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Extensive Extraneural Metastases of Cerebral Glioblastoma in a Pediatric Patient: An Extreme Case Report and Comprehensive Review of the Literature

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Established Facts

- Extraneural metastases of glioblastoma are very rare, especially in pediatric patients.

Novel Insights

- Clinicians should be aware of this condition, and further imaging techniques should be performed in patients in whom extraneural glioblastoma metastases are suspected.

Keywords
Glioblastoma · Extraneural metastases · Lung · Liver

Abstract
Introduction: Extraneural metastases of glioblastoma are very rare clinical entities, especially in pediatric patients. Because of their rarity, they can be confused with other pathological processes. ***Case Presentation:*** We report a case of 16-year-old boy with extensive extraneural metastases of glioblastoma. Lung, liver, cervical lymph nodes, skin, and bone metastases were detected in the patient. ***Conclusion:*** We describe the presentation, evaluation, and diagnosis of this rare condition with regard to pertinent literature.

Introduction

Glioblastoma is the most common and most lethal primary brain tumor. However, extraneural metastasis of this tumor is uncommon; the incidence is estimated to be <2% [1–3]. This rare clinical entity has several characteristics. The presence of multivisceral metastases is defined as a case of extensive extraneural metastases of glioblastoma, and these cases are extremely rare [4, 5]. In this case report, we describe a 16-year-old boy with extensive extraneural glioblastoma metastases, and we discuss the relevant literature.

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Case Presentation

A 16-year-old boy was admitted to our clinic with complaints of neck pain for 4 months, swelling in the head and neck area, and respiratory disorders. The patient was a Syrian refugee, and he was staying in a refugee camp. He had undergone urgent excision of an intracerebral tumor with craniectomy 8 months earlier in Syria, and the patient and his family did not have any documentation about the histopathological diagnosis. He had no history of any adjuvant treatment. On the neurological examination, he was conscious, and his pupils were equal and reactive to light. He had no lateralization symptoms in his extremities, but he was cachectic and could not move without help. He had no sign of involvement of lower cranial nerves. A huge soft swelling of 14 × 8 × 6 cm was noted in the left occipitoparietal region, and an infected solid mass lesion with purulent efflux was present in the left side of the neck (Fig. 1). Inspection over his whole body revealed no other pathological finding.

Brain magnetic resonance imaging (MRI) revealed left lateral ventricle dilatation and brain parenchyma herniation from the craniectomy defect. A necrotic and irregularly shaped mass lesion with peripheral heterogeneous contrast enhancement was adjacent to the multicystic left lateral ventricle (Fig. 2). Metastatic nodular enhancement was noted in the right subfrontal and left pontine areas. The whole brainstem and medulla spinalis in the cervical region showed pial enhancement, which was consistent with seeding metastasis (Fig. 2). Metastatic lesions were present in the left-sided cervical lymph nodes, and diffuse cutaneous and muscle involvement was detected in the left-sided cervical region (Fig. 2, 3). Because of the extent of the metastasis, detailed examination of the body with computed tomography was performed. One metastatic lesion in the right lung and multiple metastatic lesions in the liver were detected (Fig. 3).

Tumor resection was planned to relieve cerebral compression and for histopathologic sampling. Subtotal tumor resection was performed from the left occipitoparietal and left cervical regions. Histopathological examination of the samples revealed tumor cells with large cytoplasm, bizarrely shaped hyperchromatic nuclei, multinucleation, and necrosis infiltrating the dermis and upward into the epidermis (Fig. 4a, b). Immunohistochemical staining with glial fibrillary acidic protein was positive (Fig. 4c). The tumor was diagnosed as glioblastoma. A subsequent IDH 1 and 2 gene mutation analysis by PCR sequencing did not show any mutation and the diagnosis was IDH wild-type glioblastoma.

The patient was hospitalized in the intensive care unit. Medical treatment, including anti-edema and antiepileptic drugs, was started. Antibiotic therapy, including piperacillin-tazobactam and tigecycline, was started according to the wound culture isolations. However, his condition worsened, and he died 4 weeks later due to the respiratory problems.

