Extracranial Metastasis of an Anaplastic Ependymoma, RELA Fusion-Positive: A Rare Occurrence

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Abstract

Primary intracranial ependymomas originate from ependymal cells. They may migrate mainly in the spinal cord but rarely metastasize outside the central nervous system. Metastases outside the central nervous system are rare. Metastatic diffusion from the central nervous system is low due to the unique interaction of the brain and the tumor with the blood-brain barrier. Nevertheless, three main hypotheses have been mentioned in the literature, the tumor growth, the surgical manipulation (which may be considered to be the case in our patient), and the aggressiveness of the tumor according to the Ki67 index. We report the case of a 16-year-old female, who underwent complete surgical removal of a left occipital 2007 WHO grade II ependymoma. 3 years later, the patient presented multiple cervical and occipital indurated masses. MRI showed a left hemispheric meningeal infiltration, with multiple nodules located on the neck, occiput and mastoid. Histopathological study of a left temporal surgical biopsy and resection of an occipital subcutaneous nodule turned to be metastases of an anaplastic ependymoma. The ependymoma considered as a benign tumor could very quickly turn into malignancy by its metastatic potential. Early diagnosis and longer follow-up of patients would be recommended for a rapid management.

Keywords

Anaplastic Ependymoma, Extracranial, Metastasis, Extraneural, RELA Fusion

1. Introduction

Primary intracranial ependymomas are tumors derived from ependymal cells

which belong to the glioma group. The localization is supratentorial and infra-tentorial, more often intra-ventricular, sometimes para-ventricular and less frequently in the spinal cord.

Supratentorial low-grade ependymomas as well as their anaplastic forms are relatively uncommon central nervous system neoplasms. These are rare tumors, estimated at 3% to 4.7% of CNS tumors, and afflict more children than adults [1]. Ependymomas account for 2% of all intracranial tumors in adults and 2% - 9% of all neuroepithelial tumors [2]. They recur mainly in the spinal cord, but rarely metastasize outside the central nervous system. Extra-neural metastases occur mainly in lung, pleura, liver and lymph nodes [3].

The World Health Organization (WHO) classifies ependymomas into four groups based on histologic appearance: subependymoma (WHO grade 1); myxopapillary ependymoma (WHO grade 1); ependymoma with cellular, papillary, and clear cell variants (WHO grade II); and anaplastic ependymoma (WHO grade III) [4] [5]. In all subtypes of ependymomas, surgery is the mainstay of therapy and radiotherapy is often applied in the adjuvant setting. Chemotherapy has been used extensively for ependymomas, however, there is little evidence that this therapeutic modality improves overall survival [4], underscoring the role of surgery for this tumor type. Extracranial metastasis of primary intracranial tumors is extremely uncommon, and has been reported mostly for high-grade astrocytomas that have had prior surgical intervention [6] [7]. This is a rare case of anaplastic ependymoma metastazing in the cervical lymph nodes, the scalp and the mastoid.

2. Case Report

A 16-years-old Moroccan female patient presented with a story of corticosteroid-induced diabetes, bilateral blindness on chronic intracranial hypertension syndrome. Brain MRI showed an enhancing mass with a cystic component in the left temporo-parieto-occipital region measuring 9.2 × 6 × 4.5 cm (**Figure 1**).

Figure 1. Cerebral MRI showing occipital glial process.

She underwent a gross total resection (GTR), and the pathology revealed a grade II ependymoma with World Health Organization (WHO). No post-operative complications were found during the surgery.

After surgery she has been followed every six months until 03 years. MRI was performed one year after surgery and carried out a nodular meningeal infiltration in the left cerebellum with a left occipital porencephalic cavity (Figure 2, Figure 3). Three years after the surgery, she came with atonic seizures. The physical examination finds a conscious patient with bilateral blindness and a palsy of III nerve, a clinical cushing syndrome. She also had indurated masses, at the mastoid, maxillary, and cervico-occipital levels. A cerebral MRI were performed and carried out a left hemispheric meningeal infiltration in relation to a meningeal dissemination, with a multiple nodules located on the neck, occiput and mastoid (Figure 4, Figure 5). The patient underwent a biopsy on the left temporal and the complete excision of an occipital nodule. Pathological analysis of the tumor specimen found a metastasis of an anaplastic ependymoma (Table 1).
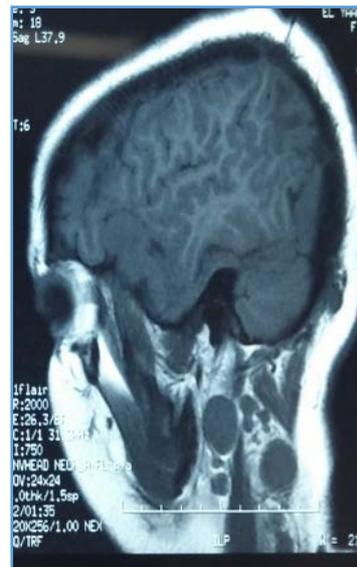

Figure 2. Post-operative MRI with post-operative remodelling.

