Patient Report

Leptomeningeal dissemination and vertebral bone involvement in a child with pilocytic astrocytoma

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Abstract In low-grade glioma, metastasis is rarely seen. Few cases of leptomeningeal dissemination have been reported in children. Vertebral bone metastasis has not been reported so far. Herein is described the case of a pediatric patient with the diagnosis of pilocytic astrocytoma, and leptomeningeal dissemination detected at the time of diagnosis, who then received radiotherapy and chemotherapy upon development of vertebral bone metastasis during treatment.

Key words bone metastasis, child, leptomeningeal dissemination, low-grade glioma.

The most common pediatric central nervous system tumor is low-grade glioma, with an incidence rate of 40%. Median age at diagnosis ranges between 6.5 and 9 years.1,2 Leptomeningeal dissemination is rarely seen in low-grade glioma. Leptomeningeal dissemination is anticipated, especially in tumors localized in the hypothalamic, and periventricular regions.3–5 In low-grade glioma, vertebral bone metastasis has not been reported so far. In this paper we describe the case of a patient with the diagnosis of grade 1 astrocytoma and leptomeningeal dissemination detected at the time of diagnosis, who also then developed vertebral bone metastasis during treatment.

Case report

In a 62-month-old girl, an inward deviation of the left eye developed 1 year previously. In a medical center she received treatment for strabismus. She was referred with the complaints of noticeable vomiting in the mornings, nystagmus, and inability to walk for the last month. On neurological examination, tendency to drowsiness, brisk deep tendon reflexes and effaced papillary contours were detected. On cranial magnetic resonance imaging (MRI), a heterogeneous multi-lobulated mass with regular contours and dimensions of 44 × 32 × 31 mm, with hypointensity on T1-, and hyperintensity on T2-weighted sequencing at the level of the third ventricle was detected. The mass obliterated the suprasellar cisterna, and compressed the optic chiasm. Following use of contrast media, inhomogeneous and intense contrast enhancement was seen apart from cystic areas. The third ventricle and lateral ventricles were extremely enlarged secondary to compression of the mass, and increased signal intensity secondary to subependymal fluid leakage into the periventricular space was detected. On post-contrast MRI, millimetric contrast-enhanced nodules on the periphery of brainstem structures, and on the cervical spinal cord consistent with leptomeningeal tumor dissemination were seen (Fig. 1a–c). The mass was excised almost totally using bifrontal craniotomy. On histopathology, solid areas were composed of spindle cells; biphasic tumor tissue consisted of microcysts; and numerous darkly stained Rosenthal fibrils were noted in the areas of spindle cells. Results of staining were as follows: CK5/6 (−), glial fibrillary acidic protein (+), ki67 15/1000 (+), neurofilament protein (−), and p53 (−). The case was defined as pilocytic astrocytoma (World Health Organization grade 1). On spinal MRI at the cervical, thoracic, and lumbar levels, and on the periphery of the spinal cord in the leptomeningeal region, circumferential and nodular contrast enhancement was observed. Leptomeningeal involvement was confirmed (Fig. 1d,e). Cerebrospinal fluid (CSF) analysis was as follows: erythrocytes, 320/mm3; glucose, 68 mg/dL; protein, 260 mg/dL; lactate dehydrogenase (LDH), 27 IU/L; and chloride, 130 mEq/L. Cytology was reported as hemorrhagic CSF. The patient, who was scheduled for observation, was referred 1 month later with headache and vomiting. On cranial MRI, residual mass and acute hydrocephalus were detected, and a ventriculo-peritoneal shunt was implanted. The patient received radiotherapy (RT) 36 Gy to the entire craniospinal axis followed by a boost to primary tumor site for a total dose 56 Gy. On cranial MRI 1 month after RT, the mass had the same size, and the same characteristics in addition to the development of subdural bleeding. On spinal MRI, the signs of leptomeningeal involvement were similar. Observation was
planned. On MRI 3 months later, the characteristics of the mass were not changed, but the subdural bleeding had regressed. Increase in the area of leptomeningeal involvement, however, was observed, and all cerebral hemispheres with intense contrast uptake were consistent with dural dissemination (Fig. 2). Because of disease progression, a vincristine (1.5 mg/m²) plus carboplatin (560 mg/m²; at 3 month intervals) chemotherapy protocol was initiated. On cranial MRI at 6 months of chemotherapy, no change was seen in the size, characteristic features of the mass, or dural, and leptomeningeal involvement. At 8 months of chemotherapy she was referred with complaints of low back pain and gait disorder. On MRI, dural, and leptomeningeal involvement were the same as before, but loss of height at the T9 vertebra, heterogeneous appearance, and marked contrast uptake were interpreted as bone metastasis (Fig. 3). Metastases to

Fig. 1 (a) T2-weighted sagittal imaging at the level of the third ventricle, showing a heterogeneous, hyperintense mass lesion with lobulated contours obliterating the suprasellar cisterna. Third ventricle, and lateral ventricles were enlarged because of compression of the mass. On contrast-enhanced T1-weighted (b) sagittal and (c) axial imaging, heterogeneous contrast uptake of the mass lesion, and millimetric contrast-enhanced nodular foci on the periphery of the brainstem structures, and spinal cord, and also in the tentorium are remarkable. (d, e) Contrast-enhanced T1-weighted sagittal imaging showing circumferential and nodular contrast uptake on the periphery of the spinal cord at the cervical, thoracic, and lumbar levels.

