South Russian Journal of Cancer. 2024. Vol. 5, No. 3. P. 111-120
https://doi.org/10.37748/2686-9039-2024-5-3-10
https://elibrary.ru/pfvhlb
REVIEW

Extraneural metastases of a cerebral glioma in a child: case report with literature review

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ABSTRACT

Malignant gliomas make up 25 % of the central nervous system (CNS) tumors in adults and 8–15 % in children. About half of such gliomas have a median localization and are designated by the term "diffuse midline gliomas" (DMG). DMG in children are typically localized in the area of the pons; in 78 % of such cases a heterozygous somatic mutation H3K27M is present. The prognosis of H3K27M-mutant DSG is very unfavorable, with 2-year overall survival rate being less than 10 %. One of the ways of progression of gliomas leading to the death of patients is the spread of the tumor in the form of metastases. Malignant gliomas metastasize mainly into various structures of the CNS (according to autopsies – in about 20 % of patients with glioblastomas), the probability of their metastases to other organs (so-called extraneural metastases), according to some evaluations, is quite rare and doesn't exceed 2 %. In our practice since 1993, which counts 1700 children with malignant gliomas, including 830 patients with DMG, we've observed only one patient with extraneural metastases. The article describes this case of a child who died of the progression of the DMG's extraneural metastases, despite the fact that chemoradiotherapy had achieved its stabilization in the CNS. This patient with the initial lesion of the pons and cerebellum had massive metastasis to the lymph nodes: supraclavicular, mediastinal, retroperitoneal and inguinal ones, as well as to both pleural cavities, which occurred about one year after treatment of the progression, which had manifested in the form of continued growth of the primary tumor and its dissemination in the central nervous system. The article provides literature data on the frequency, clinical manifestations and possible treatment approaches for extraneural metastasis of brain gliomas. Extraneural metastases of those tumors occur most often to the bones, lymphatic system, lungs, abdominal organs, soft tissues. The effective treatment for extraneural metastases of gliomas has not been developed yet, which makes it urgent to solve this problem through multicenter studies.

Keywords: malignant glioma, brain, extraneural matastases, radiotherapy, chemotherapy

For citation: Regentova O. S., Parkhomenko R. A., Shcherbenko O. I., Antonenko F. F., Zelinskaya N. I., Sidibe N., Polushkin P. V., Shevtsov A. I., Bliznichenko M. A., Deyanova V. A., Solodkiy V. A. Extraneural metastases of a cerebral glioma in a child: case report with literature review. South Russian Journal of Cancer. 2024; 5(3): 111-120. https://doi.org/10.37748/2686-9039-2024-5-3-10, https://elibrary.ru/pfvhlb

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Compliance with ethical standards: this research has been carried out in compliance with the ethical principles set forth by the World Medical Association Declaration of Helsinki, 1964, ed. 2013. The study was approved by the Committee on Biomedical Ethics at the Russian Scientific Center of Roentgen Radiology (extract from the protocol of the meeting No. 2 dated 09.12.2022). Informed consent has been received from all the participants of the study.

Funding: this work was not funded

Conflict of interest: the authors declare that there are no obvious and potential conflicts of interest associated with the publication of this article

The article was submitted 24.07.2024; approved after reviewing 15.08.2024; accepted for publication 25.08.2024

Южно-Российский онкологический журнал. 2024. Т. 5, № 3. С. 111-120
https://doi.org/10.37748/2686-9039-2024-5-3-10
https://elibrary.ru/pfvhlb
3.1.6. Онкология, лучевая терапия

ОБЗОР

Экстраневральное метастазирование глиомы головного мозга: описание случая у ребенка и обзор литературы

