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Case report

Thoracic spinal metastasis as recurrence of borderline Brenner tumor without local recurrence: A case report

Tomoaki Fujita [a,*], Aya Takeya [b], Haruka Miyata [a], Futa Ninomiya [a], Yutaka Nonoyama [a], Takuya Nakazawa [a], Yukiko Furuya [b], Yasuyuki Enoki [c], Takashi Fujii [d], Shigeharu Fukao [a]

[a] Department of Neurosurgery, Kyoto Okamoto Memorial Hospital, Sayamanishinoguchi 100, Kumiyama-cho, Kuse-gun, Kyoto 613-0034 Japan
[b] Department of Gynecology, Kyoto Okamoto Memorial Hospital, Sayamanishinoguchi 100, Kumiyama-cho, Kuse-gun, Kyoto 613-0034 Japan
[c] Department of Pathology, Kyoto Okamoto Memorial Hospital, Sayamanishinoguchi 100, Kumiyama-cho, Kuse-gun, Kyoto 613-0034 Japan
[d] Department of Radiotherapy, Kyoto Okamoto Memorial Hospital, Sayamanishinoguchi 100, Kumiyama-cho, Kuse-gun, Kyoto 613-0034 Japan

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ABSTRACT

Background: Brenner tumor is a rare epithelial ovarian neoplasm that accounts for 2–3% of all ovarian neoplasms. Herein, we report the first case of thoracic spinal metastasis of recurrent Brenner tumor without local recurrence.
Case Description.
A 70-year-old female presented with a feeling of abdominal distension. Computed tomography revealed cystic lesions in her bilateral ovaries. Blood examination revealed high CA-125 [74.9 U/ml]. We excised bilateral ovaries, uterus, and omentum. Borderline Brenner tumor was diagnosed [Ki-67 labeling index: 10 %]. Follow-up abdominal echo and CA-125 examination revealed no local recurrence. 26 months later she developed paraplegia. Magnetic resonance imaging revealed tumor in the 5th-9th thoracic vertebra and compression of spinal cord at the 6th thoracic vertebra level. Her paraplegia was progressive. We performed semi-urgent partial resection of tumor and release of spinal cord compression. Spinal metastasis from Brenner tumor was diagnosed [Ki-67 labeling index: 50–60 %]. She received adjuvant radiation of 30 Gy in 10 fractions to the 4th-10th thoracic vertebra. After radiation and rehabilitation, she was discharged home on foot. She received adjuvant radiation and chemotherapy but died 11 months after spinal surgery. An autopsy has not been performed on her, and the cause of death is unknown.
Conclusion: We report the first case of thoracic metastasis of recurrent Brenner tumor without local recurrence.

1. Introduction

Brenner tumor [BT] was first reported in 1907 by Dr. Fritz Brenner. BT is a rare epithelial ovarian neoplasm that accounts for 2–3 % of all ovarian neoplasms and is thought to derive from the surface epithelium and the underlying stroma through transitional cell metaplasia (Cuatrecasas et al., 2009; Kats et al., 2007). These tumors are classified into three groups: benign, borderline, and malignant. Most are benign. Borderline or malignant BT is exceedingly rare. Even after diagnosis as borderline BT, recurrence and metastasis may occur; however, to the best of our knowledge there is no report about thoracic spinal metastasis of recurrent Brenner tumor without local recurrence. We report the first case of metastasis of recurrent Brenner tumor at the thoracic spine without local recurrence.

2. Case Description

A 70-year-old female G0P0 without past medical history visited an outpatient clinic complaining of abdominal distension. Abdominal and pelvic computed tomography [CT] showed a cystic mass with a diameter of about 12 cm in the right ovary and 6 cm in the left ovary [Fig. 1a-b]. Blood examination revealed high serum level of CA-125 [74.9 U/ml]. She underwent bilateral salpingo-oophorectomy, hysterectomy, and omentectomy.

Abbreviations: BT, Brenner tumor; CT, computed tomography.

