Serum diagnosis

In patients with CNS metastases and leptomeningeal spread, serum analysis is important to detect barrier dysfunction and to calculate the CSF/serum quotient, so that intrathecal synthesis of tumor markers can be identified. For example, intrathecally produced CEA is detected in about 80 % of patients with metastases. However, the specificity of CEA is low.

Neoplastic Meningitis in Malignant Non-Hodgkin Lymphoma and Leukemia

M. Vogt-Schaden

Malignant Non-Hodgkin Lymphoma

Characteristics. Malignant non-Hodgkin lymphomas (NHL) are primary intracerebral lymphomas, also called primary central nervous system lymphomas (PCNSL). They now constitute 4–7 % of all primary brain tumors, and the incidence is increasing. More than 98 % of them are B-cell lymphomas, and according to the Revised European–American Lymphoma (REAL) classification, they are predominantly diffuse large-cell lymphomas. The presence of the Epstein-Barr virus (the EBV genome is detected in > 95 % of cases) and immunosuppression (in AIDS patients, or after organ transplantation) promote the occurrence of PCNSL. In immunocompetent patients, the age peak appears in the 6th and 7th decades of life (male:female ratio 3:2); in immunosuppressed patients it is considerably earlier. Clinically, PCNSL manifest with focal neurological deficits, signs of elevated intracranial pressure, and psychopathological abnormalities.

Diagnosis. The suspected diagnosis is established by CT and MRI and is supported by spectroscopy. Confirmation of the diagnosis requires detection of lymphoblasts. However, at first diagnosis of a PCNSL lymphoblasts are found in the CSF in less than 50 % of patients (Balmaceda et al., 1995). If the cytomorphology is not unambiguous, immunocytochemistry and clonality analysis may help to strengthen the diagnosis (Storch-Hagenlocher et al., 2000). If doubts still remain regarding the CSF analysis, brain biopsy must be performed to confirm the diagnosis.

Leukemia

Leptomeningeal metastasis occurs particularly in acute leukemia, the lymphoblastic type more often (about 15 % of adults) than the myelogenous type. Recurrences of acute lymphoblastic leukemia (ALL) are often primarily leptomeningeal. As with lymphomatous meningitis, a definite diagnosis requires CSF collection without blood contamination.

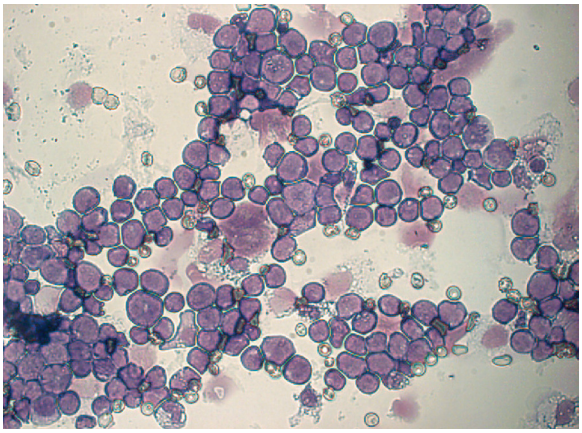

Fig. 16.6 Lymphoblastic crisis in non-Hodgkin lymphoma.

Lymphomatous Meningitis

Leptomeningeal metastases of a primary extraneural lymphoma have been described in 10–30 % of cases. In by far the majority of cases the underlying disease is NHL, particularly highly malignant NHL and Burkitt's lymphoma. CSF analysis, in addition to CT and MRI, plays an important role in confirming the diagnosis of leptomeningeal lymphomatous spread.

Cytology

The diagnosis of lymphomatous meningitis may create considerable problems at cytomorphologic assessment. It is often accompanied by an inflammatory reaction, and the transformed lymphocytes are often difficult to distinguish from neoplastic cells. However, a highly homogenous cell population associated with pathological neurochemical findings is regarded as indicating meningeal spread.

Cytomorphologically, the diagnosis of lymphomatous meningitis can be difficult because of a concomitant reactive inflammatory reaction.

Morphology. The cytomorphological criteria of malignancy apply (**Figs. 16.6**, **16.7**). Occasionally, staghorn or cloverleaf nuclei are found.

Immunological diagnosis. For immunological typing of leukocytes, membrane-bound or intracellular antigens are detected in the cytospin preparation using specific monoclonal antibodies. The cellular antigens expressed are designated as clusters of differentiation (CD) and are numbered. They can thus be assigned to the B-cell line (e. g., CD 19, CD 20), the T-cell line (e. g., CD 4, CD 8), or the myeloid cell line of leukocyte differentiation (e. g., CD 13), and also to the stage of cell maturation (**Fig. 16.8**).

