

**Bartłomiej Tyzo<sup>1</sup>, Michał Rutkowski<sup>1</sup>, Urszula Zielińska<sup>2</sup>, Karolina Thum-Tyzo<sup>3</sup>,  
Tomasz Trojanowski<sup>1</sup>, Krzysztof Turowski<sup>1</sup>, Radosław Rola<sup>1</sup>, Piotr Trojanowski<sup>4</sup>**

<sup>1</sup>Klinika Neurochirurgii i Neurochirurgii Dziecięcej, Uniwersytet Medyczny, Lublin

<sup>2</sup>I Oddział Neurologiczny Szpitala Neuropsychiatrycznego, Lublin

<sup>3</sup>Centrum Stomatologii, Uniwersytet Medyczny, Lublin

<sup>4</sup>Klinika Otolaryngologii i Onkologii Laryngologicznej SPSK4, Lublin

## Anaplastic ependymoma metastases to the scalp requiring free flap surgery

**Address for correspondence:**

Michał Rutkowski, MD  
Klinika Neurochirurgii  
i Neurochirurgii Dziecięcej  
Uniwersytet Medyczny, Lublin  
e-mail: [michal.rutkowski86@gmail.com](mailto:michal.rutkowski86@gmail.com)

**ABSTRACT**

Ependymomas are glial central nervous system tumors that derive from the ependymal lining of the ventricular system or central canal of the spinal cord. They may occur anywhere along the neuraxis, but most commonly in the posterior fossa in the floor of the fourth ventricle and in the location of the conus medullaris, cauda equina and filum terminale. According to the World Health Organization (WHO) classification ependymomas are divided into four groups on the basis of their histologic appearance: myxopapillary ependymoma; subependymoma (WHO grade I); ependymoma with cellular, papillary, clear cell and tancytic variants (WHO grade II); anaplastic ependymoma (WHO grade III). Anaplastic ependymomas are characterized by increased cellularity, cytological atypia, mitotic figures, vascular proliferation and areas of necrosis. Ependymomas, including the anaplastic type, have the potential to spread via the cerebrospinal fluid pathways; nevertheless intraspinal dissemination or metastasis of fourth ventricle tumor is a rare condition. The incidence is higher with higher WHO grade. Intracranial and spinal ependymomas frequently relapse at the primary site in case of incomplete surgical removal. For this reason, gross total resection followed by craniospinal radiation therapy is the treatment of choice. The extremely rare presence of metastases outside the central nervous system and even primary extraneural ependymomas were reported in the literature. Herein, we describe an unusual case of extraneural metastases of supratentorial anaplastic ependymoma with its treatment history.

**Key words:** anaplastic ependymoma, free flap, metastases

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### Introduction

Ependymomas are glial central nervous system tumors that derive from the ependymal line of the ventricular system or central canal of the spinal cord. They may occur anywhere along the neuraxis, but most commonly in the posterior fossa in floor of the fourth ventricle and in location of the conus medullaris, cauda equina and filum terminale. According to the World Health Organization (WHO) classification, ependymomas are divided into four groups on the basis of their histologic appearance: myxopapillary ependymoma; subependymoma (WHO grade I); ependymoma with cellular, papillary, clear cell and tancytic variants (WHO grade II); anaplastic ependymoma (WHO grade

III). Anaplastic ependymomas are characterized by increased cellularity, cytological atypia, mitotic figures, vascular proliferation and areas of necrosis. Ependymomas, including the anaplastic type, have the potential to spread via the cerebrospinal fluid pathways. Nevertheless, intraspinal dissemination or metastasis of the fourth ventricle tumor is a rare condition. The higher WHO grade is, the more frequent is the incidence of the tumor. Intracranial and spinal ependymomas frequently relapse at the primary site in case of incomplete surgical removal. For this reason, gross total resection followed by craniospinal radiation therapy is the treatment of choice. Extremely rare presence of metastases outside the central nervous system and even primary extraneural ependymomas were reported in the litera-

ture. Herein, we describe an unusual case of extraneural metastases of supratentorial anaplastic ependymoma with its treatment history.

## Case report

22-year-old patient had medical imaging examination of the head performed in March 2007 because of 2-month medical history of headaches and psychomotor retardation. Examination revealed presence of tumor in posterior part of the right parietal lobe and anterior part of the occipital lobe of the brain. Contrast enhancement of tumor was heterogeneous, there was a strand of swelling around, intracranial dislocations were present. The tumor had radiological characteristics of glia derived neoplasm. For this reason patient was operated on 23<sup>rd</sup> April 2007 in the Department of Neurosurgery and Pediatric Neurosurgery in Medical University of Lublin, where tumor was totally resected by parieto-occipital craniotomy. During histopathological examination of the intraoperative material there was anaplastic ependymoma G3 according to WHO classification diagnosed. In the postoperative course transient purulence in superior edge of wound occurred. Patient was discharged from hospital with healed wound in right parieto-occipital region and with no neurological defects symptoms. Afterwards, in period between 28<sup>th</sup> May and 2<sup>nd</sup> August 2007 he was staying in the II Department of Radiotherapy with Chemotherapy Subdivision in St. John's Cancer Center, where the cerebrospinal axis was radiated with 39.6 Gy, from the cranial area there was dose of 59.6 Gy administered. Radiotherapeutic treatment was performed with good tolerance; in later period patient's general feeling was varying; periodically general malaise occurred, patient was nauseous and vomited, he suffered from insomnia. In computed tomography examination performed on 4<sup>th</sup> November 2008 there was no pathological enhancement after intravenous contrast administration observed in the area of glial cicatrice in the place of removed anaplastic ependymoma. Since January 2009 headaches and psychomotor retardation of patient have appeared again. NMR imaging of the head performed on 20<sup>th</sup> March 2009 showed recurrence of brain tumor in the parieto-occipital region surrounded by swelling with the mass effect manifested in the right lateral ventricle compression. On 24<sup>th</sup> March 2009 recurrent brain tumor removal surgery was performed in the Department of Neurosurgery and Pediatric Neurosurgery in Medical University of Lublin. The postoperative course was uncomplicated. Afterwards, patient received three cycles of chemotherapy with temozolomide in the I Department of Chemotherapy with Ra-

diotherapy Subdivision in St. John's Cancer Center and tolerated it well. The follow-up imaging examination indicated the presence of another intensively enhanced recurrence in site of tumor removal and in area of cicatrice, which caused protuberance of skin that was moderately enhanced after contrast administration in the operated region. For this reason on 17<sup>th</sup> September 2009 recurrent supratentorial tumor was once again macroscopically totally resected in the vernacular neurosurgery department. Neoplastic lesions within the scalp were diagnosed in the occipital region. During the stay in the V Department of Oncological Surgery in St. John's Cancer Center the initial plan of surgical removal of lesions in the scalp was withdrawn because of presence of the cranium rarefaction in formerly operated region revealed by X-ray image. In October and November 2009 there were three cycles of chemotherapy after "8 in 1" scheme used (cytarabine + decarbazine + methylprednisolone + vincristine + cisplatin + lomustine + procarbazine + hydroxycarbamide), radiotherapy of recurrence in the scalp was performed by applying dose of 4 Gy five times. Afterwards, in period between December 2009 and May 2010 patient received totally five cycles of chemotherapy after ICE scheme (ifofosmide + carboplatin + etoposide). Chemical therapy was complicated by pancytopenia; patient repeatedly required blood products transfusions and administering growth factors as: filgrastim, lenograstim, darbepoetin alpha. Because of intracranial neoplastic lesions progression in postoperative site and presence of several metastatic foci in the integument of occipital and nuchal region observed in NMR images of the head performed on 21<sup>st</sup> September 2010, patient was qualified for chemical treatment with fotemustine. In course of oncological therapy patient's neurological state deterioration occurred — there were severe headaches and vision disorders. On basis of CT of the head performed on 5<sup>th</sup> November 2010, which revealed presence of massive swelling of the right hemisphere of the brain and formerly observed recurrence of anaplastic ependymoma within posterior part of the parietal lobe, antiedematous treatment was introduced and another brain tumor removal operation was performed on 16<sup>th</sup> November 2010. After four cycles of chemotherapy with fotemustine, treatment after PCV scheme (procarbazine + lomustine + vincristine) and irradiation of the occipital and nuchal region five times with dose of 4 Gy was applied. There was further progression of neoplastic lesions in head and neck tissues observed and in March 2011 it was decided to begin chemotherapy after "8 in 1" scheme; at the same time there was 10 Gy applied in the right area of the neck. Chemical treatment induced thrombocytopenia and anemia, which required transfusing thrombocytes

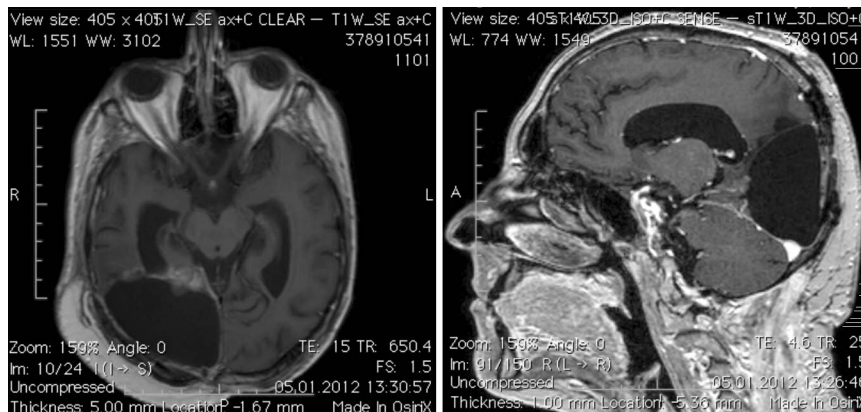
and erythrocytes concentrate and reducing doses of administered cytostatic agents. Magnetic resonance of the head performed on 29<sup>th</sup> March 2011 showed less intensity of swelling in the right hemisphere of the brain in comparison with the examination performed in September 2010 — lack of pressure on the ventricular system and no dislocation of structures in medial axis of the brain, presence of another recurrence within the parietal and occipital lobe of the brain and neoplastic infiltration enlargement in tissues of the nuchal region. NMR examination performed in July 2011 revealed further enlargement of anaplastic ependymoma inside and outside the cranium. Because of average clinical state of patient and significant toxicity of administered cytostatic agents, chemotherapy after “8 in 1” scheme was ended and starting from August 2011 therapy with cyclophosphamide was administered. Because of increasing headache and psychomotor retardation, considering enlargement of brain tumor dimensions and ischemic and swelling area around it, and size of metastases in the occipito-nuchal region integument progression shown in NMR examination performed on 3<sup>rd</sup> October 2011, patient was qualified for neurosurgical operation. On 7<sup>th</sup> November 2011 there was craniotomy performed in the right parieto-occipital region, intracranial recurrence of anaplastic ependymoma was macroscopically totally resected; in second stage of the surgery integument of the head and neck was removed in area of observed metastatic lesions and flap of skin from anterolateral part of the thigh was transplanted to this region (Figure 1). Initially after the operation patient’s state was severe and he periodically required mechanical respiratory assistance, gradually his clinical state was improving. Patient was discharged from hospital with minor paresis of the left side, he was moving on his own using a prop, with previously observed hemianopia. Transplant was engrafted except small part located in the parasagittal area, which turned into necrotic tissue and was resected on 14<sup>th</sup> December 2011. Wound was left to heal by growth of granulation tissue. Soon after the surgical treatment nodular metastatic lesions appeared in the head and right shoulder integument. Magnetic resonance examination performed on 5<sup>th</sup> January 2012 revealed presence of two pathological highly enhanced after contrast applying intracranial regions near right posterior part of the thalamus the size of 14 × 10 mm and 16 × 12 mm within postoperative site filled with the cerebrospinal fluid (Figure 2) and three polycyclic regions in neck vascular-nervous plexus area with radiological characteristics of lymph nodes with necrosis. On basis of acquired medical documentation it was decided to administer chemotherapy course with lomustine on 27<sup>th</sup> January 2012 and conduct symptomatic treatment, patient was reported to hospice for palliative care.