* Corresponding author.
E-mail addresses: fujita-kyf@umin.ac.jp (T. Fujita), f_maple1995@icloud.com (F. Ninomiya), nighthawks1@mac.com (Y. Nonoyama), nakazawa@okamoto-hp.or.jp (T. Nakazawa), furu-yuki517@kvj.biglobe.ne.jp (Y. Furuya), sachienoki@okamoto-hp.or.jp (Y. Enoki), fuji1taka4@yahoo.co.jp (T. Fujii), shigefk@okamoto-hp.or.jp (S. Fukao).

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Pathologic examination revealed a biphasic formation of cystic and solid components without clear stromal invasion. In the solid part, atypical cells similar to urothelial cells proliferated densely showing nest structure [Fig. 1c]. The atypical cells had pale eosinophilic, slightly bright cytoplasm and irregular, mildly swollen nuclei. The cystic part was covered with mildly atypical urothelial-like cells, showing nest structure. Though cytology of ascites was positive, there were no malignant findings in the fallopian tubes, uterus, or omentum. Immunohistochemical studies showed positivity for GATA3 with focal ER expression [less than 5 %]. Stains for chromogranin A, synaptophysin, CD56, PgR, and WT1 were all negative. Ki-67 labeling index was 10 %. We diagnosed borderline Brenner tumor. Follow-up abdominal echo and CA-125 examination revealed no local recurrence. Initial CA-125 serum level was high [74.9 U/ml]; however, it decreased to 24.9 U/ml 2 months after surgery and to 24.1 U/ml 18 months after surgery. Incidental plain thoracic CT 6 months later showed no obvious lesions [Fig. 2a].

26 months later, she developed hypochondrium pain and walk disturbance. Neurological findings showed paraplegia [Manual Muscle Test: 4/5] and sensory disturbance. The serum level of CA-125 was only slightly elevated [26.6 U/ml]. Magnetic resonance imaging [MRI] showed tumor in the 5th −9th thoracic vertebra, compressing the spinal cord at the 6th thoracic vertebra level. Plain CT revealed mixed osteolytic changes in the lamina and ossifying changes in the vertebral bodies. Enhanced CT did not show a strong enhancement effect [Fig. 2b-f]. Her paraplegia was progressive. We performed semi-urgent partial resection of tumor and release of spinal cord compression. Her paraplegia improved postoperatively. In pathological findings, urothelial-like cells proliferated densely showing nest-like, sheet-like, and cord-like arrangements. Atypical cells have pale eosinophilic cytoplasm and swollen elliptical to irregular nuclei. Nuclear fission figures are seen sporadically. Fibrosis was observed relatively extensively in the stroma. Immunohistochemical studies showed positivity for CK7, GATA3, and p63 with focal CK7 and S-100P. By referring to previous pathological findings, we diagnosed spinal metastasis of Brenner tumor. Ki-67 labeling index had deteriorated to 50–60 % [Fig. 3]. Fluorodeoxyglucose positron emission tomography revealed no recurrence at abdominal and pelvic space; however, positive lesion at her right 7th rib and thoracic spine was revealed. We administered adjuvant radiation of 30 Gy in 10 fractions to the 4th-10th thoracic vertebra. After rehabilitation, she was discharged home on foot.

Adjuvant chemotherapy with gemcitabine was tried; however, it had to be abandoned due to side effects. She then tried etoposide but stopped due to side effects. She was currently being treated with carboplatin/paclitaxel. She was followed up with a spine MRI every 4 months, and her thoracic lesion was under some control. But she died at home, 11 months after spinal surgery. An autopsy has not been performed on her, and the cause of death is unknown.

3. Discussion

Ovarian neoplasm is mainly composed of three groups: epithelial tumors, stromal tumors, and germ cell tumors. BT is a rare epithelial tumor, accounting for 2–3 % of all ovarian tumors. BT was first reported in 1907 by Dr. Fritz Brenner, and is now classified into three groups: benign, borderline, and malignant. Most of these tumors are benign and less than 5 % are proliferating or borderline (Ziadi et al., 2010). When malignant BT is diagnosed, histological diagnosis requires the concomitant presence of both malignant and benign and borderline BT with clear stromal invasion by the malignant epithelial components (Hull and Campbell, 1973). Ricotta et al. reported 17 borderline BT cases in their institution and 65 cases in literature (Ricotta et al., 2021). Although prognosis of borderline BT is generally good, they reported recurrence in 6 of 82 cases. The sites of recurrence were lower ureter and peritoneum [n = 1] (Cuatrecasas et al., 2009), contralateral ovary [n = 3] (Ricotta et al., 2021; Svenes and Eide, 1984; Uzan et al., 2012), liver [n = 1] (Vali et al., 2019), and subcutaneous, which was located in an abdominal laparotomic scar [n = 1] (Klasa et al., 2014). There have been no reports of recurrences to the thoracic spine. Only three cases of metastasis that involved the nervous system and spine have been reported (Baizabal-Carvallo et al., 2010; Zhang et al., 2019). Baizabal-Carvallo et al. reported a 56-year-old woman with a 6-month history of intracranial hypertension. Imaging studies showed diffuse dural enhancement, multiple lytic bone lesions, location not specified, and a tumor in the left ovary. A meningeal biopsy was performed; however, during this procedure the patient developed profuse dural hemorrhage and middle cerebral artery territory infarction and died a few hours later. Autopsy revealed a disseminated Brenner tumor that was infiltrating the intracranial dura mater. Zhang et al. reported 10 malignant BT cases in their institution and 40 cases in literature (Zhang et al., 2019). One of the

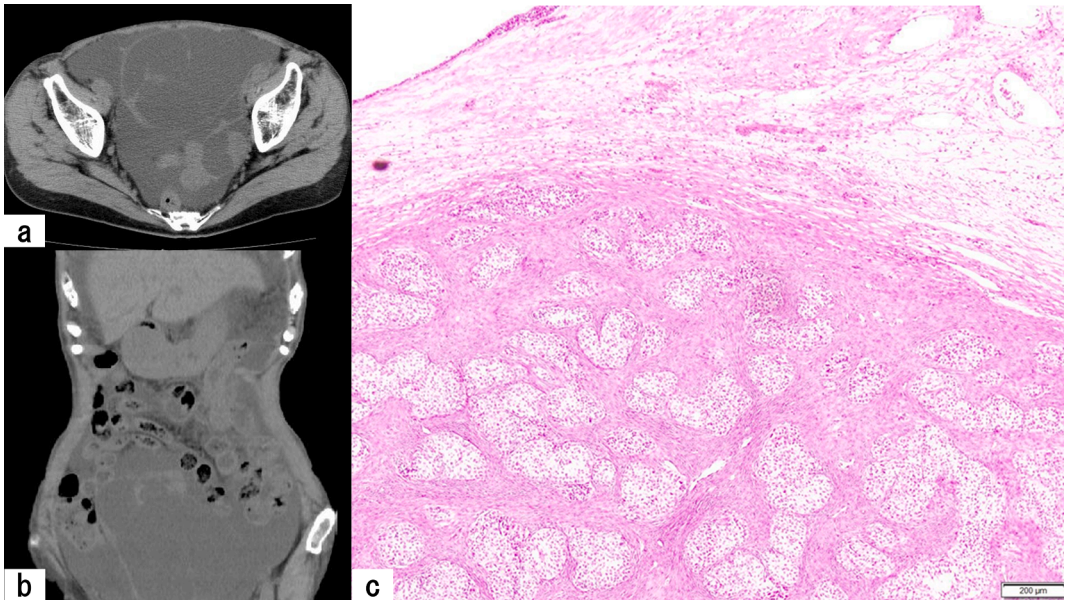

Fig. 1. (a)Axial image and (b)coronal image of initial abdominal CT. It shows large cystic lesions and ascites. (c) A pathological specimen of an excised ovary showing a biphasic formation of cystic and solid components without clear stromal invasion [hematoxylin-eosin staining, 200 μm scale bar is as shown].