Figure 3. Normal medullar MRI.
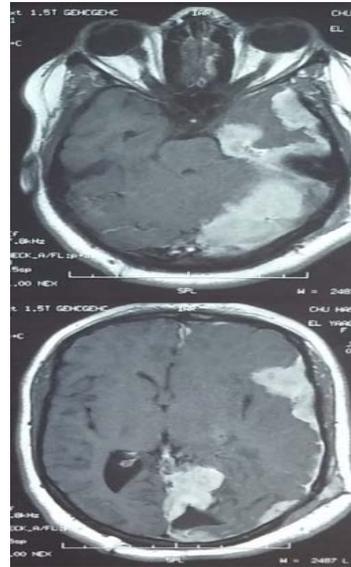
Figure 4. Hemispheric meningeal infiltration.

**Figure 5.** Cerebro-medullar MRI: multiples nodules on the neck, mastoid.

Table 1. Patient clinical characteristics.

| Age-sex	Origin	symptoms	Histopathological analysis	Treatment	Follow-up Survival period
16-*F*	Morocco	-Chronic intracranial hyertension -Blindness	Grade II Ependymoma	Surgery	No recurrence for three years
		-Atonic seizures -Intracranial hypertension -Blindness with IIIth nerve palsy -Indurated masses (mastoid, maxillary, cervico-occipital)	Grade III Ependymoma with extracranial metastasis	Biopsy and chemotherapy	Recurrence and death one year later

Pathological findings:

Neuropathologic examination Histopathology revealed a cellular high-grade glioma with large areas of central necrosis and florid microvascular proliferation (Figure 6).

Other areas showed microcalcifications, consistent with the presence of an earlier, lower-grade lesion. The tumor was extremely well demarcated from the surrounding brain, showing no evidence of infiltration in the few regions where there was brain available for evaluation. At higher magnification (Figure 7), there were extensive perivascular nuclear-free zones. Nuclei were round to ovoid and moderately pleomorphic. Mitotic activity was readily identified. Focally, there was extensive perinuclear clearing as well as a delicate branching vasculature, reminiscent of anaplastic oligodendroglioma (Figure 6). The EMA stain
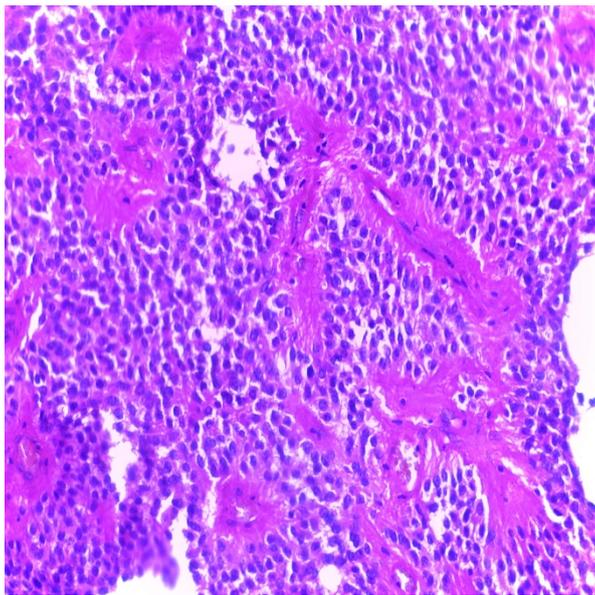

Figure 6. Pathological analysis, magnification 20.
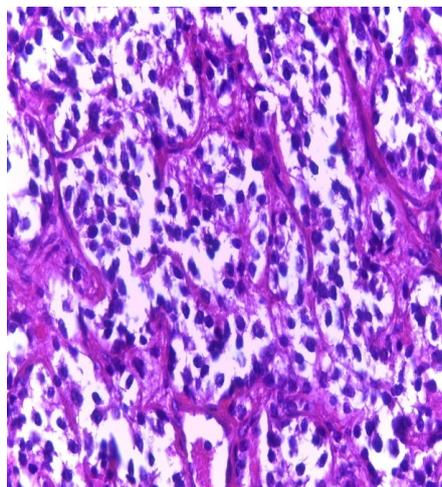
Figure 7. Higher magnification (209) shows frequent perivascular pseudorosettes as well as nuclei with moderate pleomorphism and frequent mitotic figures.

demonstrated occasional perinuclear dots (Figure 8) as well as focal true ependymal rosettes (inset).

