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Case Report

BRCA2-positive spinal intramedullary ovarian metastatic disease: case report

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Abstract

BACKGROUND CONTEXT: Ovarian cancer is the fourth leading cause of cancer death in women, but advances in treatment have led to longer survival among these patients. Tied to these advances and increased survival, however, have been new patterns of metastatic spread.
PURPOSE: The authors discuss the management and surgical decision making in patients with intramedullary ovarian metastatic disease using a case illustration and relevant literature.
STUDY DESIGN/SETTING: A case report was used.
METHODS: The authors describe a case of a 59-year-old woman with Breast Cancer gene (BRCA) 2-positive ovarian cancer who developed progressive myelopathy from a T10 to T11 intramedullary metastatic lesion.
RESULTS: The patient underwent a standard open T10–T11 laminectomy for intramedullary tumor resection. Intraoperative ultrasound was used to direct the dural opening over the lesion. After a posterior midline myelotomy, microsurgical dissection revealed the intramedullary tumor with a discolored fibrous capsule, which was carefully dissected off of the spinal tracts, and a gross total resection was achieved. Postoperative magnetic resonance imaging at 6 months demonstrated no evidence of residual or recurrent intramedullary tumor. The patient underwent adjuvant external beam radiation to the thoracic spine but succumbed to her primary disease 1 year after surgery.
CONCLUSION: Although central nervous system involvement of ovarian cancer confers a poor prognosis, patients presenting with a solitary lesion and neurologic deficit may benefit from surgical resection followed by steroids and radiation therapy, especially when tissue diagnosis is necessary.

Keywords: BRCA2; Intramedullary; Metastatic; Ovarian cancer; Spine; Surgery

Introduction

Ovarian cancer is the fourth leading cause of cancer death in women, and most affected patients die of diffuse intra-abdominal disease [1]. Women with BRCA2 mutations carry an 11%–23% risk of developing ovarian cancer [2–4], but these patients tend to respond favorably to chemotherapy and have better survival than those with BRCA wild-type mutations [5]. Treatment advances for ovarian cancer have enabled more patients to live long longer, but with the improved life spans, patients are developing metastatic lesions at locations that historically have been considered very rare, such as the spinal cord [6]. The optimal strategy to manage ovarian spinal cord metastasis has not yet been determined. Only six cases of ovarian metastasis to the spinal cord have been reported in the literature [1,6–10], and five of the six patients died from systemic manifestations of ovarian cancer shortly after treatment of the spinal cord metastasis, despite clinical improvement. Surgical resection of intramedullary lesions carries the risk for severe neurologic morbidity. Thus, management decisions must be made based on patient functional status, need for tissue diagnosis, extent of systemic disease, prognosis, and palliative goals [10]. We provide an

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illustrative case of a 59-year-old woman with BRCA2-positive ovarian cancer who presented with an intramedullary metastatic lesion at the T10–T11 levels. This case highlights the natural history, management, and surgical decision making for patients with ovarian cancer and intramedullary metastatic disease.

Case report

Presentation

A 59-year-old woman with a history of BRCA2-positive [S611X (2060C>A) deletion] ovarian cancer presented with 2 weeks of back pain, right lateral leg radicular pain, constipation, band-like numbness below her umbilicus, and patchy sensory loss to light touch throughout both lower extremities. Her ovarian cancer was diagnosed 2 years earlier and had been managed with a bilateral salpino-oophrectomy, hysterectomy, and lymph node dissections followed by six cycles of intraperitoneal paclitaxel and cisplatin; her last chemotherapy treatment was 7 months earlier. Histologic diagnosis was papillary serous carcinoma limited to the ovaries with endometrial tissue present in one ovary (stage 1B). Two months before the current presentation, she had a computed tomography (CT) scan of the abdomen and pelvis with no evidence of disease recurrence.

On physical examination, the patient had weakness in both legs. Motor strength was graded 3/5 for left hip flexion/extension, knee flexion/extension, and dorsi- and plantarflexion; 4/5 for right hip flexion/extension and knee flexion; and 5/5 for right knee extension and dorsi- and plantarflexion. She was hyporeflexive at her patella and Achilles tendons, with a positive Babinski sign bilaterally. Sensation was decreased in the perirectal region but rectal tone was intact.

Magnetic resonance imaging (MRI) of the thoracic spine demonstrated a solitary contrast-enhancing lesion at the T10–T11 levels with significant spinal cord edema (Fig. 1). The MRI of the brain and cervical and lumbar spine demonstrated no evidence of additional central nervous system (CNS) lesions or leptomeningeal disease. Computed tomography of the chest, abdomen, and pelvis showed no evidence of recurrent abdominal disease or other metastatic lesions.

Surgical intervention

The patient was immediately started on intravenous steroids (4 mg of dexamethasone every 6 hours), which resulted in modest improvement in her motor and sensory function, which was continued for 72 hours preoperatively. A radiopaque marker was placed preoperatively under fluoroscopy to aid with intraoperative localization [11]. A standard open T10–T11 laminectomy for intramedullary tumor resection was

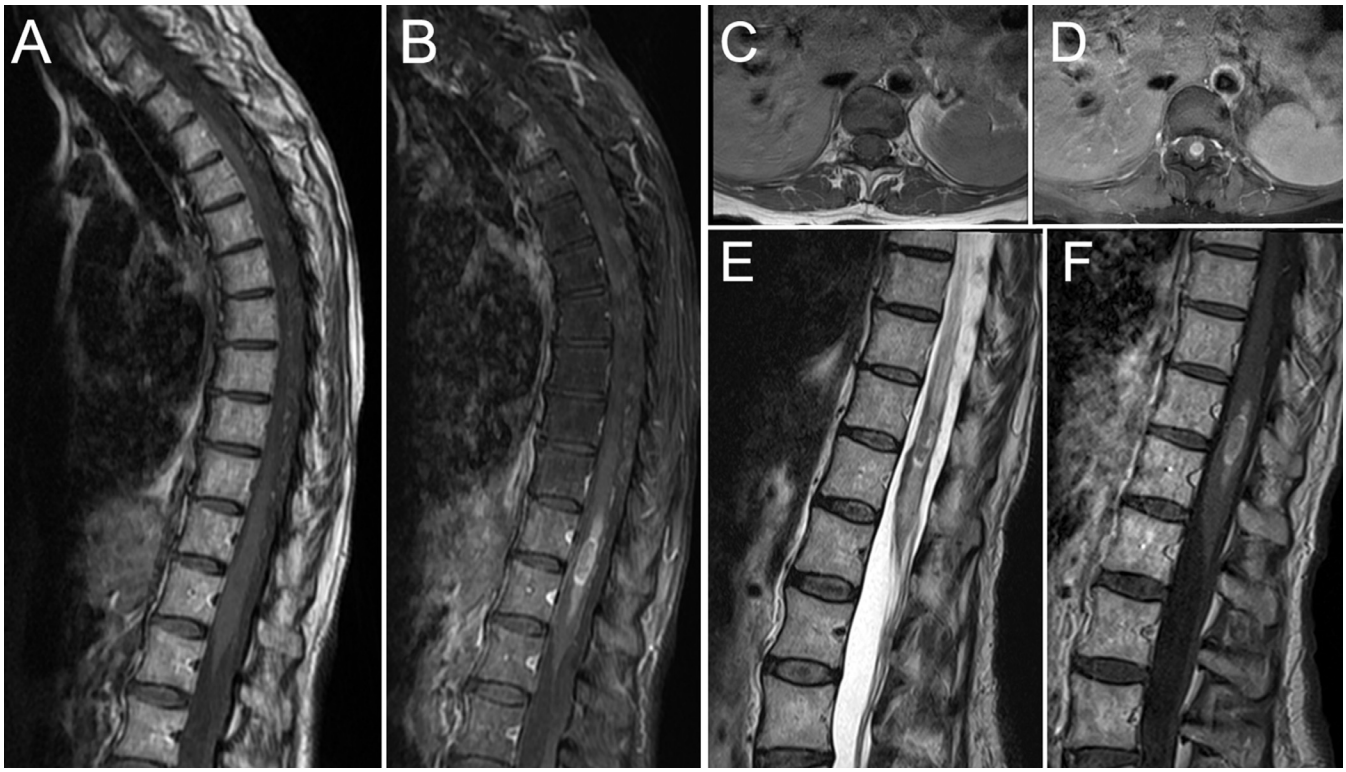

Fig. 1. (A, B) Sagittal thoracic spine T1 pre- and post-gadolinium images demonstrating an expansile, avidly contrast enhancing lesion centered at T10–T11 with significant spinal cord edema. (C, D) Axial thoracic spine T1 pre- (C) and post- (D) gadolinium images demonstrating an expansile avidly contrast-enhancing intramedullary lesion. (E, F) Sagittal lumbar spine T2 (E) and T1 post-gadolinium (F) images demonstrating the intramedullary lesion with significant spinal cord edema with hemorrhagic characteristics present.

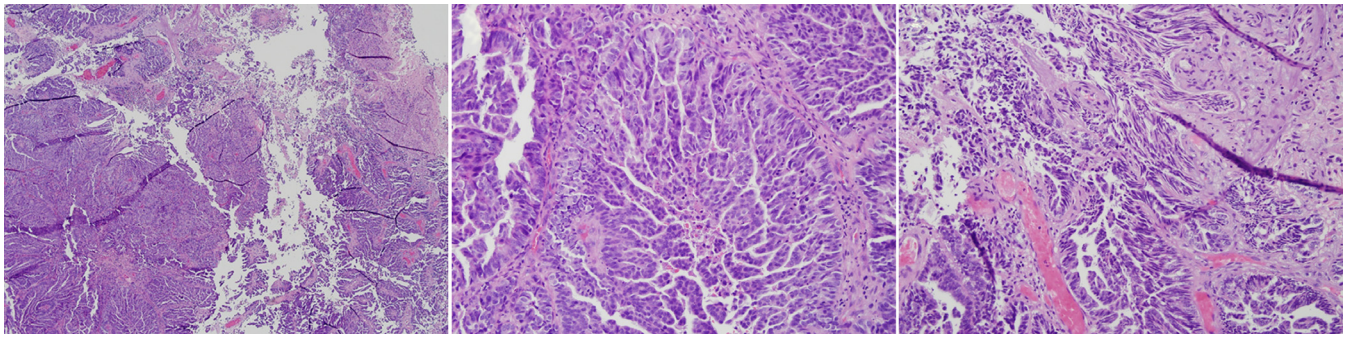

Fig. 2. (Left) Low-power image demonstrates a metastatic tumor to the spinal cord with tumor adjacent to a small focus of eosinophilic neural tissue toward the top right of the photograph. (Middle) The tumor morphology demonstrates a hypercellular metastatic adenocarcinoma with a papillary architecture. (Right) There are fibrovascular cores within the tumor, and the cells demonstrate hyperchromatic and pleomorphic nuclei. Numerous mitoses and apoptosis are scattered throughout the tumor.

planned with neurophysiologic intraoperative monitoring. Reliable and reproducible motor evoked potentials and somatosensory evoked potentials were obtained in the legs before and after positioning without changes. Once the laminectomy was performed, intraoperative ultrasound was used to direct the dural opening over the lesion, which appeared hyperechoic [12]. The spinal cord appeared expansile with hemosiderin staining. The ultrasound was again used to identify the optimal location for the myelotomy.

A posterior midline myelotomy was performed, after which the amplitude of the somatosensory evoked potentials decreased by 90% and did not recover during the operation. The motor evoked potentials remained responsive and stable throughout the surgery. Microsurgical dissection revealed the intramedullary tumor with a discolored fibrous capsule. The mass had more extensive attachments to the left side of the spinal cord than the right side, which provided a corridor to perform the tumor resection (Video). The tumor was carefully dissected off of the spinal tracts, and a gross total resection was achieved. The dural opening was repaired primarily in a water-tight fashion using a running 4-0 Nurolon suture and challenged with a Valsalva maneuver without evidence of cerebrospinal fluid leak.

Pathology

The pathologic diagnosis was metastatic ovarian adenocarcinoma composed of well-formed glands. The microscopic specimen showed marked hypercellularity with pleomorphic, hypochromatic nuclei, and numerous mitoses and apoptoses. There was evidence of scattered lymphocytic infiltration and multifocal necrosis (Fig. 2). Immunohistochemistry tests for cytokeratin-7, CA-125, and BER-EP4 were all strongly positive (Fig. 3).

Postoperative course and outcome

Postoperatively, the patient remained on the same intravenous dexamethasone dose for 48 hours (4 mg of dexamethasone every 6 hours); thereafter, she was placed on an oral dexamethasone taper over 10 days. The patient was kept flat in bed for 48 hours after surgery to ensure adequate healing of the primary dural closure and then mobilized. After 3 days of transient bilateral lower extremity paresis after surgery, the patient's motor strength improved compared with her preoperative levels. She had 5/5 motor strength throughout her right leg and for left hip extension, knee extension,

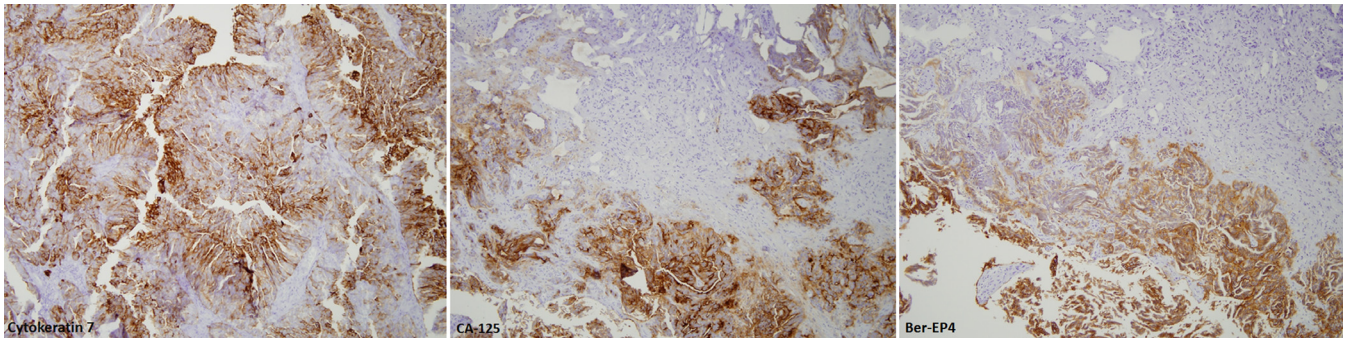

Fig. 3. High-power (100×) image of staining for cytokeratin 7 (Left), CA-125 (Middle), and Ber-EP4 (Right), which demonstrate positivity with a membranous pattern in the tumor with a sharp demarcation between the metastatic tumor and fibrotic or reactive neural tissue. The neural tissue was negative for all of the immunohistochemical markers mentioned, consistent with a metastatic adenocarcinoma.

and plantar flexion; motor strength improved to 4/5 in her left knee extension and dorsiflexion; her left hip flexion remained 3/5. Her sensation to light touch improved throughout both lower extremities, but she developed proprioceptive loss in her left foot. She also developed bladder incontinence after surgery. After an uneventful 1-week hospital course, she was discharged to inpatient rehabilitation. She could walk short distances with moderate assistance, but continued to have myelopathic symptoms with impaired balance and gait. Upright X-rays demonstrated no evidence of a kyphotic deformity (Fig. 4). Postoperative MRI at 6 months demonstrated no evidence of residual or recurrent intramedullary tumor (Fig. 5).

The patient underwent adjuvant external beam radiation to the thoracic spine and continued taking oral steroids. A total dose of 45 Gy was given (25 fractions of 1.8 Gy) over 36 days using anterior-posterior fields from a 16-mV photon beam. Postoperative chemotherapy was considered, but with the absence of other areas of disease and planned focal radiation to the only known site of recurrence, it was not clear that any benefit to adjuvant chemotherapy would be afforded. The patient died from her primary ovarian cancer 1 year after being diagnosed with the intramedullary metastatic lesion.

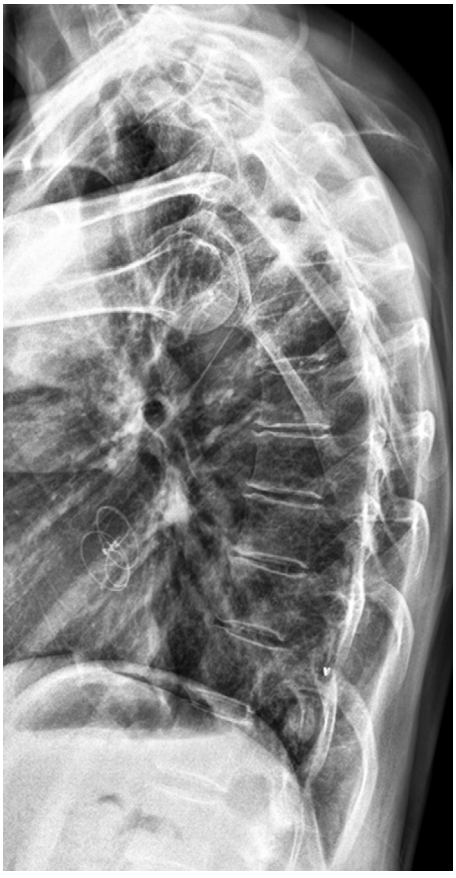

Fig. 4. Postoperative upright lateral thoracic spine radiograph demonstrating no kyphotic deformity.

Discussion

Intramedullary spinal cord metastases account for 1.3% of all spinal metastatic disease [13]. This is the seventh reported case of spinal intramedullary ovarian metastatic disease (Table 1). Four patients underwent surgical resection and had confirmed histopathologic diagnosis; three of these had an improvement in neurologic examination after surgery and were treated with adjuvant steroid and radiation therapy. The three patients treated with radiation and chemotherapy alone all had improvement in their neurologic function after treatment. Serous adenocarcinoma, as seen in our case, has been associated with BRCA2 mutations [15] Although the incidence of cancer is higher in patients who are BRCA2 positive, the mutation may confer a better prognosis on these patients once they are treated. Interestingly, BRCA2 mutation is not associated with CNS tumor formation and disease spread [5], and this is the first report of intramedullary spread in a woman with a known BRCA2 mutation.

Ovarian cancer

Aggressive management of ovarian cancer with surgery and platinum-based chemotherapy has lengthened survival. Thus, patients with ovarian cancer are now living long enough to develop metastatic lesions in rare locations, such as the spinal cord. Platinum-based compounds, such as cisplatin, however, do not penetrate the blood-brain barrier and may actually damage it, thereby facilitating metastasis into the spinal cord, which was observed in our patient [16,17]. The CNS has been thought to be an uncommon site for metastatic involvement in patients with ovarian carcinoma, with metastases occurring in approximately 2% of patients (estimates vary from 0.29% to 11.6%) [14,18–20]. In the rare cases where there is CNS involvement, the cerebrum, cerebellum, pons, and leptomeninges are the most commonly involved sites [20].

There is no standardized treatment regimen for a solitary intramedullary metastasis from ovarian cancer, with neurologic improvement documented after both surgical and medical interventional treatment. Of the cases reported in the literature, at last known follow-up, patients treated with surgery (4 patients) or medical treatment (3 patients) showed a mean survival of 17 months. Thus, patient selection for surgery versus medical management should be made on a case-by-case basis with particular attention to neurologic function and deficit. There were strong indications for surgical intervention in our patient. Although her remote history of ovarian cancer was compelling, the recent CT of the chest, abdomen, and pelvis showed no evidence of recurrent abdominal disease or other metastatic lesions. Thus, neurologic deficits guided the decision to (1) obtain tissue diagnosis and (2) decompress the neural elements to prevent further damage and promote neurologic recovery. In patients who present with a history and presentation that could confound the differential diagnosis, it is important to perform a thorough preoperative diagnostic workup, including CT of the chest,