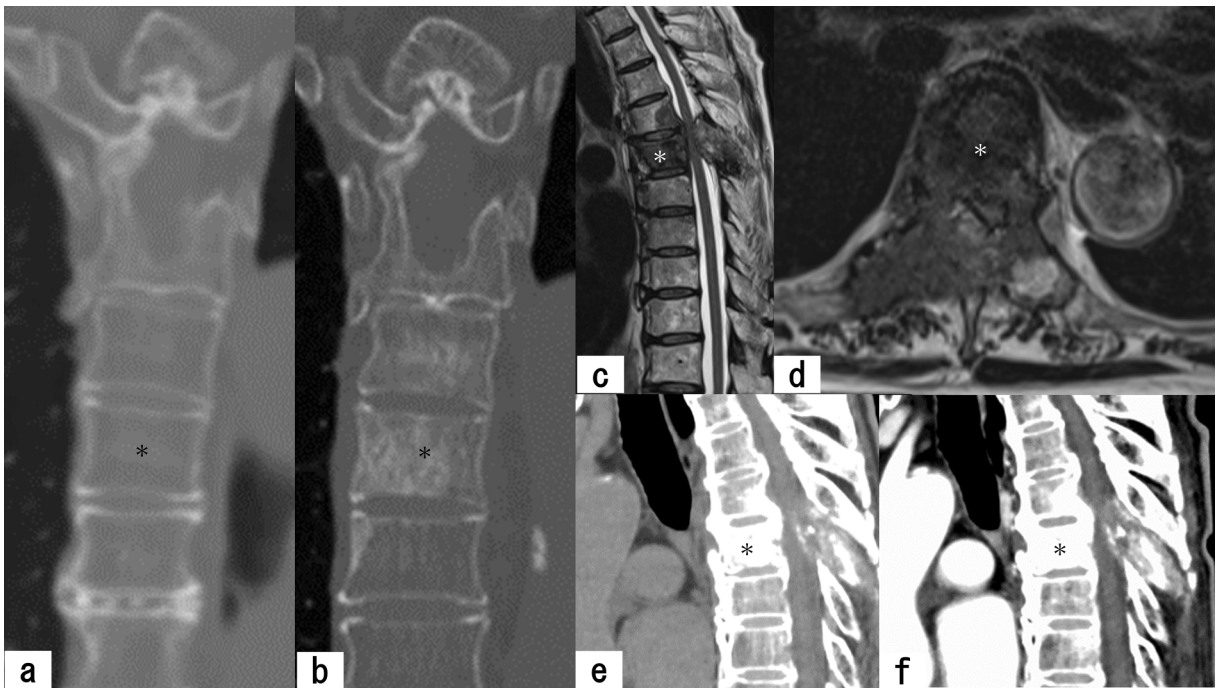

Fig. 2. (a) Coronal image of incidental thoracic CT showing no obvious lesions. (b) Twenty-six months later coronal thoracic CT shows ossifying changes in the vertebral bodies of the 5th and 6th thoracic spine. *; the 6th thoracic spine. (c) Sagittal and (d) axial images of spine MRI show tumor compressing the spinal cord around the 6th thoracic vertebra. (e) Sagittal image of plain CT shows mixed osteolytic changes in the lamina and ossifying changes in the vertebral bodies. (f) Sagittal image of enhanced CT does not show a strong enhancement effect.