## Discussion

Standard treatment of anaplastic ependymomas of the brain is total surgical resection with subsequent irradiation of operated area with its margin or of whole cerebrospinal axis [1–3]. Postsurgical radiotherapy of the brain and spinal cord is usually recommended in case of diagnosed dissemination of anaplastic ependymoma (confirmed by cytological examination of cerebrospinal fluid or NMR imaging of the spinal cord) [4] or infratentorial localization of tumor. Extent of resection is the most important prognostic factor of distant outcome of the treatment [5–10]. Total resection of tumor is not possible in case of its localization nearby vital structures or eloquent areas of the cerebral cortex. The most frequent localization of recurrence is primary focus region. Disease course observation is mainly based on periodical assessment of the central nervous system structures using magnetic resonance with contrast. Patients may require multiple operations and oncological treatment. Effectiveness of chemotherapy schemes used so far is controversial; there are trials on using drugs inhibiting angiogenesis in form of monoclonal antibodies anti-VEGF (bevacizumab) going on. Using cyclophosphamide, ifosphosphamide, methotrexate, vincristine, procarbazine and nitrosourea often combined in even up to eight cytostatic agents is related to low effectiveness [11]. Relatively greater benefit from therapy with cisplatin and carboplatin was documented so far [12]. Using chemotherapy is found reasonable in children under the age of 3, in which complementary radiotherapy is not recommended, or in patients with uncontrolled neoplasm progression [13, 14]. Possibility of using radiosurgery in combination with maximally radical neurosurgical resection of brain tumor is taken into consideration [15–17]. Ependymomas are neoplasms sensitive to radiation. There is no single scheme of procedure in case of recurrence or metastases of anaplastic ependymoma developed so far. The mechanism of forming the intracranial glial neoplasms metastases outside the central nervous system is an intensively studied phenomenon. Rare occurrence of these metastases is caused by the interaction between tumor and blood-brain barrier, microglia, matrix proteins, cytokines and growth factors. It is commonly known that ependymomas are characterized by the possible neoplastic cells dissemination via cerebrospinal fluid. This phenomenon particularly applies to infratentorial tumors with high grade histological malignancy. Typical metastases localization is lumbosacral part of the meningeal sac. There were few cases of anaplastic ependymoma metastases presence outside the central nervous system reported, most frequently in lymph nodes, lungs, liver and vertebral body. Presented case report is one out of four descriptions of anaplastic ependymoma’s of the brain metastasis in the epicranium [18–20]. At the



**Figure 1.** Intraoperative photos showing reconstruction of the head and neck integument loss by transplanting free skin flap from anterolateral part of patient's thigh



**Figure 2.** Magnetic resonance imaging of the head performed after fourth intracranial surgery showing the extent of another anaplastic ependymoma recurrence (T1 images with contrast)

same time it is the only example of surgical treatment of ependymoma's extensive metastatic lesions in skin of the head and neck using the integument reconstruction with autogenic free skin flap taken from anterolateral part of the thigh. There was photographic documentation of the

reconstructive surgery made. Presence of multiple and extensive metastases in the integument, which resection is due to creating skin loss of large surface disabling moving the wound edges closer, may constitute an indication to perform skin flap transplantation. It is claimed in the

literature that there is a possibility of forming rare glial neoplasms' metastases extracranially by: neoplastic cells penetration into the lymphatic system or veins caused by blood-brain barrier damage, by direct infiltration of dura mater and bone or ventriculo-peritoneal drainage [21]. Surgical trauma is related to opening vessels of all head layers on the way of accessing to brain tumor and it may predispose to extracranial neoplastic cells dissemination. The authors notice that all of four described cases of forming anaplastic ependymoma's metastases in the epicranium nearby craniotomies performed earlier or even in postoperative scar suggest the relation between neurosurgical intervention and increased risk of forming metastases is soft tissues of the head. This relation was reported in the literature concerning glial derived neoplasms.

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