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РЕЗЮМЕ

Глиомы высокой степени злокачественности среди всех опухолей центральной нервной системы (ЦНС) составляют до 25 % у взрослых и 8–15 % у детей. Примерно половина из них в детском возрасте имеет срединную локализацию и обозначается термином «диффузные срединные глиомы» (ДСГ). При срединных глиомах у детей, локализующихся в области моста, в 78 % случаев отмечается гетерозиготная соматическая мутация H3K27M. Прогноз H3K27M-мутантной ДСГ весьма неблагоприятный: 2-летняя общая выживаемость менее 10 %. Один из путей прогрессирования глиом, ведущий к гибели больного – это распространение опухоли в виде метастазов. Злокачественные глиомы метастазируют, главным образом, в различные структуры ЦНС (по данным аутопсий – примерно у 20 % пациентов с глиобластомами); вероятность возникновения их метастазов в других органах (так называемых, экстраневральных метастазов), по некоторым оценкам, весьма мала – не более 2 %. В нашей практике, насчитывающей 1700 детей со злокачественными глиомами, включая 830 пациентов с ДСГ (пролеченных за период с 1993 года), нам встретился лишь один больной с экстраневральными метастазами. В настоящей статье мы описываем этот случай: ребенок умер от прогрессирования экстраневральных метастазов ДСГ, несмотря на то что при химиолучевом лечении удалось достичь ее стабилизации в ЦНС. У этого больного с исходным поражением моста головного мозга и мозжечка имело место массированное метастазирование в лимфатические узлы: надключичные, медиастинальные, забрюшинные, паховые, а также в обе плевральные полости, которое произошло примерно через год после лечения прогрессирования, проявлявшегося в виде продолженного роста первичной опухоли и ее диссеминации в ЦНС. В статье приводятся данные литературы о частоте, клинических проявлениях и возможных подходах к лечению при экстраневральном метастазировании глиом головного мозга. Чаще всего наблюдается экстраневральное метастазирование этих опухолей в кости, лимфатическую систему, легкие, органы брюшной полости, мягкие ткани. Эффективного лечения при возникновении экстраневральных метастазов глиом не разработано, что делает актуальным решение этой проблемы путем многоцентровых исследований.

Ключевые слова: злокачественная глиома, головной мозг, экстраневральные метастазы, лучевая терапия, химиотерапия

Для цитирования: Регентова О. С., Пархоменко Р. А., Щербенко О. И., Антоненко Ф. Ф., Зелинская Н. И., Сидибе Н., Полушкин П. В., Шевцов А. И., Близниченко М. А., Деянова В. А., Солодкий В. А. Экстраневральное метастазирование диффузной срединной глиомы головного мозга у ребенка: описание случая и обзор литературы. Южно-Российский онкологический журнал. 2024; 5(3): 111-120.
https://doi.org/10.37748/2686-9039-2024-5-3-10, https://elibrary.ru/pfvhlb

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Соблюдение этических стандартов: в работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). Исследование одобрено Комитетом по биомедицинской этике при ФГБУ «Российский научный центр рентгенорадиологии» Министерства здравоохранения Российской Федерации (выписка из протокола заседания № 2 от 09.12.2022 г.). Информированное согласие получено от всех участников исследования

Финансирование: финансирование данной работы не проводилось

Конфликт интересов: все авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи

Статья поступила в редакцию 24.07.2024; одобрена после рецензирования 15.08.2024; принята к публикации 25.08.2024

INTRODUCTION

Malignant gliomas are one of the most complex and aggressive forms of neuro-oncological diseases. Gliomas of a high grade of malignancy among all tumors of the central nervous system (CNS) account for up to 25 % in adults and 8–15 % in children. About half of them in childhood have a median localization and are designated by the term "diffuse midline gliomas" (DMG). In midline gliomas in children localized in the pontin area, a heterozygous somatic mutation H3K27M is noted in 78 % of cases. The prognosis of H3K27M-mutant DMG is very unfavorable, with 2-year overall survival rate being less than 10 % [1–5].

One of the ways of progression of gliomas leading to the death of the patient is the metastatic spread of the tumor. Malignant gliomas metastasize mainly into various structures of the central nervous system (in about 20 % of patients with glioblastomas according to autopsies), the probability of their metastases in other organs (so-called extraneural metastases), according to some estimates, is very small and doesn't exceed 2 % [6, 7]. Extraneural metastasis, although a rare phenomenon in diffuse midline gliomas, is of critical importance in the context of prognosis and further patient management tactics, since it can significantly worsen the quality of life and reduce survival rate. The presented clinical case highlights the need for a multidisciplinary approach to the diagnosis and treatment of this pathology, as well as makes the questions about the molecular genetic mechanisms underlying the extraneural spread of the tumor crucial. A review of the available literature reflects current trends in research in this field. When compiling the review, we used Scopus, MEDLINE, and Web of Science databases.

The study purpose was to describe the case of extraneural metastases of malignant glioma in a child and compare it with the literature data, which will allow us to outline the directions of further research on this problem.

CASE REPORT

Patient N., 3.5 year old boy, began to have clubfoot and developed wide base gait in 2021. He was consulted by an orthopedist. The diagnosis was made: flat-valgus deformity of the feet. During the following month, there was a deterioration in gait in the form of an increase in shakiness, he began to limp on his left leg, began to stumble, and the motor skills of his left hand deteriorated.

From the anamnesis of life: a child from IVF pregnancy, which proceeded without any abnormalities. The delivery was urgent at 38 weeks. He was observed by a neurologist for perinatal central nervous system damage, myotonic syndrome. Prior to the present disease, he suffered from acute respiratory viral infections, right-sided purulent otitis media.

An MRI of the brain was performed on 08/03/2021: in the area of the Varolian bridge (mainly in its left half) with extension to the left pedicle and hemisphere of the cerebellum, an extensive zone of diffuse signal change was visualized, hyperintensive on T2, FLAIR, iso-hypointensive on T1, with linear restriction of diffusion along the periphery, without contrast enhancement, with the presence in the hemisphere cerebellar areas of cystic transformation. The bridge of the brain, the pedicle and the hemisphere of the cerebellum were enlarged in volume, with compression and displacement of the IV ventricle laterally to the right, displacement of the left amygdala of the cerebellum caudal to the level of the foramen magnum, displacement of the medulla oblongata ventrally; along the anterior surface of the bridge was an exophytic component with compression of the prepontine cistern, fouling of the main artery. Conclusion: the picture of a diffuse lesion of the brain stem, the left hemisphere of the cerebellum, which may correspond to a diffusely growing glial tumor (fibrillar astrocytoma? anaplastic astrocytoma?), with signs of mass effect, descending axial wedging, occlusive internal hydrocephalus.

Neurological status on 08/04/2021: one-time vomiting occured, meningeal symptoms were negative, pupils, eye slits were symmetrical, there was no violation of the volume of movement and position of the eyeballs, deviations of the head and tongue, phonation and swallowing disorders; there was horizontal fine nystagmus when looking to the sides; tendon reflexes D < S, left Achilles reflex with clonus; superficial and deep muscle sensitivity was preserved; gait was atactic, with a wide base of support; the finger-nasal test with pronounced intention; in the Romberg pose was unstable, fell.

Ultrasound of the abdominal cavity and kidneys on 08/04/2021: no pathological signs were detected.

Chest X-ray (in the posterior direct projection, lying position) on 08/04/2021: reduction of pneumatiza-

tion with increased pulmonary pattern in the projection of the medio-basal sections of both pulmonary fields was noted. Conclusion: hypostatic changes in the lungs.

He started on decongestant therapy with dexamethasone on 08/04/2021. During the treatment of the treatment, the general cerebral symptoms regressed, and status-coordination disorders persisted. MRI of the brain and spinal cord (native and with contrast enhancement) 08/12/2021: in addition to the MRI data from 08/03/2021, there were no signs of metastasis in the structures of the central nervous system.

The patient's mother refused the stereotactic biopsy or partial removal of the tumor offered by the neurosurgeon. Consultation by a radiologist revealed: considering the anamnesis data, MRI signs, the patient's age, the unresectable nature of the tumor, conformal radiation therapy was indicated. Surgical intervention was performed in the volume of installation of a ventricular-peritoneal shunt (VPS) on 09/06/2021. From 09/08/2021 to 10/18/2021, he received a course of radiation therapy to the area of the initial lesion in hyperfractionation mode (single focal dose of 1 Gy 2 times a day with an interval between fractions of 4 hours, 5 days a week), total dose of 54 Gy. Since November 2021, he has been under dynamic observation. PET/CT scan of the brain on 11/29/2021 revealed: the PET picture, together with the MRI results, corresponded to the features of diffuse glioma of the brain stem and left hemisphere of the cerebellum with low amino acid uptake (without PET signs of anaplasia). At the end of April 2022, after acute respiratory viral infection, bilateral purulent otitis media and sinus thrombosis developed.

30.05.2022 MRI of the central nervous system (native and with contrast enhancement): the picture of multidirectional dynamics was noted: stabilization of tumor growth of the brain stem and the left hemisphere of the cerebellum, negative dynamics in the form of metastatic lesions along the ventricular system and spinal cord.

Surgery was performed on 06/17/2022 with a VPS revision. A stereotactic biopsy of a tumor of the lateral ventricle was performed on 06/24/2022. Histological and immunohistochemical examination on 06/24/2022 showed: tumor cells express GFAR, OLIG2, vimentin, focally S100. There was a reaction with anti-NF in numerous axons, which indicated a diffuse type of tumor growth. Single cells were weakly positive with anti-p53. CD34 expression was only in the vascular endothelium. The proliferative index of Ki-67 reached 60–70 %, focally higher.

From 07/08/2022 to 08/16/2022, radiation therapy was performed in the volume of craniospinal irradiation, single radiation dose of 1.6 Gy, total dose of 35.2 G. From 08/08/2022 to 08/10/2022, total dose was increased to 40.0 Gy for the entire volume of the spinal cord, in parallel from 08/08/2022 to 08/16/2022, a boost was performed on the area of the ventricles of the brain, single radiation dose of 1.8 G, total dose of 46 Gy. Simultaneously with the course of radiation, he received chemotherapy with temozolomide 75 mg/m^2 daily as monotherapy.

A molecular study under the One Foundaion program revealed amplifications: PDGFRA, MDM4, PIK-3C2B, as well as ATM – R3008C. Considering the revealed amplification of PDGFRA, the patient was offered imatinib therapy, which was not carried out for organizational reasons. According to the control MRI data, there was a positive dynamics of tumor foci in the central nervous system, with further stabilization. From September 2022 to June 2023, 8 courses of temozolomide monotherapy were performed. After that, treatment was interrupted due to the development of an acute respiratory viral infection.

Since mid-July 2023, the mother began to notice that the child was limping on his left leg. CT scans of the organs of the thoracic cavity, abdominal cavity and pelvis (native and with contrast enhancement) revealed conglomerates of lymph nodes of the supraclavicular, subclavian region on the right, anterior thoracic wall, paraaortic group at the infrarenal level with spread to the inguinal canal on the left; massive right-sided pleural effusion; left-sided pleural effusion; pyelocalicectasia on the left, decreased function of the left kidneys. Considering the obtained data, the presence of a systemic disease, lymphoma, was suspected at this point. MRI of the central nervous system showed stabilization of the size of tumor foci compared to previous studies.

