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# **Heterogeneous appearance of central nervous system involvement in malignant mixed Müllerian tumors**

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**Keywords:** malignant mixed Müllerian tumors (MMMT), central nervous system (CNS) metastasis, neurosurgical resection

## **Abstract**

Involvement of the central nervous system (CNS) is rarely described in malignant mixed Müllerian tumors (MMMT). Only 4 intracranial and 2 spinal cases have been published to date. Here we report two more cases with heterogeneous clinical, radiological and pathological features and summarize the available contemporary literature.

One patient presented with aphasia due to an intraaxial contrast enhanced left temporal lesion with marked perifocal edema. After surgical resection, histology showed collections of small uniform tumor cells embedded in a myxoid matrix and compartmentalized by connective tissue septations, consistent with a MMMT. The other patient presented with trigeminal/tongue hypesthesia and double vision accompanied by left radiculopathy and paresis. MRI revealed an extraaxial lesion at the petrous tip with mild perifocal edema and multiple small intradural contrast enhancing lesions of the conus and cauda medullaris. Histological examination of the intracranial lesion showed a mainly papillary architecture, also consistent with MMMT. The spinal lesions were not excised and both patients received adjuvant radiochemotherapy. The first patient died 3 months and the second patient 12 months after surgery.

As illustrated by the heterogeneous clinicopathological features of our 2 cases as well as the reviewed literature, CNS metastasis of MMMT are diagnostically challenging, show a variable outcome, and thus require individualized treatment. In the present cases and CNS metastases reported to date, a higher histological ratio of sarcomatous to epithelial components portends a worse outcome.

## **Introduction**

Malignant mixed Müllerian tumor (MMMT) represents a subtype of uterine sarcomas composed of malignant admixed epithelial and mesenchymal sarcomatous elements.[1] MMMT typically occurs in postmenopausal women, rarely in patients under 40 years of age.

Of further note, MMMT is one of the most malignant gynecologic tumors with an overall 5 year survival of approximately 30%.<sup>[1]</sup> Prognostic indicators include the depth of myometrial invasion and the surgical stage. Recurrent and / or metastatic tumors can be exclusively sarcomatous, carcinomatous or mixed.

The origin of this rare carcinosarcoma is controversial, but suggested to be stem cells that divergently differentiate into components that resemble Müllerian epithelium and mesenchymal tissues found in the uterus.<sup>[2]</sup>

Surgical resection is generally the primary therapy of malignant mesenchymal uterine tumors. Patients who undergo surgery initially show a better prognosis in comparison to patients who are solely treated with radiotherapy.<sup>[3]</sup> Studies demonstrate that the removal of pelvic and paraaortal lymphnodes further improve the outcome of patients.<sup>[4]</sup> The 5-year survival rate for nodal negative patients is 64,2%, while it is only 26% for nodal positive patients.<sup>[5]</sup> Therefore, lymphadenectomy should be part of the primary operation. Regardless of the nodal state, adjuvant radiotherapy does not increase the survival rate.<sup>[4]</sup> Nevertheless, a reduction of the local pelvic recurrence rate after radiotherapy ranges from 48% to 28%. Adjuvant chemotherapy did not improve survival; however, palliative chemotherapy in patients with metastasis or with recurrence significantly extends survival.<sup>[6]</sup> Patients in advanced disease stages respond to a therapy with Carboplatin and Paclitaxel in 60%, while 55% show a recurrence of MMMT.<sup>[7]</sup> Combined chemotherapy with paclitaxel, carboplatin and liposomal pegylated doxorubicin administered to patients with advanced and recurred MMMT results in complete response in 34% and a partial response in 28%. The median overall survival is 16.4 month.<sup>[8]</sup>

Although only limited data are available regarding metastatic tumors in MMMT, the relative proportion of the sarcomatous component in the primary tumor is thought to be predictive of increased aggressiveness.<sup>[9]</sup> Local progression with lymphatic and hematogenous metastasis is common; however, central nervous system (CNS) involvement is rare. To our knowledge,

there are only 4 metastatic intracranial and 2 spinal cases reported in the literature.[2, 10-14] Here we report two additional CNS metastases of MMMT and summarize the literature to further analyze risk factors that predict patient outcome.