Fig. 2 Contrast-enhanced T1-weighted (a) axial and (b) sagittal imaging showing contrast enhancement in both cerebral hemispheres, tentorium, and basal cisternas due to increased leptomeningeal dissemination, and thickened dura mater because of dural invasion, and contrast uptake.

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Fig. 3 Decrease in the height of the T9 vertebra, hypointensity, and contrast enhancement consistent with bone metastasis on sagittal (a) T2-weighted, and (b) contrast-enhanced T1-weighted imaging.
other regions were not detected. Re-evaluation of CSF was as follows: erythrocytes, 330/mm³; leukocytes, 40/mm³; glucose, 64 mg/dL; protein, 427 mg/dL; LDH, 87 IU/L; chloride, 120 mEq/L. CSF cytology was interpreted as hemorrhagic CSF. Given that the disease appeared to be progressing, the chemotherapy protocol was changed, and temozolamide was initiated. Because of technical difficulties, after two cycles of chemotherapy, biopsy material was obtained from the vertebral body of T9 under fluoroscopic control. On histopathology, fragments of hyaline cartilage tissue, bone trabeculae, and components of bone marrow were noted. After the sixth cycle of temozolamide, cranial MRI indicated regression. A marked decrease in contrast uptake, rather than the size of the mass, was detected without restriction of diffusion. Marked regression in contrast enhancement at the level of the dural, tentorial, and basal cisternas was detected. Contrast-enhanced areas in the spinal region prominently decreased, and involvement of the T9 vertebra regressed (Fig. 4). Overall, findings were indicative of regression. At the time of writing, the patient was still receiving chemotherapy, and was under observation protocol.

**Discussion**

Herein is described the case of a pediatric patient with low-grade astrocytoma, and leptomeningeal and vertebral bone involvement in whom disease regression was achieved with RT and chemotherapy. In low-grade glial tumors, metastasis is not anticipated, and leptomeningeal dissemination is rarely seen. In the HIT-LGG 1996 Trial, leptomeningeal dissemination was noted in 1181 children at an incidence of 2.8% at the time of diagnosis (overall incidence, 5.2%). To our knowledge, vertebral bone metastasis in pilocytic astrocytoma has not been reported in the literature so far.

In this case, periventricular location of the tumor constituted one of the risk factors for leptomeningeal dissemination in addition to delayed diagnosis. Risk factors reported in the literature are young age, periventricular, and hypothalamic location of the tumor mass, subtotal resection, and recurrent disease. Although spinal imaging is not recommended routinely for low-grade glioma, it might be useful in patients with risk factors regarding establishment of early diagnosis. It should be kept in mind that dissemination can develop years later, and spinal imaging should be planned accordingly. Even if cytological analysis of CSF does not indicate leptomeningeal dissemination (as in the present case), this pathology can be identified on radiology.

In the present case, vertebral bone metastasis developed during treatment. To our knowledge, vertebral bone metastasis in pilocytic astrocytoma has not been reported in the literature. First, based on radiology, vertebral bone involvement was presumed. Then the treatment protocol was changed, and, following two cycles of chemotherapy, biopsy material was obtained. On histopathology, however, malignant infiltration was not seen. After six cycles of temozolamide treatment, all signs of malignancy had regressed. Inability to confirm metastasis on histopathology was attributed to the effect of chemotherapy.

Surgery was carried out as the treatment of choice, then RT was applied due to disease progression, and in consideration of the patient’s age. During the follow-up period chemotherapy was initiated. In low-grade astrocytoma, surgical resection is usually sufficient; and chemotherapy and RT are not needed, even after subtotal resection. If disease progression is detected during follow up, priority is given to safe surgical resection. Chemotherapy and RT can be considered in the case of severe neurological symptoms at the time of diagnosis or for disease progression detected during follow up. RT can be postponed after chemotherapy in consideration of the patient’s age, and the side-effects of radiation exposure.

The treatment plan is the same for patients with leptomeningeal involvement. In the case of primary tumor and metastatic foci, surgery is still the first treatment alternative.

In this case, following craniospinal RT, a carboplatin–vincristine regimen was used because of disease progression. During treatment, this was switched to temozolamide due to disease progression. The best response was observed after temozolamide therapy. Carboplatin–vincristine regimen is the optimal treatment for patients with leptomeningeal involvement.
most frequently used chemotherapeutic modality. Thioguanine, procarbazine, lomustine, and vincristine (TPCV) or PCV regimens are more frequently used in adults. Temozolamide has known effectiveness in low-grade glioma. It also provides the convenience of oral intake, and has an improved penetration ability into the CSF. With chemotherapy stabilization or minor regression of the disease, process is anticipated. Complete regression of the tumor is rarely seen.

In conclusion, in low-grade astrocytoma, metastasis depends on lesion location and time to diagnosis. In the diagnosis and follow up of high-risk patients, radiology should be taken into consideration. Treatment should be planned on a per-patient basis according to symptoms and disease progression.

**Disclosure**

The authors declare no conflicts of interest.

**Author contributions**

M.D. and B.S. contributed to the conception and design of this study; M.D. wrote the manuscript; M.D., B.S., S.G., C.D., O.T., S.Y., F.P. and S.T. collected and analyzed data; B.S., S.Y. and S.T. performed experiments; M.D. and B.S. critically reviewed the manuscript and supervised the whole study process. All authors read and approved the final manuscript.

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