Discussion

Extraneural glioblastoma metastases are rare clinical entities. The first case of this pathological process was described by Davis [6]. Since then, much researches on extraneural glioblastoma metastases have been published. The reported incidence is between 0.44 and 2% [4, 7–10]. Extensive extraneural metastases of glioblastoma are rarely observed because of the aggressive course of this cancer and the short survival of these patients. Lungs and pleura (60%), regional lymph nodes (51%), and bones (31%) are the most common sites of extraneural metastasis, respectively [1, 3–5, 11, 12]. The lymph nodes most commonly involved are in the cervical region, and the bone structures most commonly involved are the vertebral bodies. The other common sites of extraneural metastasis are the skin, liver, small bowel, and parotid glands [4, 10–13].

Color version available online

Fig. 1. Preoperative image of the patient, revealing a huge soft swelling in the left occipitoparietal region and an infected solid mass lesion with purulent efflux in the left side of the neck (black arrow).

There are several hypotheses about why extraneural metastases of glioblastoma are so rare. The absence of lymphatic vessels in the central nervous system, the dense connective tissue with dural veins that prevent neoplastic invasion, thin-walled intracerebral veins that collapse with tumor penetration, failure of neoplastic glial cells to survive in other compartments of the body, and short survival of patients with glioblastoma, are the prohibitive factors that may explain the rarity of extraneural metastases [2, 4, 7].

Despite all these factors, many cases of extraneural glioblastoma metastases have been reported. With regard to the causes of metastases, it is thought that after the surgery, the blood-brain barrier is disrupted, and tumor cells enter the systemic circulation to form distant metastases [7]. Venous invasion through intracerebral veins and lymphatic cerebrospinal fluid drainage into extraneural tissue are the other causes of extraneural glioblastoma metastases [7, 8]. Cervical lymph nodes close to the surgical site are the second most common locations of extraneural metastases [1, 3, 5, 8, 9, 14]. Another site of metastasis close to the operation site is the parotid gland; cases of parotid metastases have been reported in the literature [3, 9, 10, 15].