## Case Presentation

### Case 1

This 55 year-old female patient was initially diagnosed with MMMT and underwent hysterectomy with adnexectomy. At the time of diagnosis there was no evidence of metastasis at staging including brain MRI and the patient received adjuvant chemotherapy with carboplatin and paclitaxel. Three months after the second chemotherapy cycle, the patient developed aphasia and clinical signs of increased intracranial pressure including headache and dizziness. Epileptic events were not reported and the electroencephalogram was normal. Cranial magnetic resonance imaging (MRI) showed an intraaxial, left temporal contrast enhancing lesion (29x35x32mm) with massive perifocal edema and two small left frontal lesions (Figure 1). Antiedema therapy with steroids was started followed by craniotomy and complete resection of the left temporal lesion. Histology revealed a metastasis of the primary MMMT composed of collections of small, monomorphic tumor cells embedded in a myxoid matrix and compartmentalized by connective tissue septations. In some areas, the histological pattern of the brain metastasis resembled the primary tumor within the uterus (Figure 2). The aphasia improved after surgery and a third cycle of the adjuvant chemotherapy was applied. Postoperative MRI showed a complete resection of the lesion with persistent edema of the left hemisphere (Figure 1). Cortisone was continued and after 2 weeks of neurorehabilitation, adjuvant whole brain radiation was started. However, the patient deteriorated during radiation, suffering from vigilance problems and a general weakening. Therefore, therapy was stopped at the request of the patient. The patient died 3 months after the neurosurgical intervention.

## **Case 2**

This 66 year-old patient was diagnosed with MMMT and treated with hysterectomy and pelvic lymphadenectomy followed by adjuvant radiotherapy of the pelvis (total of 50.4 Gy) and chemotherapy with a total of 120mg epirubicin and 100mg cisplatin. Initial staging did not reveal any metastatic lesions (pT2b pN1 (4/17) M0 G3 R0). Fourteen months after diagnosis, the patient described trigeminal and tongue hypesthesia as well as double vision. In addition, examination showed left-sided radiculopathy with M3 paresis of the left leg without evidence of cauda equina involvement. MRI revealed an extraaxial lesion at the petrous tip in the cerebello-pontine angle with mild perifocal edema and multiple small intradural lumbar lesions along the cauda and conus medullaris (Figure 2). Histological examination after resection of the intracranial lesion showed a mainly papillary epithelial architecture consistent with a MMT (Figure 3). Postoperative CT showed a complete resection of the lesion (Figure 2). The multiple spinal lesions were not excised. Postoperatively, the patient received adjuvant radiotherapy of the thoracolumbar spine (BWK 11 to LWK 5) with 30 Gy plus whole brain to a total of 30 Gy. After neurorehabilitation, preoperative cranial nerve symptoms resolved; however, the patient died one year after neurosurgical resection due to primary pelvic tumor progression.

## **Discussion**

Uterine sarcomas are rare neoplasms that commonly show local and extraabdominal metastasis; however, the incidence of CNS metastases is very low. The likelihood of metastasis of MMMTs seems to be associated with stage of the disease, deep myometrial invasion, cervical tumor extension and positive retroperitoneal lymphnodes.[1] So far it remains unclear, which element of MMMTs is more likely to determine the metastasis. While

some studies favor the epithelial component to be more predictive of aggressive behavior,[15] other studies indicate that the sarcomatous component is associated with a poorer outcome.[2] A study by Silverberg and colleagues comparing primary MMT lesions with metastases found high-grade, serous, and clear cell carcinomatous components of the primary tumor to be associated with a higher frequency of metastases suggesting an aggressive/invasive behavior of the epithelial component.[16]

According to our literature review, only one case was reported that demonstrated a composition similar to the primary tumor.[10] In all other reports with CNS metastasis, details a comparison of the proportion of the epithelial and sarcomatous components in the metastasis and primary tumor was not reported.[2, 11, 13, 14] Table 1 summarizes the literature with regards to the histopathological composition of the cerebral metastasis and highlights the variability of the sarcomatous or epithelial components. This is also reflected in the histopathological findings of our two cases, including one predominantly sarcomatous and another with predominantly epithelial composition. Interestingly, the life expectancy of patients with sarcomatous CNS metastases was clearly lower with a mean overall survival of 2.5 months (range 1-3), compared to patients with metastases lacking a mainly sarcomatous composition (n=3, mean overall survival of 28.3 months, range 24-36) (Table 1). Even though a complete resection was performed in patients with sarcomatous metastasis, life expectancy still remained very low, as illustrated by our case 1 and the case reported by Kim et al.[14] Additionally, the time between primary MMT diagnosis to CNS metastasis was lower in the sarcomatous CNS metastasis group with a time of 0, 0, 1 and 3 months and 7 and 14 months in the epithelial group.[2, 10, 11, 14] Of note, a single patient without a predominant composition was diagnosed with a CNS metastasis 6 months after primary diagnosis.[13] Besides the heterogeneous histopathological findings, the clinical presentations and radiological findings vary greatly. For example, one of our patients showed an intradural cranial metastasis and the other an extradural cranial and intradural spinal metastasis. Cormio