For preference, cytospin preparations are analyzed using the immunoenzyme technique. The primary monoclonal

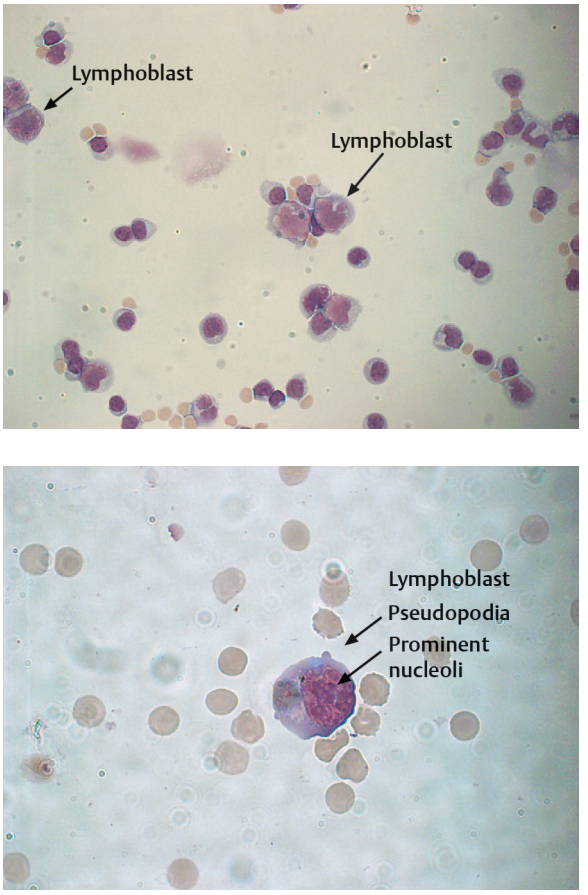

Fig. 16.7 a, b Primary central nervous system lymphoma (PCNSL).

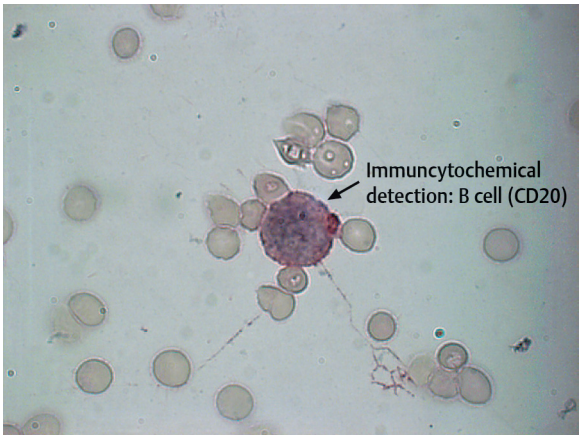

Fig. 16.8 Immunocytochemistry of PCNSL: positive staining of a B lymphoblast for CD 20 antigen.

antibody binds to cells expressing the antigen for which it has specificity. Binding of this antibody is made visible using a second antibody linked to an enzyme (peroxidase, alkaline phosphatase) that catalyzes the cytochemical staining.

The direct immunofluorescence technique is used to study CSF cells in suspension. For this purpose, the specific primary antibody is coupled with a fluorescence dye. Using different fluorochromes, several antibodies can be used simultaneously, and the cells are then analyzed by fluorescence-activated cell sorting (FACS). However, this method is limited in its usefulness as the quantity of CSF available is often insufficient.

Clonality analysis. Molecular clonality studies can confirm a diagnosis of lymphomatous or leukemic meningitis when the cytomorphology remains unclear. The nuclear DNA from CSF cells is used as the starting material. The CDR3 region of the immunoglobulin heavy chain (IgH) is selectively amplified by PCR. The highly variable CDR3 region is specific for every B-cell clone and is formed during B-cell maturation by rearrangement of various segments of the IgH genes (**Fig. 16.9 a**). Further analysis of the PCR products by automated fluorescence analysis may detect a monoclonal neoplastic B-cell population (**Fig. 16.9 b**).

Molecular analysis of CSF cells (clonality analysis) may confirm the diagnosis of lymphomatous and leukemic meningitis.

Neurochemistry

Elevated total protein and CSF lactate levels together with a low CSF glucose level are typical signs of meningeal infiltration. The specificity of soluble surface markers (e. g., sCD 25) is not sufficient. Intrathecal IgM production may indicate a lymphoma (**Fig. 19.4 d**).

Serum analysis. Serum tests are important to detect blood–CSF barrier dysfunction and intrathecal immunoglobulin production.

There are no specific diagnostic serum markers of lymphoma or leukemia. Serum albumin is often decreased. Elevated β_2-microglobulin and/or LDH levels may indicate meningeal infiltration. β_2-Microglobulin is detected in the serum by immunoassay: values above 4.0 mg/L are pathological.