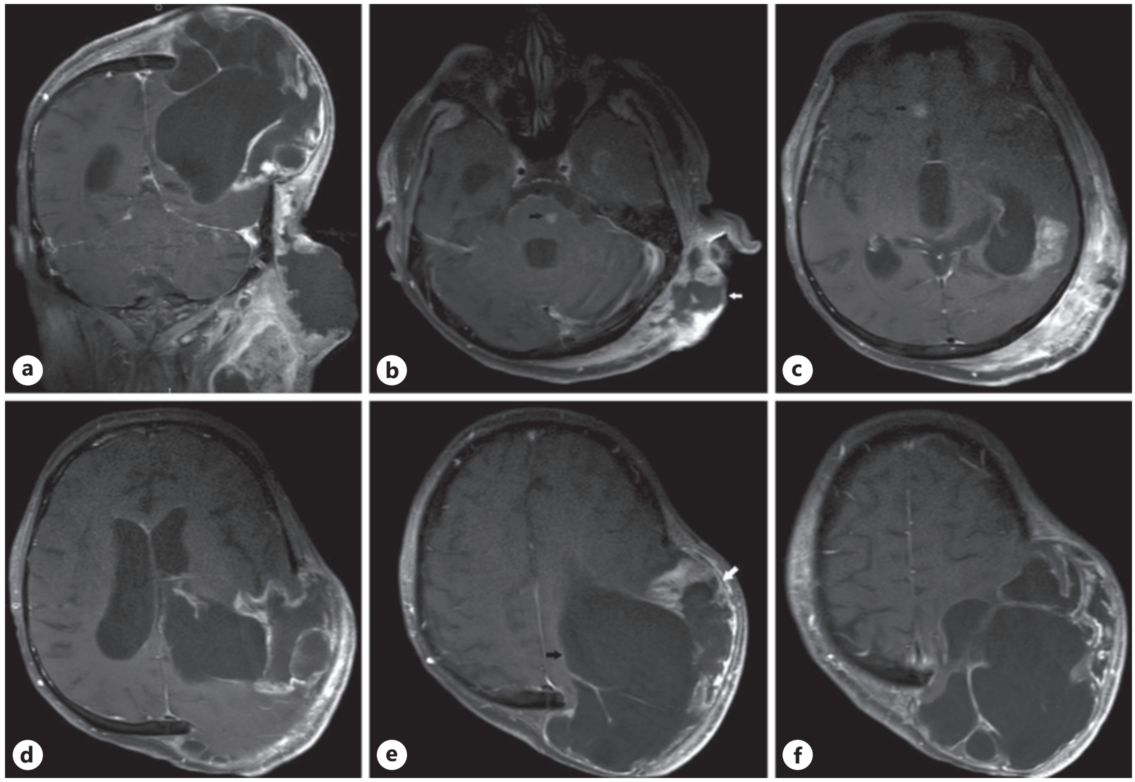

Fig. 2. a Coronal brain magnetic resonance image, revealing a necrotic and irregularly shaped mass lesion with peripheral heterogeneous contrast enhancement and multicystic left lateral ventricle herniating from the craniectomy defect. Metastatic lesions and diffuse cutaneous and muscle involvement were also detected in the left-sided cervical region. **b** Axial brain magnetic resonance image, revealing metastatic nodular enhancement in the left pontine area (black arrow) and the skin, bone, and muscle involvement in the left occipital region (white arrow). **c** Axial brain magnetic resonance image, revealing nodular enhancement in the right subfrontal area (black arrow). **d–f** Axial brain magnetic resonance images, revealing a necrotic and irregularly shaped mass lesion with peripheral heterogeneous contrast enhancement (white arrow) adjacent to the multicystic left lateral ventricle.

Direct invasion through the dura, bone, and skin and tumor cell migration along ventriculoperitoneal shunts are the other mechanisms of extraneural glioblastoma metastasis. Cases of skin metastasis followed by distant metastases have been reported [1, 5, 16, 17]. Studies of patients who underwent stereotactic interventions demonstrated seeding metastases, followed by distant metastases in the body [7]. Russel et al. [16] described 3 pediatric patients with glioblastoma who had ventriculoperitoneal shunts and extraneural metastases.

We performed a MEDLINE search with the key words: “glioblastoma” and “extraneural metastasis” for reports published between 1954 and 2019. A total of 54 documents were found in the English-language literature. In addition, the reference lists of all articles were reviewed, and additional articles were selected for background information. Cases of multivisceral extraneural glioblastoma metastases were defined as the cases with extensive extraneural metastases of glioblastoma. This literature review revealed 22 cases with extensive extraneural glioblastoma metastases (Table 1) [1–3, 5–23]. Based on our literature review, we present the second pediatric case of glioblastoma with extensive extraneural metastases in the present report.

Conclusion

Extraneural glioblastoma metastases are very rare, especially in pediatric patients. As survival of glioblastoma patients increases, the incidence of this rare clinical entity is expected to rise. Clinicians should be aware of this condition, and further imaging techniques should be performed in patients in whom extraneural glioblastoma metastases are suspected.

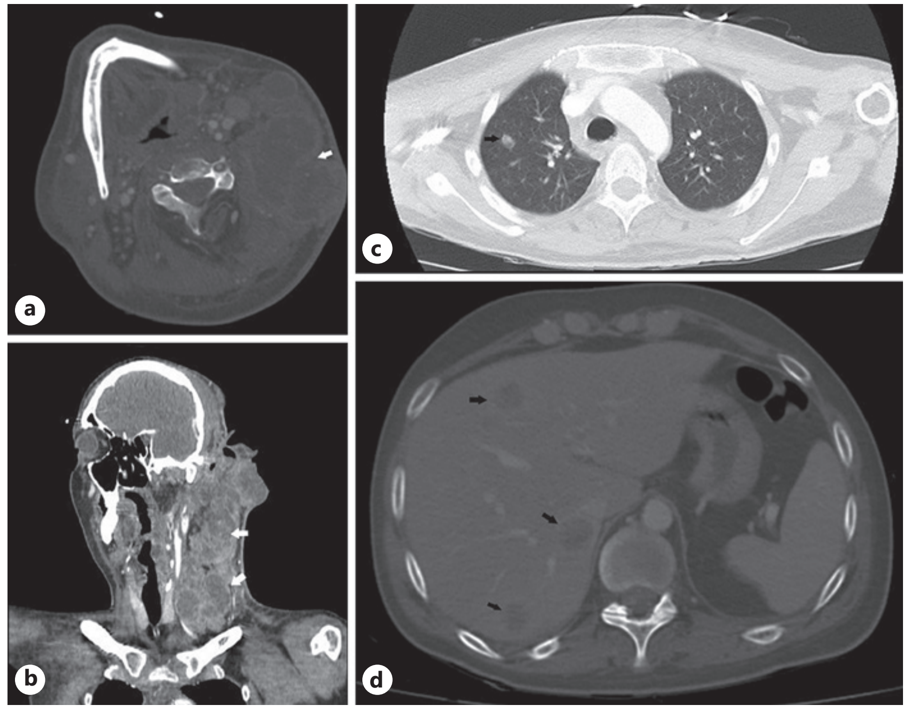

Fig. 3. Axial (**a**) and coronal (**b**) cervical computed tomography images, revealing metastatic lesions in the left-sided cervical lymph nodes (white arrows). **c** Axial thoracic computed tomography image, revealing a metastatic lesion in the right lung (black arrow). **d** Axial abdominal computed tomography image, revealing multiple metastatic lesions in the liver (black arrows).

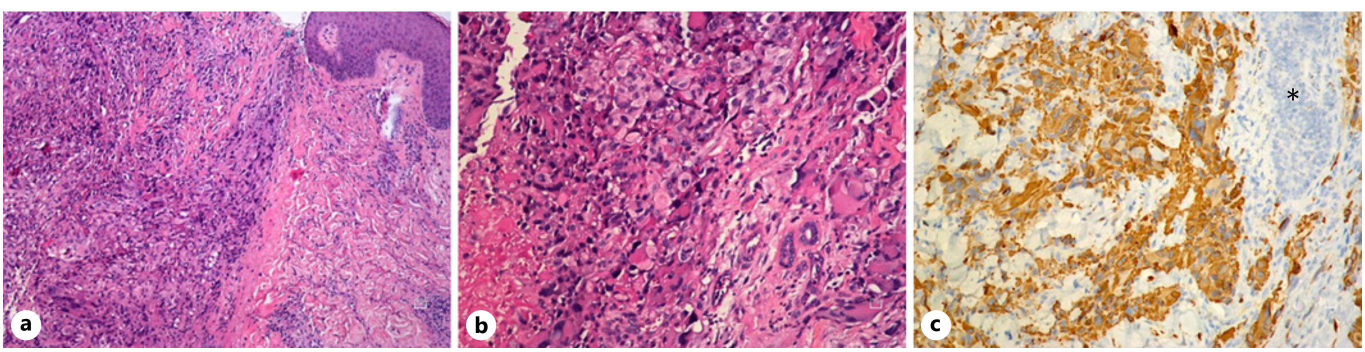

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Fig. 4. a Pleomorphic tumor cells infiltrating the dermis and upwards into the epidermis (H&E, ×100 magnification). **b** Higher magnification of the tumor cells, showing large cytoplasm, bizarrely shaped hyperchromatic nuclei, multinucleation, and necrosis infiltrating the dermis and upwards into the epidermis (H&E, ×400 magnification). **c** Immunohistochemical examination, revealing GFAP-positive tumor cells surrounding a hair follicle (black asterisk, ×200 magnification). GFAP, glial fibrillary acidic protein.

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Statement of Ethics

The authors state that the research complies with the guidelines for human studies, and the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The authors state that the father of the patient has given their written informed consent for publication of data and images.

Conflict of Interest Statement

The authors report no conflicts of interest concerning the materials or methods used in this study or the findings specified in this paper.