et al. described a patient with multiple intracranial intradural lesions in addition to epidural spinal occurrence.[11] Another patient from Stienen et al. presented with a spinal intradural, intramedullary symptomatic lesion, without an intracranial localization.[13] Therefore, it is important to report and collect more cases of this rare entity to acquire more accurate prognostic data to direct the development of future therapeutic strategies.

## Conclusion

Despite surgical intervention and multimodal therapy, the prognosis of patients with MMMTs remains poor. Although CNS metastases from MMMTs are extremely rare, surgery is recommended for symptomatic lesions. Our cases and the scarce literature indicate that overall survival for patients with predominantly sarcomatous metastatic tumors is lower than for those in patients with predominantly epithelial tumor composition.

## Figure / Table Legend

**Figure 1:** Corresponding images for case 1 (55yo female): Preoperative MRI T1 with contrast in coronal, axial and sagittal planes (**A-C**) and axial T2 (**D**) of the intraaxial, left temporal contrast enhancing lesion (29x35x32mm) lesion. Arrows in **E** show the two small left frontal lesions in T1 axial planes with contrast. **F**: Intraoperative high-frequency ultrasound (Real-time L15-7 intraoperative probe, iU22 Ultrasound System, Philips, Bothell, USA) shows edge of craniotomy (\*), solide (\*\*) and cystic (\*\*\*) tumor parts. Postoperative T1 with contrast in coronal and axial planes (**G, H**) showed complete resection of the lesion.

**Figure 2:** Corresponding images for case 2 (66yo female): Preoperative MRI T1 with contrast in axial and coronal planes (**A, B**) and axial T2 (**C**) of the extraaxial lesion at the petrous tip in the cerebello-pontine angle. Postoperative CT in axial plane with contrast showed complete

resection (**D**). Lumbar MRI in sagittal T2 (**E**) and in T1 with contrast (**F**) planes showed multiple small intradural lumbar lesions along the cauda and conus medullaris.

**Figure 3:** (**A**) The brain metastasis from Patient 1 comprises closely packed collections of small, monomorphic tumor cells compartmentalized by connective tissue septations.

\*Focally, the tumor elaborates a bluish, myxoid matrix (HE, x10). (**B**) Scattered tumor cells show vimentin immunoreactivity (x20) (**C**) Clusters of neoplastic cells immunolabel with cytokeratin (x20) (**D**) In some areas, the tumor within the uterus resembles the brain metastasis (HE, x20) (**E**) Malignant epithelial component of the brain metastasis from the second patient demonstrates a papillary architecture (HE, x20) and (**F**) stains with cytokeratin (x20).

**Table 1:** Characteristics of MMMT cases presented in the literature and our new described two cases

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Figure 1:

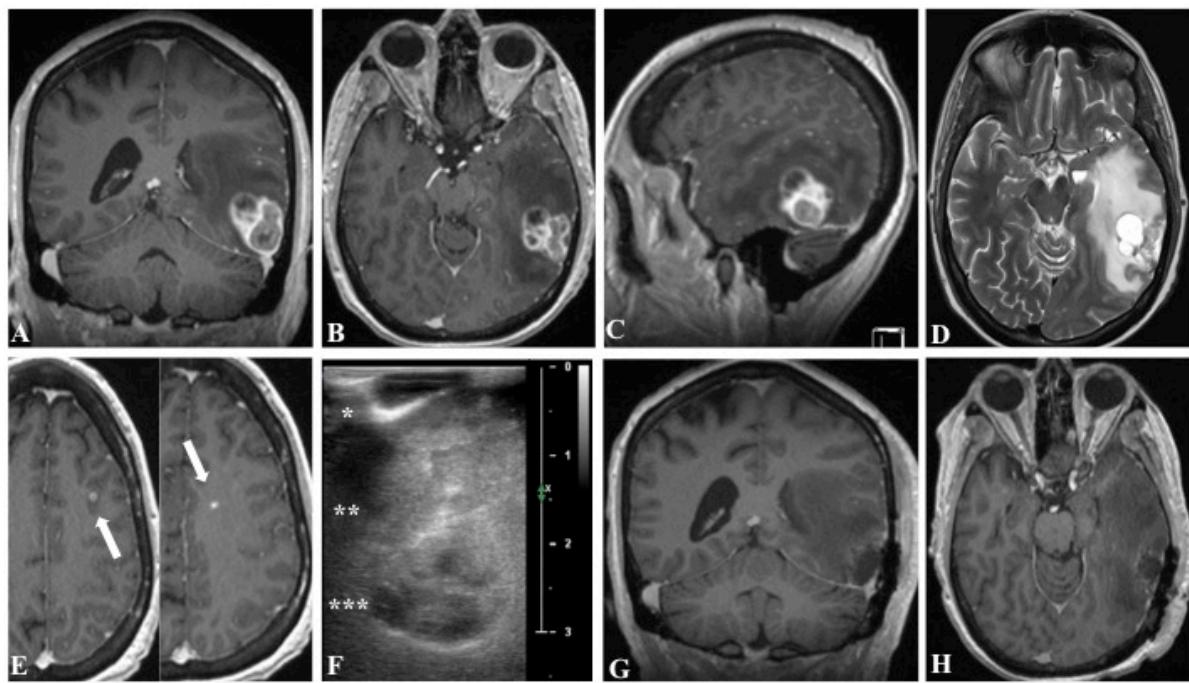


Figure 2:

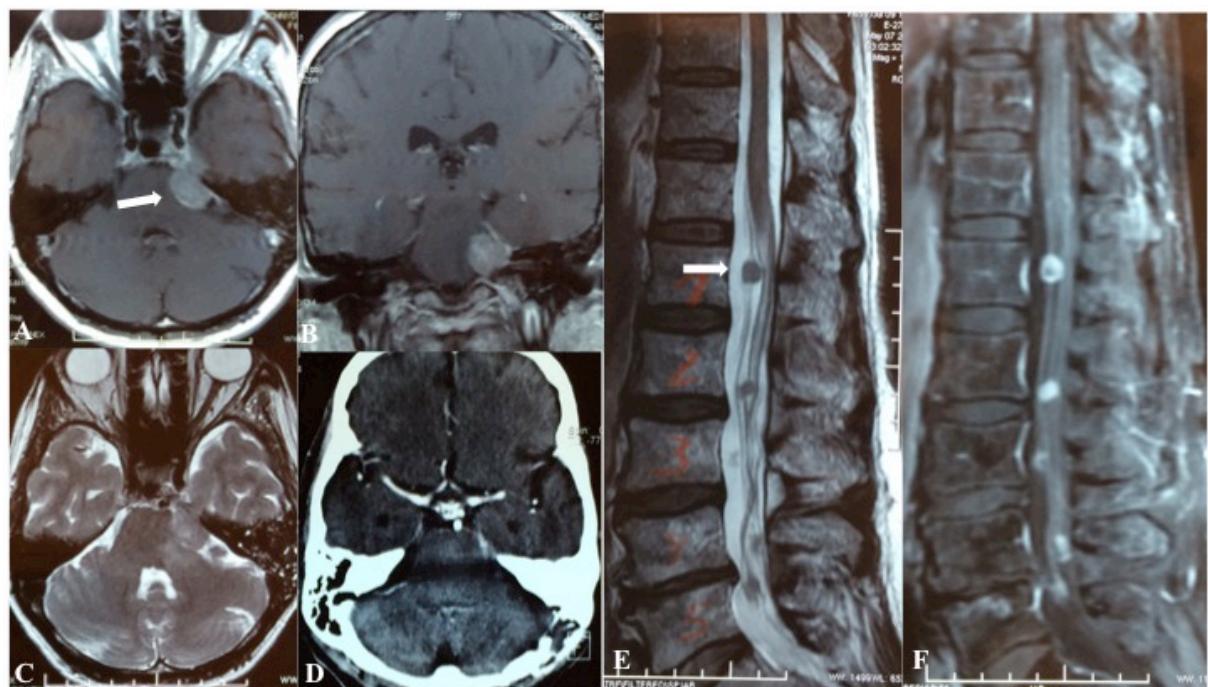


Figure 3:

