CNS metastasis secondary to malignant-mixed Müllerian tumor: case report and review of therapeutics

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This paper reviews CNS involvement secondary to malignant-mixed Müllerian tumor or uterine carcinosarcoma, a rare aggressive biphasic Müllerian tumor. We report a cerebellar metastasis with epithelial and mesenchymal components, demonstrating heterologous rhabdomyogenic and chondroblastic differentiation. The patient had undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy for palliation of symptomatic chemotherapy-resistant node-positive disease. CNS involvement is rare, and prognostically poor, and suggestively poorer in predominantly sarcomatous metastases. Multimodal therapy is indicated; in solitary metastases, surgical resection or stereotactic radiosurgery is included, followed by whole brain radiotherapy. In unresectable brain metastases, stereotactic radiosurgery and whole brain radiotherapy warrant consideration in up to 2–3 metastases. In multiple metastases, palliative steroid therapy or cranial irradiation may be considered. Combination or platinum-based chemotherapy (i.e., ifosfamide-paclitaxel or carboplatin-paclitaxel) is indicated in all stages, with a role in both disease cure and control-directed management. Targeted therapeutics have thus far not demonstrated significant clinical efficacy.

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Practice points

- Multimodal therapy is indicated in CNS involvement secondary to malignant-mixed Müllerian tumor, a rare aggressive biphasic Müllerian tumor.
- Complete surgical staging of the primary tumor/cytoreduction in advanced stage, including retroperitoneal lymphadenectomy in Stage I–III, confers a survival benefit.
- In solitary CNS metastases, surgical resection or stereotactic radiosurgery is indicated, as dependent on lesion location and overall prognosis, followed by whole brain radiotherapy.
- In unresectable CNS metastases, stereotactic radiosurgery and whole brain radiotherapy warrant consideration in up to 2–3 metastases.
- In multiple CNS metastases, palliative steroid therapy and cranial irradiation may be considered.
- Combination or platinum-based chemotherapy (i.e., ifosfamide-paclitaxel or carboplatin-paclitaxel) is indicated in all stages as tolerated, with a role in both disease cure and control-directed management.
- Targeted therapeutics have thus far not demonstrated significant clinical efficacy.
- Future therapeutic strategies should incorporate as yet unpublished data from trials ascertaining optimal adjuvant therapy, including the GOG 261 (i.e., noninferiority of carboplatin-paclitaxel vs the more poorly tolerated ifosfamide-paclitaxel).

CNS involvement secondary to malignant-mixed Müllerian tumors (MMMT), also known as uterine carcinosarcoma (UCS), is very rarely described. Five intracranial, one spinal and two mixed intracranial-spinal cases have been published to date [1–6].

We report the following case of a right cerebellar lesion diagnosed as an MMMT with epithelial (high-grade serous and squamous carcinoma) and mesenchymal components, with readily identifiable heterologous myogenic (rhabdomyosarcoma) and chondroblastic (chondrosarcoma) differentiation. The patient had undergone total abdominal hysterectomy, bilateral salpingo-oophorectomy (TAH BSO) for chemotherapy-resistant node-positive disease diagnosed 15 months previously. In addition, we summarize the contemporary literature and therapeutic strategies.

Mixed Müllerian tumor refers to a neoplasm comprising of both epithelial and mesenchymal tissues of Müllerian (paramesonephric duct) origin, in other words, uterus, ovaries, Fallopian tubes and upper a third of the vagina. The MMMT is a subclassification for rare and aggressive biphasic neoplasms comprising of both epithelial (carcinomatous) and mesenchymal (sarcomatous) components [7]. Two subtypes exist based on the sarcomatous component differentiation being: homologous (i.e., uterine tissue) or heterologous (i.e., nonuterine) [7]. Predominantly, it is the epithelial component that metastasizes and recurs [8].

MMMT represents 4.3% of uterine corpus malignancies while accounting for 15% of deaths [7]. Typically, MMMT has a worse prognosis and is more aggressive than stage III endometrial carcinoma, with 5-year overall survival (OS) of 50% in stage I disease, while median survival is 2 years [7,9]. Risk factors for MMMT may include increased estrogen levels, black race, nulliparity, prolonged Tamoxifen use and pelvic irradiation, while the oral contraceptive pill is protective [8].

Search methods

The search strategy employed was a systematic search of PubMed and Medline (1966 to present). Subsequent hand-searching of bibliographies of existing literature/reviews, neurosurgical conference proceedings and contact with field experts was carried out to ensure capture of all existing cases. The electronic search took place in March 2017. All languages were included and dates of reference (1966 to present) defined.

Three concepts were searched to capture case reports, with explosion of MeSH terms to map searches. The first search exploded MeSH heading 'mixed tumor, mullerian' with explosion of terms to map search, in other words, 'MMMT,' 'UCS' – among others. The second search exploded the term 'metastasis' – among others. The third search exploded the term 'brain' or 'spine' or 'central nervous system' and used the terms 'brain tumor,' 'brain neo-plasm' – among others. Terms for each of the three searches were connected through Boolean operator 'OR.' Concepts were combined using the Boolean operator 'AND.' Abstracts were screened to ensure relevance.

Noncase report material was captured using PubMed search builder using MeSH term 'mixed tumor, Mullerian' included exploded terms as restricted to MeSH major topic on initial search, followed by secondary re-expansion with inclusion of defined subheadings 'cytology,' 'diagnosis,' 'diagnostic imaging,' 'drug therapy,' 'epidemiology,' 'etiology,' 'genetics,' 'mortality,' 'pathology,' 'physiopathology,' 'radiotherapy,' 'secondary,' 'surgery' and 'therapy' restricted to 'review' and review bibliography hand-searches as appropriate.

Case

A 74-year-old woman presented in March 2017 with a 5-week history of nausea, headache and unsteady gait on a background of an MMMT diagnosed in November 2015.

She reported nausea and vomiting for 1 week, and a 5-week history of morning headache and unsteady gait. Relatives also reported mild confusion. Neurological examination was significant only for mild gait ataxia.

The patient's history was significant for Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stage 4, peritoneal node-positive MMMT. This had presented with postmenopausal bleeding in July 2015, grossly abnormal endometrium on hysteroscopy and was biopsied in November 2015. Histological examination demonstrated fragments of high-grade serous carcinoma only.

She proceeded to neoadjuvant chemotherapy as first line with consideration for interval debulking surgery. Surgery was not performed as primary treatment due to the initial impression the patient was suffering from stage 4 disease with nodal involvement of the peritoneum and transverse colon. Radiotherapy was not performed as this would have targeted local disease in the pelvis and was deemed not to confer OS benefit in this case. Chemotherapy comprised six cycles of paclitaxel and carboplatin from January to June 2016.

Figure 1. MRI brain (T2-TSE-TRA-448) depicting a 4.3 cm × 4.2 cm enhancing solid/cystic mass.

The patient demonstrated partial response following three cycles of chemotherapy. An April PET computed tomography (CT) demonstrated response with marked interval reduction in size and degree of fluorodeoxyglucose (FDG) accumulation in the large endometrial mass while metastatic adenopathy had markedly diminished in size, with no significant residual FDG accumulation within the nodes. However, by completion of six full cycles of chemotherapy, while there appeared to be no extrauterine disease on PET CT, this demonstrated increased uterine bulk and FDG uptake and the patient was symptomatic with vaginal bleeding. Surgery was then performed on the basis that there was no surface disease at diagnostic laparoscopy, and the patient underwent TAH BSO for palliation and symptom control in August 2016.

Histological examination demonstrated a pT3a endometrial high-grade serous-type carcinoma with sarcomatous foci (MMMT), without definite heterologous elements. Subsequent serial PET CT whole body demonstrated no disease recurrence or metastatic disease.

CT brain on presentation in February 2017 demonstrated a right cerebellar lesion with central low attenuation and peripheral enhancement consistent with a cerebellar metastasis. CT TAP (Thorax Abdomen Pelvis) found no evidence of metastatic or recurrent disease in the thorax, abdomen or pelvis. MRI reported a 4.3 cm × 4.2 cm enhancing solid/cystic mass within the right cerebellar hemisphere (see Figure 1). The solid component of the mass posteriorly demonstrated marked nodular enhancement with no restricted diffusion. There was associated moderate perilesional oedema, moderate mass effect on the fourth ventricle and no associated hydrocephalus. There was a mild 4 mm descent of the right cerebellar tonsil. A possible small second lesion was noted within the left cerebellum measuring 5 mm.

The patient underwent stereotactic right cerebellar craniotomy and resection of the right cerebellar lesion. No postoperative complications or neurological deficits were experienced and the patient returned to baseline. Postoperative MRI reported complete excision of the right cerebellum hemisphere lesion. Postcontrast, a tiny dot of enhancement was noted in the left cerebellar hemisphere, which will be followed up on subsequent imaging. The patient proceeded to Whole Brain Radiotherapy (WBRT).

Histological examination demonstrated metastatic carcinosarcoma (MMMT) with epithelial (high-grade serous and squamous carcinoma) and mesenchymal components, with readily identifiable heterologous myogenic (rhabdomyosarcoma) and chondroblastic (chondrosarcoma) differentiation, consistent with origin from the patient's known endometrial primary.

Discussion

Cases

There are eight cases of CNS involvement including our case: five of cerebral involvement only, one case of spinal involvement only and two cases of mixed cerebral-spinal disease (see Table 1). Five cases demonstrated predominantly sarcomatous differentiation of the metastases, two were epithelial predominant while one showed

Table 1. CNS involvement in malignant-mixed Müllerian tumor, reported cases and characteristics.

Study (year)	Age, year (interval between primary diagnosis and CNS metastasis, months)	Predominant pathologic differentiation of metastasis	Cerebral involvement	Lesion location	Surgical resection	Spinal involvement	Lesion location	Surgical resection	Adjuvant therapy	Long-term follow-up (months)	Deceased at long-term follow-up	Ref.
This study – Healy <i>et al.</i> (2017)	73 (+15)	Sarcomatous	Y	Right cerebellar	Y	N	–	–	RT	2	N	
Könnecke <i>et al.</i> (2016)	66 (+14)	Epithelial	Y	Extra-axial infratentorial	Y	Y	Intradural cauda/conus medullaris	N	RT/CT	24	Y	[6]
Könnecke <i>et al.</i> (2016)	55 (+3)	Sarcomatous	Y	Left temporal; two small frontal	Y	NA	NA	NA	RT/CT	3	Y	[6]
Stienen <i>et al.</i> (2013)	66 (+6)	NA	NA	NA	NA	Y	Intramedullary C2	Y	N	36	N	[5]
Kim <i>et al.</i> (2009)	57 (+0)	Sarcomatous	Y	Cerebellar	Y	NA	–	–	N	2	Y	[4]
N'Kaza <i>et al.</i> (2005)	61 (+0)	Sarcomatous	Y	Multiple	N	N	–	–	RT	3	Y	[3]
Cormio <i>et al.</i> (1997)	48 (+1)	Sarcomatous	Y	Multiple	N	Y	Epidural T10-L1	Y	N	1	Y	[2]
Iqbal and Ironside (1993)	51 (+7)	Epithelial, cartilage	Y	Left frontal	Y	N	–	–	RT	25	N	[1]

CT: Chemotherapy; N: No; NA: Not applicable; RT: Radiotherapy; Y: Yes.
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no predominance. Median age at diagnosis of primary disease was 59 years, while median interval to presentation with CNS involvement was 4.5 months. Median survival prior to our case was 3 months, however, existing cases support an association between known sarcomatous predominance of the metastasis and shorter OS; median <2.5 months.

Clinical

MMMT typically arises in postmenopausal women, median age 70, as a bulky polypoidal mass with large areas of hemorrhage and necrosis, deeply invading the myometrium and presenting with postmenopausal bleeding, abdominal mass and pain [8]. It presents with extrauterine disease in 35–60%, with recurrence in over 50% despite surgery and adjuvant therapy, even in apparently confined disease [8,9]. High recurrence rates are associated with depth of myometrial invasion, lymphovascular invasion, involvement of the serosa and adnexae, in addition to positive cytology [7]. CNS involvement is rare and carries a poor prognosis. A reported case and extrapolated endometrial carcinoma data suggest that gynecological primaries warrant consideration in the work-up of metastatic CNS disease of unknown primary [10].

Pathogenesis

MMMT is a biphasic malignant neoplasm with carcinomatous and sarcomatous components, subtyped based on the sarcomatous component differentiation being either: homologous, (i.e., uterine tissue); or heterologous (i.e., nonuterine) [7]. MMMTs were previously considered sarcomas, with debate as to their origin, however, immunohistochemistry, molecular studies and clinical behavior – including response to chemotherapy – support reclassification under the revised FIGO 2009 as metaplastic carcinomas. The widely accepted ‘metaplastic monoclonal or conversion theory’ describes formation by metaplastic transformation of epithelial elements of monoclonal origin, thus better classifying them as dedifferentiated endometrial carcinomas or metaplastic carcinomas [7,8,11]. However, while most MMMTs are monoclonal in origin, studies do report a small cohort of tumors with distinct biclonal origin [12,13]. Notably, newer transdifferentiation theories including epithelial-mesenchymal transition and mesenchymal-epithelial transition suggest a phenotypic plasticity, whereby cancers may transdifferentiate or

Figure 2. Composite image. Clockwise from top left: **(A)** Morphologically heterogeneous tumor with carcinomatous (blue arrow) and sarcomatous (yellow arrow) components. Carcinoma predominantly high-grade serous carcinoma with glandular, tubular and papillary pattern. Focally positive for PAX-8 immunohistochemical stain (inset). **(B)** Carcinoma component showing focal squamous differentiation – cells with abundant eosinophilic/clear cytoplasm and distinct cell membranes. Positive for cytokeratin 5/6 immunohistochemical stain (inset). **(C)** Sarcomatous component showing focal chondroblastic differentiation (i.e., chondrosarcoma). **(D)** Many cells within the sarcomatous component demonstrated eosinophilic ‘rhabdoid’ cytoplasmic inclusions (arrows) – consistent with rhabdomyoblasts. Many sarcomatous cells showed strong nuclear positivity with myogenin (specific skeletal muscle marker), (inset, lower inner). Large areas of the sarcomatous component were strongly positive for desmin (muscle marker), (inset, lower outer).

interconvert between phenotypes, generating cells with more invasive or metastatic potential, explaining histological duality and aggressiveness [7,14]. Evidence suggests that the carcinomatous component drives aggression, and disputes the influence of heterologous elements as determining behavior [8].

In primary tumors, most commonly only a single epithelial and single sarcomatous component is found, while homologous differentiation is most common [7]. Typically, the most common epithelial component is a serous or endometrioid carcinoma, while the most common sarcomatous heterologous differentiation is rhabdomyosarcoma, followed by chondrosarcoma [7].

Extrauterine metastasis usually comprises mostly, although not exclusively, carcinomatous elements [7,8]. However, of reported CNS metastases, five metastases were predominantly sarcomatous, two were epithelial, while one showed no predominance. Carcinomatous elements typically exhibit lymphatic nodal spread, while sarcomatous components frequently metastasize to the peritoneum and hematogenously [7].

We report a metastatic MMMT with epithelial (high-grade serous and squamous carcinoma) and mesenchymal components, with readily identifiable heterologous myogenic (rhabdomyosarcoma) and chondroblastic (chondrosarcoma) differentiation – see Figure 2.

Microscopic examination demonstrated fragments of a malignant neoplasm with heterogeneous morphology, composed of in part by foci of high-grade serous and squamous cell carcinoma (positive for PAX8 and CK5/6, respectively) and predominated by sheets and fascicles of spindled cells with atypical hyperchromatic nuclei and rather elongated cytoplasmic processes. Several cells had relatively abundant eosinophilic ‘inclusion like’ cytoplasm,

some with recognizable cytoplasmic whorls or cross striations, consistent with rhabdomyoblasts (positive for desmin, myoglobin and MYF4). In some areas, occasional tumor cells were seen to be embedded within clear lacunar spaces and associated with a pale chondro-myxoid matrix, consistent with heterologous chondroblastic differentiation.

Surgery & radiotherapy

International guidelines favor multimodality treatment as a high-risk, nonendometrioid cancer similar to serous or clear cell carcinoma, with evidence largely extrapolated from carcinoma and sarcoma trials [9]. Complete surgical staging (hysterectomy, bilateral salpingo-oophorectomy, lymphadenectomy, cytoreduction and consideration for cytology and omental biopsy) demonstrates a survival benefit, including cytoreduction in advanced-stage disease [8,15]. Retroperitoneal lymphadenectomy is indicated; both for demonstrating a survival benefit in Stage I–III, and in upstaging disease in 20% of apparently confined diseases [16,17]. However, lomboarctic lymphadenectomy lacks sufficient evidence, risking lymphedema in the context of low loco-regional recurrence rates (<10%) [8,17].

Studies suggest some response to adjuvant radiation therapy versus surgery alone in achieving local control for Stage I–II pelvic disease, however, no improvement in OS or progression-free survival (PFS) [18,19]. A study comparing whole abdominal irradiation versus chemotherapy found no statistical difference in recurrence or survival, however, small differences favored combination chemotherapy [20]. A 2013 Cochrane review of adjuvant therapies finds no improved survival from the addition of radiotherapy in advanced disease [21].

In favor of pelvic irradiation in select patients, a small trial ($n = 31$) suggests improved outcomes in those with adverse histologic risk factors, while a 2015 review favors consideration of radiotherapy in individualised cases [8,22]. Notably three large Gynecologic Oncology Group (GOG) trials (GOG 249, GOG 261 and GOG 86P) are ongoing to assess optimal adjuvant therapy, including the inclusion of brachytherapy [8].

In CNS metastases, a paucity of cases precludes an evidence-based standard of care, instead favoring individualized therapy with extrapolation of principles. The few reported MMT cases suggest resection is indicated for symptomatic disease, in line with standard neurosurgical principles, as dependent on lesion number, location and overall prognosis. Standard neurosurgical principles, not specific to MMT, find that in solitary CNS metastases, OS, performance status and local control are increased by surgery or stereotactic radiosurgery (SRS) and WBRT, versus WBRT alone [23,24]. In unresectable brain metastasis, SRS and WBRT warrant consideration in 2–3 metastases [25]. Finally in multiple metastases, palliative steroid or radiotherapy is usually favored [26].

This approach is supported by extrapolation of data with similarity to MMT, including studies in endometrial carcinoma with CNS involvement, finding a survival benefit in surgical resection or stereotactic radiosurgery, followed by WBRT and/or chemotherapy, superior to WBRT alone [10]. Similarly a case series in serous carcinoma, which demonstrates a similar clinical behavior to MMT, favors multimodal therapy for CNS metastases [27]. Of course, the authors acknowledge that these are not true comparators of MMT, and ideally clinical trials would best determine therapy. In MMT, all reported cases with solitary CNS lesions underwent resection, while those with multiple cerebral metastases did not. Adjuvant radiotherapy alone was utilized in two CNS involvement cases, while two other patients underwent chemoradiotherapy. Cranial irradiation as a palliative measure warrants consideration in CNS involvement [3,26].

Chemotherapy & targeted therapy

The Gynaecology Oncology Group have conducted most trials in MMT, finding in favor of combination adjuvant chemotherapy in all stages. Adjuvant chemotherapy is indicated in even early disease, increasing PFS in FIGO stage I–II disease, and increased OS except in cases of lymphovascular invasion [28].

Single-agent regimens demonstrated a response rate (RR) sufficient to warrant further trials, most notably ifosfamide (36%), paclitaxel (18%) and carboplatin (18%) [29–31]. This led to combination therapies, with ifosfamide-paclitaxel demonstrating increased PFS and OS over ifosfamide monotherapy: ifosfamide monotherapy PFS-OS (3.6–8.4 months) versus ifosfamide-paclitaxel PFS-OS (5.8–13.5 months) [32]. In contrast, the ifosfamide-cisplatin combination demonstrates significant toxicity, and while it increases RR versus ifosfamide monotherapy (54 vs 36%), it does not increase OS with statistical significance: PFS-OS (6–9.4 months) [29]. Carboplatin-paclitaxel has found favor as a well-tolerated combination avoiding the toxicity of ifosfamide, and demonstrates a RR of up to 62%, and complete response of 13%: PFS-OS (7.6–14.7 months) [33,34]. A prospective noninferiority Phase III study, the GOG 261, has not yet released results of randomized ifosfamide-paclitaxel versus carboplatin-paclitaxel. In recurrence postchemotherapy, the GOG 230 demonstrates a poor prognosis with a 5% RR and 6-month PFS

of 15%. A small trial added pegylated liposomal doxorubicin to carboplatin-paclitaxel, demonstrating a 62% RR and PFS-OS (8.2–16.4 months) [35].

In clinical trials for CNS metastases from lung cancer, cisplatin-paclitaxel and carboplatin-paclitaxel regimens have both demonstrated intracranial RRs comparable to systemic RRs, despite limited CNS penetrance [36–38]. This suggests a meaningful role for platinum-based chemotherapy in the treatment of MMMT.

Trials of targeted therapeutics have thus far not successfully tackled identified mutations in MMMT including: PARP-1 overexpression, ErbB-2 (Her2/Neu) amplification, VEGF expression (100% epithelial and 93% mesenchymal components) and PIK3CA/AKT pathway aberrations. The addition of iniparib (PARP-1 inhibitor) to cisplatin-paclitaxel does further increase RR [34]. Similarly, aflibercept (VEGF trap), ridaforolimus (mTOR/Rapamycin inhibitor) and Tyrosine Kinase Inhibitors (TKIs) sorafenib, imatinib and pazopanib all demonstrate minimal activity [39–43]. Her2-directed Trastuzumab-EM-Tansine has demonstrated efficacy in MMMT cell lines, however, awaits clinical application [44].

Conclusion

MMMT/UCS is a rare and aggressive tumor carrying a poor prognosis for recurrence and metastasis. Acknowledging MMMT as a metaplastic carcinoma with dedifferentiated component, rather than a sarcoma, has led to more focused clinical trials and therapies. We report a metastatic MMMT demonstrating heterologous myogenic (rhabdomyosarcoma) and chondroblastic (chondrosarcoma) differentiation. CNS involvement secondary to MMMT is rare and carries a poor prognosis. The few reported cases suggest a poorer survival in predominantly sarcomatous metastases. Gynecological primaries warrant consideration in the work-up of metastatic CNS disease of unknown primary. Multimodal therapy is indicated; in solitary metastases, surgical resection or SRS is included, followed by WBRT. In unresectable brain metastases, SRS and WBRT warrant consideration in up to 2–3 metastases. In multiple metastases, palliative steroid therapy or cranial irradiation may be considered. Combination or platinum-based chemotherapy (i.e., ifosfamide-paclitaxel or carboplatin-paclitaxel) is indicated in all stages, with a role in both disease cure and control-directed management. Targeted therapeutics have thus far not demonstrated significant clinical efficacy.

Future perspective

In terms of future perspectives, the treatment of MMMT can be expected to develop over the coming years. Firstly, the results of the prospective noninferiority Phase III study, the GOG 261, is anticipated to release results of randomized ifosfamide-paclitaxel versus carboplatin-paclitaxel chemotherapy. Secondly, in terms of targeted therapeutics, the more refined molecular stratification of tumours beyond established targets may yield more favourable results in terms of individualised and targeted therapeutics. As discussed, Her2-directed Trastuzumab-EM-Tansine has demonstrated efficacy in MMMT cell lines, however, awaits clinical application, and may prove promising. Finally, the evolving role of immunotherapy in intracranial tumours holds great therapeutic potential, such as research into the use of dendritic cell immunotherapy for solid tumours or glioma [45,46,47,48]. Future therapeutic strategies incorporating advances in such areas may yield considerable therapeutic gains over the next 5 to 10 years.

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