Table 1. Comprehensive review of the patients with extensive extraneural glioblastoma metastases in the literature

Author	Age/ gender	Sites of metastases	Treatment (glioblastoma)	Treatment (metastasis)	Survival, months	Time to ENM, months
Davis [6]	31/F	Lung, bone, and skin	Surgery	–	9	7
Cross and Cooper [18]	20/M	Lung, orbit, and abdominal wall	Surgery	–	9	9 (autopsy)
Rubinstein [19]	37/M	Pelvic and pancreatic lymph nodes, bone, and retroperitoneum	RT	–	17	17 (autopsy)
Smith et al. [8]	49/M	Liver, pancreas, cervical lymph nodes, and bone	Surgery	–	16	na
Wakamatsu et al. [20]	22/M	Lung, pleura, diaphragm, and pericardium	Surgery + RT	–	9	9 (autopsy)
Hulbanni and Goodman [21]	63/M	Lung, lymph nodes, and bone	Surgery + RT	–	2	2 (autopsy)
Liwnicz and Rubinstein [22]	26/M	Lung, pleura, hilar lymph nodes, and diaphragm	Surgery + RT	–	9	9 (autopsy)
Yokoyama et al. [14]	22/F	Lung, cervical lymph nodes, liver, and bone	Surgery + RT	Surgery (cervical mass) + CT	4	3
Beauchesne et al. [23]	54/M	Bone, lung, and heart	Surgery + RT + CT	Bx (bone marrow) + CT	9	7
Houston et al. [12]	32/M	Lung, liver, lymph nodes, and skin	Surgery + RT + brachytherapy + CT	–	13	12
Ueda et al. [17]	42/M	Lung, epicardium, kidney, pancreas, liver, bone, skin, and lymph nodes	Surgery + RT + CT	CT	16	12
Didelot et al. [13]	74/M	Bone, spleen, lung, and mediastinal lymph nodes	Surgery	Bx (bone marrow)	2	1
Mujic et al. [7]	39/M	Lung, pleura, small bowel, and pancreas	Surgery + RT	CNB (pancreas)	26	25
Saad et al. [16]	14/M	Lung, liver, and skin	Surgery + RT + CT	CT	10	9
Kraft et al. [15]	58/M	Parotid gland, lung, orbita, bone, pleura, lymph nodes, liver, and heart	Surgery + RT + CT	CNB (parotid) + CT	16	15
Beauchesne [2]	59/M	Lung, pleura, liver, and mediastinal lymph nodes	Stx bx + RT + CT	CT	na	na
Taskapilioglu et al. [10]	30/F	Parotid gland, bone, and cervical lymph nodes	Surgery + RT + CT	Paroidectomy + radical neck dissection	16	10
Hamilton et al. [3]	24/M	Orbita, parotid gland, cervical lymph nodes, and bone	Surgery (multiple) + RT + CT	Hemi-neck nodal + parotid dissection	22	5
Anghileri et al. [11]	30/M	Lung, skin, bone, and cervical lymph nodes	Surgery + RT + CT	Cervical lesion resection	77	74
Xu et al. [1]	58/F	Bone, skin, cervical lymph nodes, and lung	Surgery + RT + CT	Neck dissection + CT + gama knife (bone)	54	29
Rosen et al. [5]	48/F	Lung, pleura, liver, bone, skin, and cervical lymph nodes	Surgery + RT + CT	CT	13	5
Swinnen et al. [9]	56/F	Lung, parotid gland, and cervical lymph nodes	Surgery + RT + CT	FNB (parotid) + CT	14	6
Present case	16/M	Lung, liver, cervical lymph nodes, skin, and bone	Surgery	Subtotal resection (cervical metastasis)	9	4

ENM, extraneural metastasis; F, female; M, male; RT, radiotherapy; CT, chemotherapy; Bx, biopsy; Stx Bx, stereotactic biopsy; CNB, core needle biopsy; FNB, fine needle biopsy; na, not available.

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Author Contributions

Kadir Oktay and Tahsin Erman were involved with the conception and design; acquisition, analysis, and interpretation of data; drafting; revising; and final approval of the manuscript. Dogu Cihan Yildirim, Kerem Mazhar Ozsoy, and Nuri Eralp Cetinalp were involved with the acquisition, analysis, and interpretation of data and revising the manuscript. Arbil Acikalin was involved with the acquisition, analysis, and interpretation of data.

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