Rare Phenomenon: Liver Metastases From Glioblastoma Multiforme

Introduction
We report the case of a 69-year-old man who presented in our department with previously diagnosed glioblastoma multiforme (GBM). He suffered from severe frontal lobe syndrome and rapid progressive failure of the liver and died within a few days. Using ultrasound imaging of the liver, we could detect at least 10 lesions of necrotic and hemorrhagic aspect suspicious for metastases. The autopsy results confirmed massive metastasization of the liver with wide necrotic confluent parts. Also, immunohistopathologic analyses were positive for glial fibrillary acidic protein (GFAP) and S100 protein and met all the morphologic criteria for metastases of GBM. This case demonstrates that GBM can pass through the brain-blood barrier and may present as a generalized disease with poor outcome.

Case Report
A 69-year-old man was admitted to our department. The reason for admission was severe agitation in the context of the progression of GBM with frontal lobe participation. The frontal lobe syndrome had been known for approximately 1 month. Primary symptoms were treated with a patch of fentanyl and lorazepam orally. Because of inadequate clinical improvement, his private physician suggested hospitalization.

Almost 2 years ago, we were able to detect WHO grade 4 GBM and confirm the diagnosis by histopathologic processing. The tumor was located in the left temporal lobe (Fig 1A). Because of the dimension of the tumor, resection was not completely possible (resection level R2). Subsequently, irradiation at a dose of 59.4 Gy followed the surgical intervention, which led to remission confirmed by magnetic resonance imaging (Fig 1B).

One month later, the patient relapsed (Fig 1C). The next procedure was a micronester coil–navigated extirpation of the relapsed part.
Afterward, we suggested oral chemotherapy with temozolomide (Temodal; Essex Pharma, München, Germany) with palliative intention. This led to an acceptable improvement of the clinical performance state for 9 months. Then we switched the therapy from temozolomide to bevacizumab (Avastin; Roche, Grenzach-Wyhlen, Germany). Because of meningeal enhancement on magnetic resonance imaging, we performed a CSF puncture. Cytomorphologically, we could detect a population of tumor cells (Figs 2A, 2B) in addition to ependymal cells (Figs 2C, 2D, asterisk) and lymphocytes (Fig 2D, double asterisk). We started treatment with intrathecal therapy using liposomal cytarabine (Depocyte; Mundipharma, Limburg an der Lahn, Germany). Two months later, we combined radiotherapy at a radiation dose of 39.6 Gy with temozolomide (160 mg/d). At that time, more clinical symptoms appeared successively in terms of frontal lobe syndrome, including dysarthria, articulation disorder, aggressiveness, and agitation.

The latest image of the brain again showed progressive disease (Fig 1D), so we stopped maintenance chemotherapy (temozolomide 100 mg/d). Laboratory findings showed a massively elevated value for lactate dehydrogenase (LDH; 2,530 U/L [normal range, <250 U/L]) and moderate elevation for liver-related values (alkaline phosphatase, 278 U/L [normal range, <130 U/L]; AST, 68 U/L [normal range, <44 U/L]; gamma-glutamyltransferase, 114 U/L [normal range, <55 U/L]). Initially, these findings were considered signs of progression of the GBM in the brain. We interpreted the elevated liver enzymes as toxic alteration after chemotherapy with temozolomide.

Laboratory results during the current hospitalization approximately 3 weeks after the last consultation were alarming. LDH had increased to a value of 4,993 U/L. Liver enzymes had not changed significantly. Such massive increases in LDH are often correlated with rapid liver failure, as in cases of Budd-Chiari syndrome, viral infection, or metastasization. Ultrasound imaging showed multiple lesions with central necrotic colliquation all over the liver, consistent with metastasization of a cancer disease (Figs 3A to 3D, arrows). The differential
diagnosis of primary liver abscessation was considered possible but unlikely.

Because of the futility of any medical intervention, we abandoned additional invasive diagnostic steps like a liver biopsy. Last laboratory control of LDH yielded a value of more than 6,000 U/L. To exclude common entities of cancer metastases of the liver, we analyzed the blood for α-fetoprotein, cancer antigen 19-9, carcinoembryonic antigen, and human chorionic gonadotropin. All values were in normal range or did not have any clinical impact, so a secondary malignant disease seemed to be implausible. The patient presented in comatose condition. He died 6 days after hospitalization as a result of rapid failure of the liver resulting from progressive metastases.

After the patient’s death, we performed an autopsy of the liver. Macroscopically, in the 1,920-g liver, we found multiple necrotic lesions (Fig 4A), some of them with hemorrhagic aspect, corresponding to generalized liver metastasization. Furthermore, we diagnosed a so-called nutmeg liver, corresponding to stasis inside the liver. Histopathologic analyses were positive for S100 protein and GFAP (Figs 4B to 4D). Antibodies against microtubulin-associated protein 2 were detected intracytoplasmatically and in
the cell processes. Other entities could be excluded by processing the samples with epithelial membrane antigen, neurofilament protein, pan cytokeratin, B-lymphocyte marker CD20, melanoma antigen HMN45, and melan-A. The primary tumor was positive for GFAP and MIB-1 (Figs 5A, 5B). The patient’s death probably occurred by a right heart failure resulting from massive progression of hepatic metastasization of GBM.

Discussion

Within the last few years, incidence of GBM has increased steadily. Nevertheless, extracranial metastasization is still extremely rare. There are only three cases reported in the current literature of metastases in the liver. The most recently published cases of metastasized GBM date from 2010. Gotway et al described pleural metastasization. Soft tissue metastases were reported by Armstrong et al. All patients with extracranial metastasization were characterized by poor prognosis.

There are no data available regarding why some GBM pass through the brain-blood barrier and some do not. Theoretically, one pathway could be contamination of blood during surgical tumor resection, with the consecutive possibility of the formation of metastases. Because of the rareness of this phenomenon, it does not seem to be a common occurrence of transmission. Looking ahead, we must take into account extracranial metastasization, the incidence of which may perhaps increase if further systematic research is carried out.

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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES


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