Immunohistochemistry revealed strong staining for GFAP (Figure 9). Mixed keratins AE1/3 were present in perivascular pseudorosettes.

Tumor cells also expressed low levels of synaptophysin consistent with prior reports of neuronal differentiation in ependyomas [8]. Additional neuronal markers (NeuN, chromogranin, neurofilament) were all negative. The MIB-1 (KI-67) proliferation index was high, estimated to be around 12% - 15%.

In the metastatic temporal mass, some regions still retained a morphology that was similar to the original tumor while others had a "gemistocytic" appearance with abundant eosinophilic cytoplasm and small nuclei. In the temporal subcutaneous mass, the cellular regions showed a MIB-1 proliferation level that far exceeded that of the original tumor, estimated at around 20%. In contrast, proliferative activity was largely absent in the regions with gemistocytic morphology. These morphologic and immunohistochemical features are consistent with radiation-related changes in part of the neck mass.
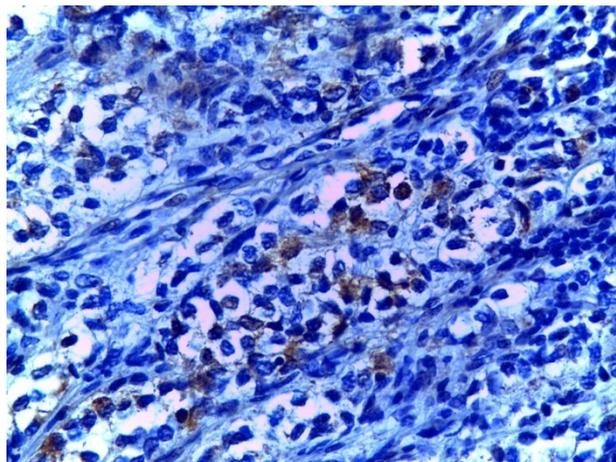
Figure 8. EMA, on the EMA stain, there are occasional perinuclear dots as well as true ependymal rosettes (inset).
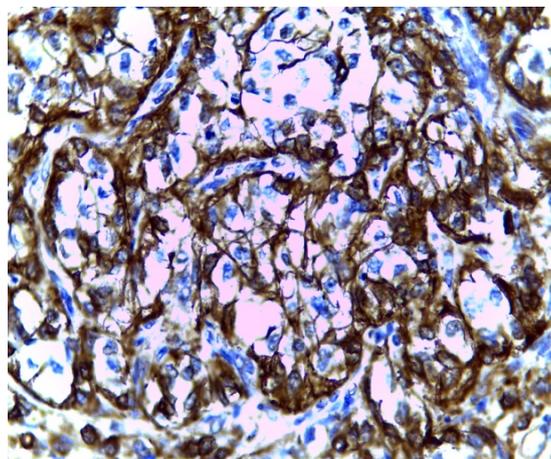
Figure 9. GFAP: Immunohistochemistry reveals strong staining for GFAP.

All specimens shows that the L1CAM (San Francisco, US) was robustly positive in the entire tumor cell cytoplasm that confirm the *RELA* fusion-positive ependymoma.

Follow-up:

The patient was sent for radiotherapy sessions as well as complementary chemotherapy.

The patient was initiated on two cycles of chemotherapy according to the Children's Oncology Group study, ACNS0121 with vincristine, carboplatin, and cyclophosphamide followed by vincristine, carboplatin, and etoposide. The patient had a good response to the chemotherapy and focal conformal radiation therapy of 59.4 Gy was delivered to the tumor over a 6-week period. Then unfortunately, the disease progressed and her condition worsened. She died on year later.

3. Discussion

Ependymomas are rare glial neoplasms comprising 5% of all intracranial tumors in adults and 10% in children. They usually arise intracranially in an infratentorial or supratentorial brain location and less commonly from the spinal cord, but rarely metastasize outside the central nervous system (CNS).

Extraneural metastases of brain tumors with or without concurrent recurrence of the primary tumor have been reported to occur in 0.5% - 0.98% of cases [8] [9]. In pediatric patients, the most common CNS tumor types leading to extraneural metastases were medulloblastoma (56.3%), germinomas (9.8%), glioblastomas (6.9%), ependymomas (3.7%), and pilocytic astrocytomas (2.9%) [8]. Interestingly, the site of metastasis varied with tumor type and likely reflects yet incompletely understood tumor biology. Medulloblastoma showed a preference for bone (88.3%), germinomas for bones (77.8%), and visceral organs (66.7%), while ependymomas were most entirely encountered in lymph nodes and visceral organs particularly the lungs (71.5% - 100%) [10]. The presence of extraneural metastases carries a very poor prognosis and the majority (62% - 80%) of patients died of their disease after a mean of 9.4 months in one study and median of 2.6 months in another study [9].