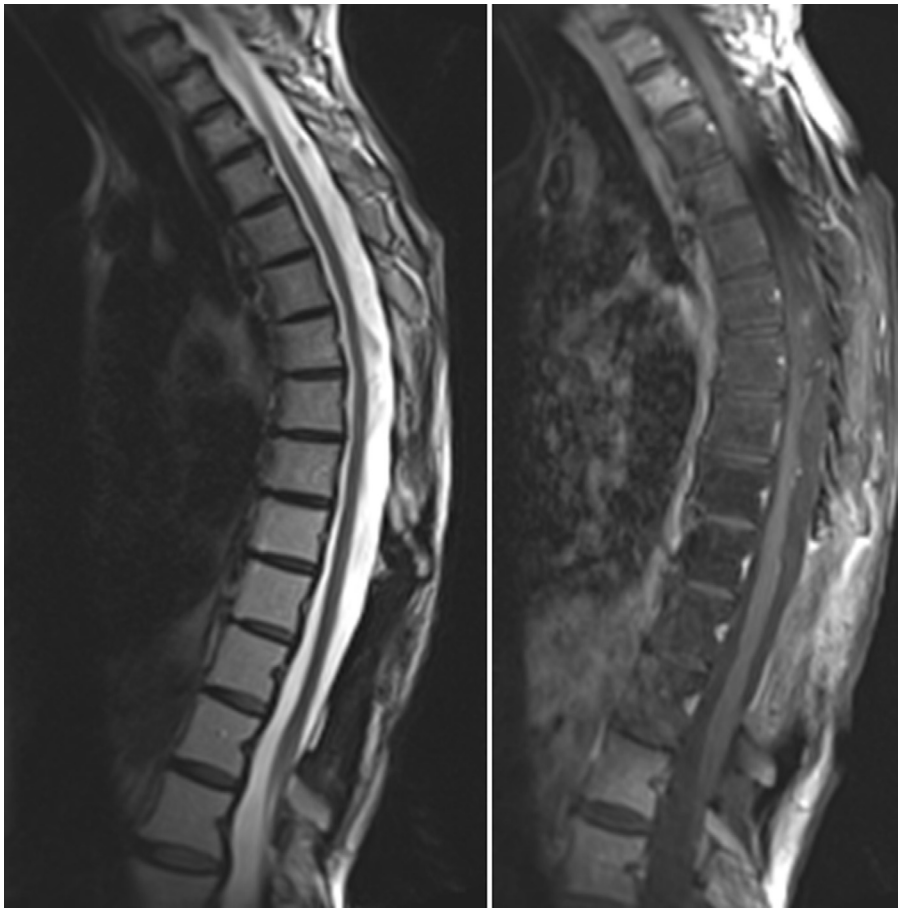

Fig. 5. Postoperative sagittal T2 (Left) and T1 post-gadolinium (Right) magnetic resonance imagings (MRIs) obtained 6 months after surgery, demonstrating no evidence of residual or recurrent intramedullary tumor or leptomeningeal disease.

abdomen, and pelvis, and MRI with and without contrast of the remaining neural axis. Although presenting symptoms may be impressive, judicious use of preoperative steroids may significantly improve neurologic deficits and allow for further, necessary preoperative workup.

Chemotherapy in the management of CNS disease from ovarian carcinoma is limited to control of local disease without improvement of progression free-intervals [21]. Previous studies have shown a response to platinum-based chemotherapy agents for multiple CNS metastases; however, there has been no improvement in median survival [22,23]. Staging for ovarian carcinoma does not factor in CNS involvement and thus routine imaging of the brain and spinal cord are not performed, and CA-125, which was not elevated in our case, does not reliably predict CNS metastases [21].

The use of chemotherapy for intramedullary metastases has been reported previously [24–27], although its specific role has been unproven. Historically, it was reserved for patients with carcinomatous meningitis [28]. The addition of chemotherapy was significantly associated with prolonged survival ($p<.05$); however, only 10% of patients lived longer than 6 months after presentation. In our case, postoperative chemotherapy was considered, but given the lack of evidence concerning treatment of BRCA2-positive intramedullary ovarian lesions and the absence of other areas of disease and planned focal radiation to the spinal cord, it was unclear whether there would be any direct benefit to adjuvant chemotherapy.

Previously, it was thought that surgical resection was reserved for well-encapsulated tumors with systemic disease that was under control [29,30]; however, given the advances in microsurgical technique for intradural spinal cord tumor resection and neurologic monitoring, surgical resection may offer an improved quality of life and functionality for patients [31,32].

Surgical strategy and decision making

Despite advances in surgical technique and neurologic monitoring, surgical resection of intramedullary tumors still poses a significant challenge to neurosurgeons [9]. The most significant risk is postoperative neurologic worsening, including, but not limited to, motor weakness, sensory loss, and autonomic dysfunction. Although steps are taken to mitigate neurologic damage, some risk remains. In 2011, Karikari et al. [9] found that preoperative neurologic status ($p=.02$),

Table 1
Reported cases of intramedullary ovarian metastatic lesions

Study	Patient age (years)	Primary ovarian disease	Level of lesion	Time from initial diagnosis to spinal lesion diagnosis **(years)**	Surgical treatment	Adjuvant therapy	Outcomes
Miranpuri et al. [10]	65	Papillary serous adenocarcinoma Stage IV	C2–C5	2	Laminectomy, subtotal resection	Radiation (30 Gy) and steroids	Improved strength; died 5 mo later
Thomas et al. [6]	49	Epithelial ovarian carcinoma	C6–T1	4.5	None	30 Gy and steroids	Improved strength; died 6 mo
Cormio et al. [1]	58	Serous cystadenocarcinoma Stage IV	C5–C6 (with concurrent brain metastases)	1.5	None	Steroids, chemotherapy, radiation (30 Gy)	Improved strength; died 10 mo later
Isoya et al. [8]	59	Adenocarcinoma Stage IIIC	T10	4	Laminectomy, subtotal resection	Radiation therapy, steroids	No change in neurologic status; alive 2 y after surgery
Rastelli et al. [14]	73	Cystadenocarcinoma Stage IB	T11	2	Laminectomy, gross total resection	Steroids, radiation (30 Gy, 10 fractions)	Improved strength; MRI with no recurrence 16 mo later
Bakshi et al. [7]	40	Papillary serous adenocarcinoma Stage III (from previous ovarian tumor specimen)	Conus medullaris and cauda equina	2	None	Steroids, radiation therapy, chemotherapy	Improved; complete remission at 3 y
Current case	59	Papillary serous adenocarcinoma (Stage 1B)	T11–T12	2.5	Laminectomy, gross total resection	Steroids, radiation (45 Gy, 25 fractions)	Improved strength and sensation, died 1 y later

MRI, magnetic resonance imaging.

tumor histology (p=.005), and extent of resection (p<.0001) were predictive of functional neurologic outcomes. In 2008, Manzano et al. [33] reported no statistically significant correlations between negative changes in intraoperative neurophysiologic monitoring, the use of hypothermia, and outcome.

Patients may be treated primarily or with adjuvant radiation therapy; in fact, radiosurgery has been successfully used for treatment of intramedullary metastatic lesions [34,35]. Radiation therapy is not without risk, however; complications may include neurologic worsening from tissue edema, radiation necrosis, and potential wound healing complications after surgery [33]. All previous reports of intramedullary ovarian lesions were treated with corticosteroids, which may independently contribute to poor wound healing. Surgery was pursued in this case to provide tissue diagnosis and facilitate neurologic recovery.

At our institution, the use of steroids and neurophysiologic monitoring is standard practice. The additional measure of using a radiopaque percutaneous pedicle marker to aid with intraoperative localization limits the amount of bone removed and the length of the incision [11]. Although duraplasty and cerebrospinal fluid diversion were not used in this case, there have been no previous reports of a significant relationship between these measures and postoperative wound complications [33].

Conclusion

We present the rare case of a 59-year-old woman with BRCA2-positive ovarian cancer who presented with an intramedullary spinal cord lesion at the T10–T11 levels and was treated successfully with surgery. Although CNS involvement of ovarian cancer confers a poor prognosis, patients presenting with a solitary lesion and neurologic deficit may benefit from surgical resection followed by steroids and radiation therapy, especially when tissue diagnosis is necessary. Careful patient selection and ascertainment of goals of surgery are key in preoperative planning. Expanded studies on larger cohorts are needed to study this entity and form concrete surgical recommendations.

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Appendix: Supplementary material

Supplementary material related to this article can be found at http://dx.doi.org/10.1016/j.spinee.2015.10.053.

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