In August 2023, the child underwent a pleural puncture, as well as a puncture biopsy of the bone marrow with its morphological examination and immunophenotyping: data for systemic blood disease were not received. A tumor population of cells was detected in the pleural fluid, which, according to immunophenotyping data, did not express mark-

ers specific to lymphoproliferative diseases. On 08/21/2023, a biopsy of the inguinal lymph node was performed, its histological examination from 09/01/2023 revealed signs of a malignant tumor with a glial phenotype. Conclusion: extraneural metastasis of the primary tumor of the central nervous system could not be excluded. Protocol of immunohistochemical examination dated 09/01/2023 of inguinal lymph node tissues: neoplastic cells diffusely expressed OLIG2, H2K27me3, CD56, SOX-10, INI1. Subtotal expression of NKX2.2, GFAP, vimenin was detected. Weak focal expression of NSE, FLI1, S100, cyclin D1. Tumor cells were negative in reactions with antibodies to panCK, EMA, TLE1, WT1, SMA, mean-A, BCOR, ERG, synapophysin, myogenin, p53, chromogranin A, TdT, desmin, CD20, CD3, CD99, MSA. Protocol of molecular genetic research dated 09/01/2023: during the FISH study, no amplification of the N-MYC gene, deletion of the SRD (1p36) gene, deletion of the KMT2A (MLL) gene, rearrangements of the FOXR2 gene, translocation of the EWSR1 gene were found.

Palliative irradiation of tumor conglomerates in areas of extraneural metastases was proposed, but the patient did not come for this treatment. He died on 01/11/2024 on the background of the progression of extraneural metastases.

DISCUSSION AND LITERATURE REVIEW

The patient case reported above with an initial lesion of the pons and cerebellum (DMG) had massive metastases to the lymph nodes: supraclavicular, mediastinal, retroperitoneal, inguinal, as well as to both pleural cavities, which occurred about one year after treatment of progression, which had manifested in the form of continued growth of the primary tumor and its dissemination in the central nervous system. It is not surprising that before biopsy and molecular genetic studies, the development of a second tumor, including lymphoma, was not ruled out. It is noteworthy that at the stage of diagnosis of the progression of DMG, a stereotactic biopsy was performed, which, of course, was necessary to clarify the diagnosis, nevertheless, could potentially contribute to the spread of the tumor, as indicated by some publications listed below. At the initial diagnosis in 2021, before the start the special treatment, the patient underwent a complete examination, including ultrasound of the abdominal cavity, kidneys, chest X-ray, according to which no signs of extraneural metastases were detected.

The first extraneural metastasis of glioblastoma was described by Davis L. back in 1928. He called it "spongioblastoma." The primary tumor in the 31-year-old patient was localized in the left hemisphere of the brain. Histologically confirmed metastases developed in the soft tissues of the upper limb and in the scapular region on the right, as well as in the left lung; they appeared approximately 5.5 months after partial removal of the primary tumor [8].

Pietschmann S et al. (2015) analyzed 109 articles and abstracts published in English or German for the period from 1928 to 2013 (85 years), which reported a total of 150 patients with extraneural metastases of malignant gliomas of the brain. It is noteworthy that more than half of the publications they analyzed (describing 95 cases) were made after 1993. The age of patients at the initial diagnosis ranged from 4 to 83 years (median 42 years). There were only four children (under the age of 18) in this combined cohort. The majority of patients had a pathomorphological diagnosis of glioblastoma (137, that is, 91.3 %), the remaining 13 (8.7 %) had gliosarcoma. The time from the initial diagnosis to the detection of extraneural metastases from these publications was accurately determined for 71 patients. Of these, 7 (that is, one in ten) had a primary tumor and metastases diagnosed simultaneously. Taking into account these patients, the period from the diagnosis of glioblastoma or gliosarcoma to the detection of metastases ranged from 0 to 81 months (median 9 months). The localization of metastases was diverse: in 52 cases they developed in the organs of the chest (including in 45 patients – in the lungs), in 31 cases in the organs of the abdominal cavity and retroperitoneal space (including in 23 patients – in the liver). In addition, metastases to bone or bone marrow were described in 53 patients, to lymph nodes in 51, to muscles and other soft tissues in 35, to skin in 11, to thyroid and parathyroid glands in 6, to other organs (including eyes and mammary glands) in 4. A significant proportion patients had several localizations of metastases. In the publications included in this review [9], a sufficient description of treatment after detection of metastases was provided for 60 out of 150 patients (40 %), in the rest, treatment was either not

reported or it did not include antitumor methods. Twenty-nine patients after the detection of metastases were treated with any one antitumor method: 17 of them underwent surgery, 4 had radiation and 8 had chemotherapy. In 31 patients in such a situation, various combinations of these methods were used, most often: chemotherapy + radiotherapy (in 15) and surgery + chemotherapy + radiotherapy (in 10). In this review [9], it was noted that extraneural metastases of malignant glial tumors are more often found in relatively young people, which can serve as one of the arguments for the use of active antitumor treatment in them. However, the authors did not reveal a clear increase in survival with such treatment tactics. Overall survival in extraneural metastases was slightly better than survival in CNS metastases, although this difference did not reach the confidence limit. The authors were unable to formulate any specific recommendations for the treatment of patients with extraneural metastases of malignant glial tumors, since in the combined cohort analyzed by them, treatment was very diverse and selected individually [9].

Of high interest is the work of De Martino L. et al, 2023 [10], which describes the authors' own observation of two children with extraneural metastases of diffuse midline gliomas. In one of them, an 11-year-old boy, diffuse midline bridge glioma was confirmed by stereotactic biopsy. Loss of H3K27me3 and expression of a protein associated with H3K27M mutation were detected in tumor cells. At the first stage of treatment, the patient underwent induction chemotherapy with vinorelbine and nimotuzumab, followed by irradiation of the tumor zone in the mode of conventional fractionation, total dose 54 Gy (according to the VMAT method). 5 months after diagnosis, CT and MRI scans revealed extensive metastasis to the soft meninges of the brain and spinal cord, as well as extraneural metastases: in the sternum, vertebrae and pelvic bones. Bone metastases were confirmed by examining a biopsy of the left iliac bone. He died a month later. The second patient, a girl of the same age, was diagnosed with median glioma in the region of the IV ventricle with the H3K27M mutation. Total resection of the tumor was performed, the diagnosis was confirmed on the basis of histological and molecular genetic examination of its tissue. As in the first patient, after chemotherapy with vinorelbine and nimotuzumab, she underwent local radiation therapy (total dose 54 Gy, VMAT technique). However, 3 months after the end of the course of treatment, she was diagnosed with progression in the area of the original tumor, as well as in the ependyma of the ventricles of the brain and its soft membranes. Craniospinal irradiation (CSI) was performed in the mode of classical fractionation, total dose 36 Gy, followed by 15-month chemotherapy with irinotecan and bevacizumab. After completion of CSR, according to MRI data, a partial response of tumor foci in the brain was detected, however, signs of metastases in the vertebrae appeared. CT scan of the whole body made it possible to detect osteosclerotic foci not only in the spine, but also in the ribs, sternum, pelvic bones, in both shoulder and femur bones. PET/CT with ^{18}F-FDG revealed foci of moderate hyperfixation in the bones, however, repeated biopsies of these foci did not reveal metastases. Subsequently, she developed a lesion of a large number of intra-thoracic and abdominal lymph nodes, as well as pleural effusion, the study of which by drip digital polymerase chain reaction revealed a mutation H3.3A (c.83A>T, p.K28M), although cytological examination of pleural effusion of tumor cells did not detect. The patient died 2 years after the diagnosis of median glioma, that is, 3 months after the detection of pleural effusion. The authors of the description of these two patients, while studying the medical literature, found publications about 12 similar patients: their age ranged from 4 to 36 years, the localization of extraneural relapses was diverse: bones, lymph nodes, lungs, pleural cavity, liver, peritoneum, muscles. One of these patients had abdominal metastasis due to the spread of tumor cells along the ventriculo-peritoneal shunt [11]. It is noteworthy that the descriptions of 12 cases collected in the mentioned review by De Martino L et al. (2023), were published no earlier than 2014, that is, starting from the time when the concept of "diffuse midline glioma" was formed. The authors of this review express concern that, probably, the frequency of ectraneural metastases in patients with diffuse midline gliomas is underestimated, since they are not routinely examined to identify such metastases. The article points to the possibility of increasing the risk of extraneural metastases in connection with surgical interventions on primary tumors. The following expressed in the article may explain why extraneural metastases are rare in malignant gliomas. Probably, outside the

central nervous system, glioma cells are most often destroyed by the immune system, and in the brain these cells are protected, being in a microenvironment favorable them. This hypothesis is confirmed by descriptions of cases of extraneural glioblastoma metastases in patients who had previously undergone organ transplantation [12, 13].

The literature review made in the mentioned article by De Martino L et al. [10], did not include the work of Chinese researchers Ge X et al [5], which describes the development of extraneural metastases of diffuse median glioma of the brain stem region in a 9-year-old boy. His primary tumor was diagnosed based on CNS MRI data followed by stereotactic biopsy. The histological picture corresponded to anaplastic astrocytic glioma (grade IV malignancy according to World Health Organization (WHO)), immunohistochemical examination revealed a protein formed by the H3K27M mutation. Initially, there was no dissemination in the brain and spinal cord. Due to hydrocephalus, ventriculo-peritoneal bypass surgery was performed. The patient underwent local irradiation of the tumor area, total dose 50 Gy for 25 fractions with simultaneous of chemotherapy with temozolomide at a daily dose of 75 mg/mg^2. A month after the end of irradiation, MRI showed a slight decrease in tumor volume. The patient received adjuvant chemotherapy with temozolomide: 5 cycles of 5 days, every 28 days, the daily dose of this drug was 150 mg/mg^2 in the first cycle, 200 mg/m^2 in all subsequent cycles. 2 months after the end of chemotherapy, the patient complained of lowering of the right corner of the mouth, as well as back and lumbar pain. MRI revealed the progression of the primary tumor, dissemination in the spinal cord and along the soft meninges, as well as foci of destruction of the lumbar and sacral vertebrae with pathological contrast enhancement. PET-CT revealed a diffuse increase in metabolism in the cervical, thoracic and lumbosacral spine. The patient soon developed neck pain and urinary retention. Despite an attempt at chemotherapy (one cycle with vincristine and cyclophosphamide), no improvement was achieved, and the patient died 1 month after the detection of tumor metastases.

The authors of all the above publications emphasize that effective treatment programs for patients with extraneural metastases of malignant gliomas of the central nervous system have not yet been developed. This is due to both the relative rarity of such cases and their severity. Therefore, at least isolated reports that indicate the possibility of prolonging the life of such patients are so valuable.

As an example of such an observation, one can cite the description of the case made by Yang G et al [14]. Initially, an MRI scan revealed a tumor lesion of the right temporal and occipital lobes in the form of several nodes in a 58-year-old man. In the tissue of a totally removed tumor, histological examination revealed signs of glioblastoma with areas of oligodendroglioma. After the combined treatment (surgery, local radiation therapy, total dose 60 Gy in conventional fractions and chemotherapy with temozlolomide), no tumor remnants were observed according to MRI. However, six months after the end of treatment, a local relapse was detected, repeated radiation therapy was performed to its area, total dose 30 Gy in five fractions and several cycles of bevacizumab. It was possible to achieve a partial response and an improvement in the quality of life. However, after 2 years, while there was stabilization of tumor foci in the brain, multiple histologically confirmed metastases were found in the right lung, and then in the bones. Since PD-L1 expression was detected in lung metastasis tissue, and a slight increase in lung foci was noted during treatment with bevacizumab and temozolomide, it was decided to add pembrolizumab to the treatment. 5 cycles were performed with this drug. As a result, a partial response was noted in the lung, with a stable state of tumor tissue in the brain. Temozolomide was discontinued due to fatigue syndrome and lack of methylation of the MGMT promoter in tumor tissue; treatment with bevacizumab and pembrolizumab continued. However, after a few months, bone metastases developed, but the patient continued to receive the same treatment due to the lack of any alternatives at the disposal of his doctors. The progression of metastases continued. However, the authors believe that these drugs allowed to slow down this process. As a result, the patient lived quite a long time after the diagnosis of pulmonary metastases: 27 months, while in a series of patients with glioblastoma extraneural metastases published by Noch EK et al [15], the average life expectancy after their detection was 5 months (from 1 to 16 months), it is noteworthy that pembrolizumab was not used in them.

