



CASE REPORT

Cauda equina syndrome in an ovarian malignant-mixed müllerian tumor with leptomeningeal spread

Joshua D. Bernstock¹  | Stuart Ostby² | Brandon Fox³  | Houman Sotoudeh⁴ | Andrew Janssen³ | Yun Jee Kang⁵ | Jason Chen⁶ | Veeranjanyulu Prattipati⁴ | Galal Elsayed⁷ | Gustavo Chagoya⁷ | Daisuke Yamashita¹ | Gregory K. Friedman⁸ | Burt Nabors⁹ | Warner K. Huh² | Mina Lobbous⁹

¹Department of Neurosurgery, Brigham and Women's Hospital, Harvard University, Boston, MA, USA

²Division of Gynecologic Oncology, University of Alabama at Birmingham, Birmingham, AL, USA

³School of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA

⁴Department of Radiology, Neuroradiology Section, University of Alabama at Birmingham, Birmingham, AL, USA

⁵Harvard Medical School, Boston, MA, USA

⁶Medical Scientist Training Program, University of California, Los Angeles, CA, USA

⁷Department of Neurosurgery, University of Alabama at Birmingham, Birmingham, AL, USA

⁸Division of Pediatric Hematology and Oncology, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL, USA

⁹Department of Neurology, University of Alabama at Birmingham, Birmingham, AL, USA

Correspondence

Joshua D. Bernstock, Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, Hale Building, 60 Fenwood Road, Boston, MA 02115.

Email: jbernstock@partners.org

Mina Lobbous, Department of Neurology, University of Alabama at Birmingham, 1802 6th Ave S, Birmingham, AL 35233. Email: mlobbous@uabmc.edu

Abstract

Leptomeningeal metastasis is extremely rare in patients with ovarian cancer, but should be considered in patients presenting with neurologic deficits such as cauda equine syndrome. Given its poor prognosis and lack of data currently on management, additional studies are needed to optimize treatment regimens and improve outcomes.

KEYWORDS

cauda equina syndrome, leptomeningeal carcinomatosis, metastasis, ovarian carcinosarcoma, ovarian malignant-mixed müllerian tumor

1 | INTRODUCTION

Ovarian cancer is the most common cause of mortality among women with gynecologic malignancies and the fifth leading cause of death in all women.¹⁻³ Ovarian cancer is comprised of a diverse group of tumors that arise from multiple cell types and anatomical sites.⁴ Epithelial-derived tumors represent ~90% of ovarian cancers and are classified based upon

cellular histology as well as clinical and pathologic profiling.^{3,5} The majority of epithelial ovarian cancer cases are diagnosed at stage III or IV, and 5-year overall survival is less than 50%.³ Rarely, primary ovarian cancer can be made up of both malignant epithelial and mesenchymal components, and these tumors, termed ovarian malignant-mixed müllerian tumor (OMMT), or alternately known as ovarian carcinosarcomas, are highly malignant and carry a poor prognosis.⁶

Joshua D. Bernstock and Stuart Ostby contributed equally to this work.

Warner K. Huh and Mina Lobbous jointly supervised this work.

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Central nervous system (CNS) metastasis is uncommon in ovarian cancer and occurs in approximately 1% of patients.^{7,8} Leptomeningeal metastatic disease (LMD) is a rare pattern of CNS metastasis most commonly involving the basal cisterns, posterior fossa, and cauda equina.⁹ While LMD may present with focal symptoms, most frequently patients experience nonspecific symptoms including confusion, nausea, and headache. When the cauda equina is widely affected, cauda equina syndrome may result and be the first presenting symptom indicating CNS metastasis.^{10,11}

Herein, we describe a case of OMMMT with LMD presenting with cauda equina syndrome and review the clinical course, neuroradiological findings, and pertinent literature.

2 | CASE

A 62-year-old postmenopausal female who was otherwise healthy presented with an adnexal mass measuring 11 × 8 × 9 cm and recurrent fevers. Computerized tomography (CT) imaging demonstrated a right adnexal mass with ascites, a separate cystic pelvic mass, and intraparenchymal liver lesions concerning for advanced ovarian cancer. Initial CA125 was 1480, and her albumin was 3.1. Given her diminished nutritional status and normal performance status, laparoscopic biopsies were performed with a preliminary diagnosis of metastatic high-grade serous carcinoma. She underwent genetic counseling and testing, which was negative for Lynch syndrome; she declined BRCA 1 and 2 testing. Next-generation sequencing of the tumor identified somatic mutations in *FGFR1*, *TP53*, and *ZNF703*.

Neoadjuvant chemotherapy followed by interval debulking surgery was recommended and the patient participated in clinical trial GOG 3005 (NCT02470585). Following randomization, she was treated in the control arm with paclitaxel and carboplatin without veliparib. While receiving neoadjuvant chemotherapy, she suffered a deep venous thrombosis (DVT) and underwent anticoagulation and placement of an IVC filter. After cycle four, she underwent radical cytoreduction with exploratory laparotomy, hysterectomy, bilateral salpingo-oophorectomy with removal of bilateral adnexal masses, and pelvic peritonectomy, and was found to have miliary carcinoma of small bowel mesentery, right hemidiaphragm, and gastrocolic ligament. Estimated resection was subtotal with removal of ~90% percent of visualized disease. After an uncomplicated postoperative course, her IVC filter was removed. After cycle five, she had a biochemical increase in CA125 leading to discontinuation in the clinical trial due to possible progression of disease.

The patient was transitioned to a nonplatinum doublet consisting of doxorubicin and bevacizumab. She displayed symptomatic improvement and an objective response by RECIST criteria despite an increasing CA125 after eight

cycles. Due to the discrepancy, positron-emission tomography (PET)/CT was utilized and demonstrated fluorodeoxyglucose (¹⁸F]FDG) activity in the right humerus and bilateral femurs consistent with metastatic disease for which the patient was asymptomatic. Given partial response to retesting with platinum, she transitioned to rucaparib for maintenance therapy. This was continued until developing progression with carcinomatosis after three months.

Operative laparoscopy was repeated with biopsies and followed by intraperitoneal cisplatin therapy for six cycles. Next-generation sequencing of repeat tumor biopsies demonstrated microsatellite stability without new targetable therapies. Following her sixth cycle of intraperitoneal cisplatin, she had progressive hepatic disease and a new right axillary mass. In the absence of alternative therapies, she sought use of immunotherapy with pembrolizumab.

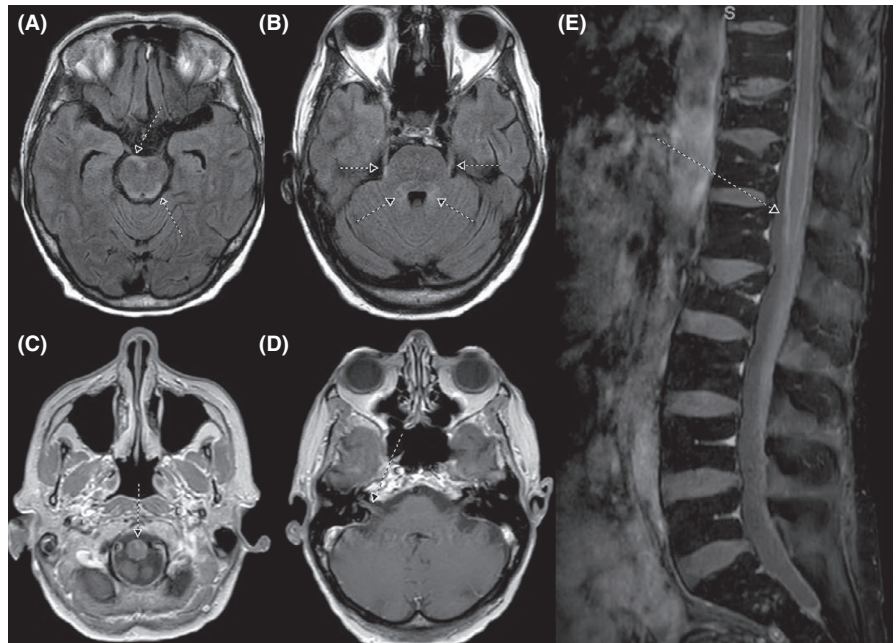
After 18 months from original diagnosis, she developed difficulty voiding and was concerned about a possible urinary tract infection. Her intraperitoneal port was removed, and she started on pembrolizumab. Following cycle one she was directly admitted to the hospital from home due to acute urinary retention, gait imbalance, headache, vision changes, and a CT scan which demonstrated a lesion in her right temporal lobe. Her urinary retention was relieved via the placement of a catheter, and she subsequently underwent magnetic resonance imaging (MRI) of the brain and spine which demonstrated leptomeningeal enhancement of the ventral surface of the pons, right cerebral hemisphere, and the spinal cord (ie, from thoracic spine to the cauda equine; Figure 1). Of note, there was also enhancement of the trigeminal, facial, and vestibulocochlear cranial nerves.

The patient was continued on pembrolizumab and additionally treated with systemic high-dose methotrexate. Cerebrospinal fluid (CSF) analysis demonstrated increased leukocytes, macrophages, and protein with decreased glucose, with an opening pressure of 22 cm of H₂O; anti-Yo antibodies were negative, and the CSF cytology was positive for malignancy. She demonstrated no response to high-dose intrathecal (IT) methotrexate without change in cauda equina symptoms and ultimately decided to pursue hospice care.

3 | DISCUSSION

Ovarian malignant-mixed müllerian tumor, also referred to as carcinosarcoma of the ovary, is a very rare and aggressive histologic subtype typically presenting in older patients and at more advanced stages.¹² OMMMT is a neoplasm comprised of epithelial and mesenchymal tissues of müllerian (paramesonephric duct) origin. The complete pathobiology/pathogenesis of OMMMT remains unclear with immunologic studies supporting malignant elements as originating from a common epithelial stem cell as opposed to convergence of two separate malignancies.¹³ As a rare subtype

FIGURE 1 Axial FLAIR sequence shows mild FLAIR signal hyperintensity within the ventral aspect of pons, dorsal brainstem, along the trigeminal nerves, and surrounding the fourth ventricle (arrows, A and B). Axial postcontrast T1 sequence shows leptomeningeal enhancement around the upper cervical cord and enhancement along the right 7th and 8th nerves (arrows, C and D). Postcontrast sagittal fat suppression sequence shows mild leptomeningeal enhancement around the conus medullaris (arrow, E) with an incidental old compression deformity of the L2 vertebral body



of ovarian cancer which is partly of epithelial origin, the International Federation of Gynecology and Obstetrics (FIGO) staging system is used¹⁴ and platinum-based chemotherapy is recommended despite lower response rates.¹⁵⁻¹⁷ Overall survival is significantly lower with median survival of 4-14 months.^{18,19} Unlike uterine carcinosarcoma, lung, and other distant metastases are still uncommon, occurring in ~5% of patients diagnosed with OMMMT.^{18,20}

3.1 | Leptomeningeal disease in ovarian cancers

The common sites for metastasis from epithelial ovarian cancer include the abdomen, liver, and lungs; the metastases are typically spread by seeding of the peritoneal cavity, and only occasionally hematogenously. CNS metastasis in ovarian cancer is reported in approximately 1% of cases and typically localizes to the parenchyma; once in the CNS, metastatic disease can spread by direct seeding through the CSF. Leptomeningeal disease (LMD) is exceedingly rare.^{7,21,22} In a case series of 23 patients with CNS metastases from primary ovarian carcinoma,²³ only 1 patient was found to have LMD. A 2005 retrospective study of 1,450 patients with primary ovarian malignancies found CNS metastases in only 17 patients (ie, 1.17%) without a case of meningeal involvement.

The molecular understanding of OMMMT through next-generation whole-exome sequencing²⁴ has identified serous adenomatous components and shared alterations in *TP53* within high-grade serous tumors.²⁵ Generally, epithelial ovarian cancers are capable of inducing strong immune responses, highlighting the potential use of PD-1 and PD-L1 inhibitors in ovarian cancer²⁶⁻²⁹ with overall response rates ranging from 9.7% to 25%.

Leptomeningeal metastatic disease usually presents with symptoms of increased intracranial pressure, manifesting clinically as headaches, nausea, and/or vomiting; however, it may also cause focal neurologic deficits such as cranial nerve deficits, cerebellar symptoms, and/or cauda equine, as in our patient.^{30,31} Gadolinium-enhanced MRI of the neuroaxis may show increased enhancement in the leptomeninges, dura, cranial nerves, or cauda equina especially helpful in patients raising high suspicion of CNS metastasis and LMD. The gold standard in diagnosing LMD is the detection of malignant cells on CSF cytology; however, false-negative results may affect half of patients on initial lumbar puncture.³² Imaging should be performed prior to lumbar puncture whenever possible as lumbar puncture may occasionally produce false-positive signal intensity on gadolinium MRI.³⁰ The standard treatment of LMD, regardless of the tumor histology, includes palliative CSF diversion for hydrocephalus, radiation therapy, and either IT or systemic chemotherapy.³³ Median survival for LMD is generally from 8 to 16 weeks with standard interventions.³⁴⁻³⁷

Very limited information exists regarding LMD in patients with epithelial ovarian carcinoma. Once LMD has developed, prognosis is extremely poor with median survival of 60 days.³⁸⁻⁴⁷ Of note, new treatment regimens for ovarian cancers have increased survival time leading to new opportunity in treating CNS metastases.⁴⁸ Given the extreme rarity of LMD in ovarian cancers, there is no general consensus on the best treatment approach. Historically, treatment has focused on an IT chemotherapy and most commonly methotrexate has been used with or without whole-brain radiotherapy (WBRT).⁴⁴ Additional chemotherapeutic agents with appropriate CNS penetration

include cisplatin, systemic methotrexate, IT thiotepa, and IT topotecan.²¹ High-dose systemic methotrexate (8 g/m²) was studied in a prospective, nonrandomized cohort compared to IT methotrexate for treatment of LMD and favored systemic administration (survival 13.8 versus 2.3 months, $P = .003$). Most recently, systemic therapy with agents producing adequate CSF concentrations has been promoted as preferred therapy for LMD.^{49–51} Despite such advances prognosis remains dismal and more work is therefore required to advance treatment for patients in need.

4 | CONCLUSION

Ovarian malignant-mixed müllerian tumor with LMD presenting is extremely rare and remains clinically difficult to manage. Further studies and clinical trials examining novel therapeutics as well as combinations of therapies are needed to provide improvements in overall survival for ovarian patients with LMD.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

All authors participated in the clinical care of the patient and/or the drafting/revising of the manuscript.

ORCID

Joshua D. Bernstock  <https://orcid.org/0000-0002-7814-3867>

Brandon Fox  <https://orcid.org/0000-0003-2242-2477>

REFERENCES

- Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin*. 2010;60(5):277-300.
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69(1):7-34.
- Torre LA, Trabert B, DeSantis CE, et al. Ovarian cancer statistics, 2018. *CA Cancer J Clin*. 2018;68(4):284-296.
- Karnezis AN, Cho KR, Gilks CB, Pearce CL, Huntsman DG. The disparate origins of ovarian cancers: pathogenesis and prevention strategies. *Nat Rev Cancer*. 2017;17(1):65-74.
- Kurman RJ, Shih Ie M. The dualistic model of ovarian carcinogenesis: revisited, revised, and expanded. *Am J Pathol*. 2016;186(4):733-747.
- delCarmen MG, Birrer M, Schorge JO. Carcinosarcoma of the ovary: a review of the literature. *Gynecol Oncol*. 2012;125(1):271-277.
- Pectasides D, Aravantinos G, Fountzilias G, et al. Brain metastases from epithelial ovarian cancer. The hellenic cooperative oncology group (HeCOG) experience and review of the literature. *Anticancer Res*. 2005;25(5):3553-3558.
- Sanderson A, Bonington SC, Carrington BM, Alison DL, Spencer JA. Cerebral metastasis and other cerebral events in women with ovarian cancer. *Clin Radiol*. 2002;57(9):815-819.
- Wang N, Bertalan MS, Brastianos PK. Leptomeningeal metastasis from systemic cancer: Review and update on management. *Cancer*. 2018;124(1):21-35.
- Liu Y, Wang B, Qian Y, Di D, Wang M, Zhang X. Cauda equine syndrome as the primary symptom of leptomeningeal metastases from lung cancer: a case report and review of literature. *Onco Targets Ther*. 2018;11:5009-5013.
- Alkhotani A, Alrishi N, Alhalabi MS, Hamid T. Cauda equina syndrome secondary to leptomeningeal carcinomatosis of gastroesophageal junction cancer. *Case Rep Neurol*. 2016;8(1):87-91.
- Cantrell LA, Van Le L. Carcinosarcoma of the ovary a review. *Obstet Gynecol Surv*. 2009;64(10):673-680; quiz 697.
- Jin Z, Ogata S, Tamura G, et al. Carcinosarcomas (malignant müllerian mixed tumors) of the uterus and ovary: a genetic study with special reference to histogenesis. *Int J Gynecol Pathol*. 2003;22(4):368-373.
- Shepherd JH. Revised FIGO staging for gynaecological cancer. *Br J Obstet Gynaecol*. 1989;96(8):889-892.
- Bicher A, Levenback C, Silva EG, Burke TW, Morris M, Gershenson DM. Ovarian malignant mixed müllerian tumors treated with platinum-based chemotherapy. *Obstet Gynecol*. 1995;85(5 Pt 1):735-739.
- Inthasorn P, Beale P, Dalrymple C, Carter J. Malignant mixed müllerian tumour of the ovary: prognostic factor and response of adjuvant platinum-based chemotherapy. *Aust N Z J Obstet Gynaecol*. 2003;43(1):61-64.
- Sit AS, Price FV, Kelley JL, et al. Chemotherapy for malignant mixed Müllerian tumors of the ovary. *Gynecol Oncol*. 2000;79(2):196-200.
- Harris MA, Delap LM, Sengupta PS et al. Carcinosarcoma of the ovary. *Br J Cancer*. 2003;88(5):654-657.
- Chang J, Sharpe JC, A'Hern RP, et al. Carcinosarcoma of the ovary: incidence, prognosis, treatment and survival of patients. *Ann Oncol*. 1995;6(8):755-758.
- Barnholtz-Sloan JS, Morris R, Malone J, Munkarah A. Survival of women diagnosed with malignant, mixed müllerian tumors of the ovary (OMMMT). *Gynecol Oncol*. 2004;93(2):506-512.
- Miller E, Dy I, Herzog T. Leptomeningeal carcinomatosis from ovarian cancer. *Med Oncol*. 2012;29(3):2010-2015.
- Krupa M, Byun K. Leptomeningeal carcinomatosis and bilateral internal auditory canal metastases from ovarian carcinoma. *Radiol Case Rep*. 2017;12(2):386-390.
- Cormio G, Maneo A, Parma G, Pittelli MR, Miceli MD, Bonazzi C. Central nervous system metastases in patients with ovarian carcinoma. A report of 23 cases and a literature review. *Ann Oncol*. 1995;6(6):571-574.
- Zhao S, Bellone S, Lopez S, et al. Mutational landscape of uterine and ovarian carcinosarcomas implicates histone genes in epithelial-mesenchymal transition. *Proc Natl Acad Sci U S A*. 2016;113(43):12238-12243.
- Ardighieri L, Mori L, Conzadori S, et al. Identical TP53 mutations in pelvic carcinosarcomas and associated serous tubal intraepithelial carcinomas provide evidence of their clonal relationship. *Virchows Arch*. 2016;469(1):61-69.

26. Hamanishi J, Mandai M, Ikeda T, et al. Safety and antitumor activity of anti-PD-1 antibody, nivolumab, in patients with platinum-resistant ovarian cancer. *J Clin Oncol*. 2015;33(34):4015-4022.
27. Le Roux PD, Jardine DS, Kanev PM, Loeser JD. Pediatric intracranial pressure monitoring in hypoxic and nonhypoxic brain injury. *Childs Nerv Syst*. 1991;7(1):34-39.
28. Toft E, Sinkjaer T, Rasmussen A. Stretch reflex variation in the relaxed and the pre-activated quadriceps muscle of normal humans. *Acta Neurol Scand*. 1991;84(4):311-315.
29. Mittica G, Genta S, Aglietta M, Valabrega G. Immune Checkpoint inhibitors: a new opportunity in the treatment of ovarian cancer? *Int J Mol Sci*. 2016;17(7):1169.
30. DeAngelis LM. Current diagnosis and treatment of leptomeningeal metastasis. *J Neurooncol*. 1998;38(2-3):245-252.
31. Chamberlain MC. Neoplastic meningitis. *Oncologist*. 2008;13(9):967-977.
32. Glass JP, Melamed M, Chernik NL, Posner JB. Malignant cells in cerebrospinal fluid (CSF): the meaning of a positive CSF cytology. *Neurology*. 1979;29(10):1369-1375.
33. Jaeckle KA. Neoplastic meningitis from systemic malignancies: diagnosis, prognosis and treatment. *Semin Oncol*. 2006;33(3):312-323.
34. Gleissner B, Chamberlain MC. Neoplastic meningitis. *Lancet Neurol*. 2006;5(5):443-452.
35. Jaeckle KA, Phuphanich S, Bent MJ, et al. Intrathecal treatment of neoplastic meningitis due to breast cancer with a slow-release formulation of cytarabine. *Br J Cancer*. 2001;84(2):157-163.
36. Chamberlain MC, Kormanik P. Carcinoma meningitis secondary to non-small cell lung cancer: combined modality therapy. *Arch Neurol*. 1998;55(4):506-512.
37. Chamberlain MC, Kormanik PR. Carcinomatous meningitis secondary to breast cancer: predictors of response to combined modality therapy. *J Neurooncol*. 1997;35(1):55-64.
38. Stein M, Steiner M, Ben-Schachar M. Leptomeningeal involvement by epithelial ovarian carcinoma: a case report. *Gynecol Oncol*. 1987;27(2):241-245.
39. Murthy LK, Chandrashekar HR, Hiremath SS, Shashikala P, Arun KN. Meningeal carcinomatosis complicating ovarian malignancy. *J Assoc Physicians India*. 1991;39(10):773-774.
40. Delord JP, Fizazi K, Hajj M, Pautier P, Lhommé C. Isolated leptomeningeal metastasis from ovarian carcinoma: an unusual event. *Eur J Cancer*. 1998;34(5):758-759.
41. Ohta H, Koyama R, Nagai T, Hirayama Y, Saito S, Yonesaka A. Meningeal carcinomatosis from an ovarian primary with complete response to adjuvant chemotherapy after cranial irradiation. *Int J Clin Oncol*. 2001;6(3):157-162.
42. Melichar B, Tomsová M, Reháč S, Malířová E, Simonová G. Meningeal carcinomatosis as a late complication of brain metastases of epithelial ovarian carcinoma. *Eur J Gynaecol Oncol*. 2008;29(4):402-404.
43. Jackson P. Carcinomatous meningitis associated with carcinoma of the ovary. *Case report. Br J Obstet Gynaecol*. 1984;91(8):824-825.
44. Gordon AN, Kavanagh JJ, Wharton JT, Rutledge FN, Obbens E, Bodey GP. Successful treatment of leptomeningeal relapse of epithelial ovarian cancer. *Gynecol Oncol*. 1984;18(1):119-124.
45. Behnam K, Aguilera AJ, Kornfeld M, Jordan SW, Hilgers RD. Meningeal carcinomatosis from an ovarian primary: a clinicopathologic study. *Gynecol Oncol*. 1984;19(1):104-109.
46. Bakri YN, Lee JH, Lewis GC, Lublin FD, Danoff B. Meningeal carcinomatosis complicating gynecologic malignancies: a literature review and report of a case. *Obstet Gynecol Surv*. 1983;38(1):1-5.
47. Mayer RJ, Berkowitz RS, Griffiths CT. Central nervous system involvement by ovarian carcinoma: a complication of prolonged survival with metastatic disease. *Cancer*. 1978;41(2):776-783.
48. Zibetti Dal Molin G, et al. Response to pembrolizumab in a heavily treated patient with metastatic ovarian carcinosarcoma. *Gynecol Oncol Res Pract*. 2018;5:6.
49. Grant R, Naylor B, Greenberg HS, Junck L. Clinical outcome in aggressively treated meningeal carcinomatosis. *Arch Neurol*. 1994;51(5):457-461.
50. Boogerd W, van den Bent MJ, Koehler PJ, et al. The relevance of intraventricular chemotherapy for leptomeningeal metastasis in breast cancer: a randomised study. *Eur J Cancer*. 2004;40(18):2726-2733.
51. Siegal T. Leptomeningeal metastases: rationale for systemic chemotherapy or what is the role of intra-CSF-chemotherapy? *J Neurooncol*. 1998;38(2-3):151-157.

How to cite this article: Bernstock JD, Ostby S, Fox B, et al. Cauda equina syndrome in an ovarian malignant-mixed müllerian tumor with leptomeningeal spread. *Clin Case Rep*. 2019;7:2341-2345. <https://doi.org/10.1002/ccr3.2472>