of Twijnstra *et al.* This may be a true difference, but more likely reflects the smaller number of patients in Koch's study. We agree with Koch *et al.* that caution is required in the interpretation of one, isolated, slightly elevated CSF β2m, since measurements that show a trend are much more reliable. Mavligit *et al.* [3] measured CSF β2m in 51 patients with acute leukemia and lymphoma. Their results agree with those of Twijnstra and Koch. They introduced the valid concept that elevated β2m levels should only be used as an ancillary tool for the diagnosis of LM. It is certainly not justifiable to administer intrathecal chemotherapy on the basis of a high β2m alone. Starmans *et al.* [4] measured β2m levels in the CSF of 125 patients with neurologic disease. They extended Mavligit's observations by showing no relationship between β2m and CSF protein or cell count. β2m was often elevated in meningeal and CNS infections. There was no clear relationship between serum and CSF β2m. Nagelkerke *et al.* [5], using a micro-ELISA assay, measured CSF β2m in 30 children with ALL. They found a disappointing 40% sensitivity and 8% predictive value. Perhaps differences in methodology (micro-ELISA vs. RIA) account for the discrepancy between their paper and the others reviewed here.

Thus, CSF β2m is not diagnostic for LM, but when used in conjunction with other measurements, especially cytology and other tumor markers (see below), may be very helpful in diagnosis. β2m seems especially useful in following the course of CNS disease.

Other markers are also commonly measured in CSF to detect and follow LM [6–10]. β-glucuronidase (β-glu) is an intracellular enzyme, distributed in lysosomes and microsomes. It hydrolyzes the β-glycosidic bond between glucuronic acid and an aglucone. It is normally found in brain (gray and white matter), pia-arachnoid, and choroid plexus, and is normally detected in small amounts in the CSF. β-glu rises with massive brain necrosis, glioblastoma and demyelination. Carcinoembryonic antigen (CEA) is a high molecular weight glycoprotein produced by several solid tumors. Patients with intraparenchymal metastases have elevated CSF CEA levels when the metastases are in close proximity to the ventricular or ependymal surfaces; this corresponds to Twijnstra's speculation concerning β2m. LDH is ubiquitous in brain, and has an isoenzyme pattern with predominance of the electrophoretically fast-moving isoenzyme fractions 1 and 2. Studies of brain tissue homogenates have indicated that neoplasms cause a shift in the isoenzyme pattern from fractions 1 and 2, to 4 and 5, attributable to a shift to anaerobic metabolism.

At Memorial Sloan-Kettering Cancer Center (MSKCC) we have found at least one abnormal marker level in 75–90% of patients with LM from melanoma, lung cancer and breast cancer, and concluded that measurement of these markers assisted in early diagnosis [8–10]. This observation emphasizes the fact that the greatest sensitivity, specificity, and predictive value will be achieved by measuring several markers. However, the profile to be measured must correspond to the primary disease. Thus, β2m is most helpful in hematologic malignancies, CEA in solid tumors, and human chorionic gonadotropin (HCG) and alphafetoprotein (AFP) (see below) in germ cell tumors. β-glu was occasionally elevated in patients with LM in the absence of any other CSF abnormalities. All markers approached control levels with favorable treatment of LM. None of these markers reliably detected leptomeningeal infiltration by lymphoma. β2m is the most useful in that regard. LDH-5 was increased in CSF infections with a granulocytic pleocytosis. β-glu was moderately elevated in

chronic infectious meningitis; CEA was not.

Tallman *et al.* [11] studied CSF β-glu. Their findings were in concordance with the MSKCC experience. As with β2m, β-glu levels did not correlate well with CSF protein, glucose or cell count.

The results reported by Yap et al. [12] with CSF CEA in 23 cases of LM from breast cancer also corroborate the MSKCC experience. Again, there was no correlation between CSF CEA, and CSF protein, glucose or cell count. Neither was there a relationship between CEA in serum and CSF, implying independent CEA synthesis within the CSF.

Allen *et al.* [13] measured HCG and AFP in the CSF of 6 patients with intracranial germ cell tumors. As expected, the 2 embryonal carcinomas were AFP- and HCG-positive, the 2 choriocarcinomas were HCG-positive, and the 2 dysgerminomas were marker-negative. Two of the 4 patients with positive markers had malignant cells in the CSF. Marker levels declined with therapy, and usually rose prior to the development of clinical symptoms if the patient's tumor recurred.

Phillips *et al.* [14] performed CSF polyamine determinations in 35 children with brain tumors. Putrescine was consistently increased in active disease in patients with medulloblastomas, ependymomas, pineal region germ cell tumors, primitive neuroectodermal tumors and brainstem gliomas. The highest putrescine values were found in patients with widely disseminated, recurrent tumors.

Monoclonal antibodies may provide a powerful and reliable method to assess LM. Coakham *et al.* [15] have systematically applied a panel of monoclonal antibodies to the CSF of patients with suspected LM. The antibodies were directed against neuroectodermal tissue, epithelial cytokeratin, leukocytes and neoplastic neuroblasts. Whereas routine cytology was positive for malignant cells in 10 of 14 cases, and accurately categorized the cell type in 3 of 14, immunocytology increased the accuracy of categorization to 16 of 17 cases. Ezrin-Waters *et al.* [16], using monoclonal antibodies directed against lymphocyte cell surface markers, revealed a clone of malignant B cells in the CSF of a patient with LM from lymphoma. This finding allowed accurate diagnosis and initiation of treatment.

The perfect tumor marker would be elevated in all tumor-bearing patients, and would be within normal limits in all patients without tumors. It would be cell type-specific. Its level would rise or fall prior to any clinical, radiographic or biochemical indication of relapse or remission. No such ideal marker exists. Our present state of knowledge dictates that serial CSF cell counts, protein and glucose, cytology, biochemical markers, and monoclonal antibodies should all be used, together with the clinical and radiographic information, to improve the diagnosis and management of patients with LM.

REFERENCES

1. Twijnstra A, van Zanten AP, Nooyen WJ, Hart AAM, Ongerboer de Visser BW. Cerebrospinal fluid beta$_2$-microglobulin: a study in controls and patients with metastatic and non-metastatic neurological diseases. *Eur J Cancer Clin Oncol* 1986, **22**, 387–392.
2. Koch TR, Lichtenfeld KM, Wiernik PH. Detection of central nervous system metastasis with cerebrospinal fluid beta-2-microglobulin. *Cancer* 1983, **52**, 101–104.
3. Mavligit GM, Stuckey SE, Cabanillas FF, Keating MJ, Tourtellotte WW, Schold SC, Freireich EJ. Diagnosis of leukemia or lymphoma in the central nervous system by beta$_2$-microglobulin determination. *N Engl J Med* 1980, **303**, 718–722.
4. Starmans JJP, Vos J, van der Helm HJ. The β_2-microglobulin content of the cerebrospinal fluid in neurological disease. *J Neurol Sci* 1977, **33**, 45–49.
5. Nagelkerke AF, van Kamp GJ, Veerman AJP, de Waal FC. Unreliability of β-2-microglobulin in early detection of central nervous system relapse in acute lymphoblastic leukemia. *Eur J Cancer Clin Oncol* 1985, **21**, 659–663.
6. Seidenfeld J, Marton LJ. Biochemical markers of central nervous system tumors measured in cerebrospinal fluid and their potential use in diagnosis and patient management: a review. *J Natl Cancer Inst* 1979, **63**, 919–931.
7. Wasserstrom WR, Schwartz MK, Fleisher M, Posner JB. Cerebrospinal fluid biochemical markers in central nervous system tumors: a review. *Ann Clin Lab Sci* 1981, **11**, 239–251.
8. Wasserstrom WR, Glass JP, Posner JB. Diagnosis and treatment of leptomeningeal metastases from solid tumors: experience with 90 patients. *Cancer* 1982, **49**, 759–772.
9. Schold SC, Wasserstrom WR, Fleisher M, Schwartz MK, Posner JB. Cerebrospinal fluid biochemical markers of central nervous system metastases. *Ann Neurol* 1980, **8**, 597–604.
10. Fleisher M, Wasserstrom WR, Schold SC, Schwartz MK, Posner JB. Lactic dehydrogenase isoenzymes in the cerebrospinal fluid of patients with systemic cancer. *Cancer* 1981, **47**, 2654–2659.
11. Tallman RD, Kimbrough SM, O'Brien JF, Goellner JR, Yanagihara T. Assay for β-glucuronidase in cerebrospinal fluid: usefulness for the detection of neoplastic meningitis. *Mayo Clin Proc* 1985, **60**, 293–298.

12. Yap BS, Yap HY, Fritsche HA, Blumenschein G, Bodey GP. CSF carcinoembryonic antigen in meningeal carcinomtosis from breast cancer. *JAMA* 1980, **244**, 1601–1603.
13. Allen JC, Nisselbaum J, Epstein F, Rosen G, Schwartz MK. Alphafetoprotein and human chorionic gonadotropin determination in cerebrospinal fluid. An aid to the diagnosis and management of intracranial germ-cell tumors. *J Neurosurg* 1979, **51**, 368–374.
14. Phillips PC, Kremzner LT, DeVivo DC. Cerebrospinal fluid polyamines: biochemical markers of malignant childhood brain tumors. *Ann Neurol* 1986, **19**, 360–364.
15. Coakham HB, Brownell B, Harper EI, Garson JA, Allan PM, Lane EB, Kemshead JT. Use of monoclonal antibody panel to identify malignant cells in cerebrospinal fluid. *Lancet* 1984, **1**, 1095–1098.
16. Ezrin-Waters C, Klein M, Deck J, Lang AE. Diagnostic importance of immunological markers in lymphoma involving the central nervous system. *Ann Neurol* 1984, **16**, 668–672.