Undabeitia J et al [16] describe a case of extraneural glioblastoma metastases in a 20-year-old

patient. The primary tumor was localized in the right temporal region of the brain; its total removal was performed, followed by chemoradiotherapy. Metastases to both lungs and pleural cavities, as well as to the pancreas and vertebrae, occurred 5 months after surgery. Lung metastases were in the form of infiltrations, and they were confirmed by biopsy. Chemotherapy with irinotecan and bevacizumab was attempted, but the patient died.

In the case report by Kim A. V. et al. a 16-year-old patient is described, whose glioblastoma was initially localized in the left parietal lobe of the brain. 6 months after the operation, supplemented by local radiation and chemotherapy, it metastasized to the V cervical vertebra, which was confirmed by histological and immunohistochemical examination of the tissue of this vertebra [17].

Razmologova O. Yu. and Sokolova T. V. reported a case of glioblastoma metastases in the lungs at autopsy in a 64-year-old patient who died shortly after surgery on glioblastoma of the left parietal lobe of the brain. These metastases were confirmed by immunohistochemical method with determination of glial fibrillary acid protein expression [18]. A similar patient was described by Zhetpisbaev B. and Isakhanova B.: a 53-year-old man underwent partial removal of a tumor from the temporal lobe of the right hemisphere, in the postoperative period there was a deterioration in the condition in the form of depression of consciousness, unstable hemodynamics, the patient died. Histological examination of the removed tumor tissue revealed glioblastoma. While examining the left lung, a tumor focus was accidentally discovered, which, according to histological and immunohistochemical studies, corresponded to glioblastoma metastasis [19].

The information we have provided on the problem of extraneural metastases of brain gliomas is based on two major reviews [9 and 10] and descriptions of individual cases that were not included in them. In the last 20–30 years, there has been an increasing trend in the number of such publications. This can be explained by the improvement of various components of neuro-oncology, especially pathomorphology and diagnostic radiology. In addition, the development of surgical techniques, radiation therapy and drug treatment gives patients a chance to prolong their life span, during which such metastases can manifest. Despite the relative rarity of the occurrence of extraneural metastases in patients with malignant gliomas, there is still reason to believe that evaluations of their frequency are underestimated. Apparently, they remain unrecognized in many patients during tumor progression in the central nervous system, nevertheless, exacerbating the severity of the disease. The validity of this assumption is confirmed by the cases of occult metastases in the lungs [18 and 19].

CONCLUSION

In summary, extraneural metastases of malignant gliomas of the brain are rare, but their probability should be taken into account both when making an initial diagnosis and during subsequent control examinations, especially in patients who have undergone various surgical interventions on tumors or bypass operations. Despite the steadily increasing number of publications on this topic, there is still no accurate information about the frequency of such metastases, about the optimal ways of their early diagnosis, and effective therapeutic tactics have not been developed in case of their occurrence. In addition, the reason for the rarity of extraneural metastases in CNS tumors is not clear; a meticulous study of this issue could shed light on aspects of the pathogenesis of these tumors, and therefore open up new directions for their therapy. To solve these problems, multicenter studies involving the efforts of the leading neuro-oncological clinics are highly needed.

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