Metastization to and from the CNS is low due to the unique brain and tumor interaction with the blood-brain barrier, microglia, matrix protein, cytokines and growth factors [11]. There are a number of theories on the mechanism of distant metastasis.

One hypothesis postulates that craniotomy and shunt surgeries may contribute to extraneural metastases by disrupting the blood-brain barrier and promoting vascular seeding to distant sites, though not all patients with CNS tumors with extraneural metastases have had priorsurgery [11]. Surgical manipulation, however, appears to be the most important risk factor for extraneural spread with spontaneous extracranial metastases occurring in only 8.5% of brain tumor cases [12]. This could be the case in our patient, and would therefore re-

sult in direct extension of the primary tumor (re-growth through the dural defect). Alternatively, tumor spread may have occurred intraoperatively as seeding of tumor cells into the craniotomy site. Such involvement of the prior operative site has been observed for high-grade astrocytomas [13].

Rickert published a review article on extracranial metastasis of pediatric brain tumors that included six cases of ependymoma, not otherwise specified, and two cases of anaplastic ependymoma [9]. Among them, one had metastasis without prior surgical intervention, including biopsy, and seven had metastasis after surgical intervention. The mean latency, which is the latency between brain surgery and extracranial metastasis, for metastasis was 25.7 months for non-shunt related metastasis.

In our case, although one surgery had been done before extracranial metastasis, the latency for extracranial metastasis was 24 months from the first surgery. We assume that the surgery might have played a major role in metastasis to the neck, occiput and mastoid; however, the tumor infiltration in meningeal tissues and its extracranial localizations might suggest its aggressive nature, which might be due to its genetic alteration of RELA fusion positivity and 1q25 gain.

Another hypothesis suggests that extension of the tumor into the cranial structures may allow seeding into the lymph system. Extracranial metastases of intracranial ependymoma to the lungs are rare. This could theoretically be attributed to invasion of the dural venous sinuses or through direct spread after implantation of an atrioventricular shunt [11].

Histopathologically, the propensity of anaplastic ependymoma to metastasize as well as its aggressiveness may be correlated to a Ki67 index above 10%. In our patient the tumor at the original site had fairly typical features of an anaplastic ependymoma.

The rather high KI-67 proliferation index of over 10% may have been an early indication of possible aggressive clinical behavior.

This marker has been shown to be an independent prognostic factor in patients with ependymoma, affecting parameters such as 5 years survival and overall survival. Increasing numbers of reports have demonstrated neuronal differentiation and its prognostic significance in ependymomas [14].

Ependymomas are divided into three groups according to their location: supratentorial (ST), posterior fossa (PF), and spinal cord (SC). Supratentorial ependymoma is further categorized as RELA-C11 or f 95 fusion and YAP1-MAMDL1 (mastermind like domain containing 1) or YAP1-FAM118B (Family with sequence similarity 118 B Members) fusion [15]. RELA fusion subtype comprises 70% of supratentorial ependymomas, and the rest is YAP1 fusion [16]. The RELA fusion group has remarkably worse survival than that of YAP1 fusion group. RELA fusion can be detected via reverse transcriptase-polymerase chain reaction or immunohistochemical marker L1CAM. In case of posterior fossa ependymomas, LAMA2-expressing ependymomas (group A) has worse outcome than NELL2-expressing ependymomas (group B) [17].

Among the few reported cases of ependymal neoplasms with extracranial metastasis, the main therapeutic modality was radiotherapy, with only a small role of chemotherapy. This may be a reflection of the often poor response to chemotherapy in CNS tumors, which is often explained by the poor penetration of antineoplastic agents through the blood brain barrier.

The site of metastasis varied with tumor type and likely reflects yet incompletely understood tumor biology. Ependymomas were almost entirely encountered in lymph nodes and visceral organs particularly the lungs (71.5% - 100%) [17].

The presence of extraneural metastases carries a very poor prognosis and the majority (62% - 80%) of patients died of their disease after a mean of 9.4 months in one study and median of 2.6 months in another study [18].

The ependymoma considered as a benign tumor could very quickly turn into malignancy by its metastatic potential. Early diagnosis and longer follow-up of patients would be recommended for a rapid management. The case of our patient is unusual in its location as well as its aggressive and unexpected clinical course with extracranial metastasis.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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