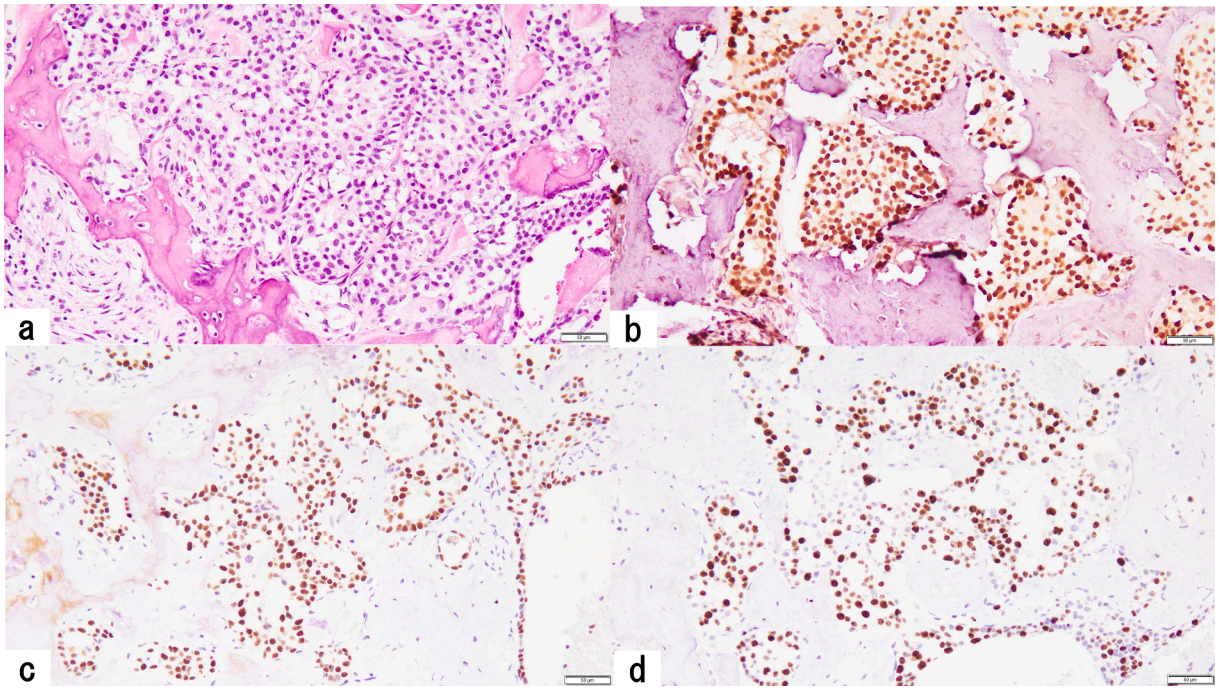

Fig. 3. (a) Hematoxylin-eosin staining, (b) GATA-3 staining, (c) p63 staining, (d) Ki-67 staining. Cells similar to urothelial cells proliferate densely showing nest-like, sheet-like, and cord-like arrangements. Immunohistochemical studies show positivity for GATA3 and p63. Ki-67 labeling index is 50–60 %, 200 μm scale bar is as shown.

patients had brain metastasis, and another had lumbar spine metastasis. BT can be considered ovarian tumor based on its slow biological progression and stepwise acquisition of molecular genetic alterations (Kuhn et al., 2012; Kurman and IeM, 2010). In particular, a previous study reported that CDKN2A loss, and to a lesser extent KRAS and PIK3CA mutations, may have a role in the progression of a benign Brenner tumor to an atypical proliferative Brenner tumor (Kuhn et al., 2014).

In the present patient, no clear metastatic lesion was identified by initial CT examination, and no clear stromal invasion was found in pathological findings; thus, borderline BT was diagnosed. However,

since there was no local recurrence and metastasis was observed in the spine and lymph node, we speculated that the tumor had metastasized to the spine before the initial primary tumor resection under the same mechanism as dissemination of prostate cancer (Fukui et al., 1996). However, incidental CT scan 6 months after primary tumor resection did not clearly show any lesions. There was a difference in Ki-67 labeling index between the specimen of the primary tumor and spinal metastasis. Furthermore, the elevated serum levels of tumor marker CA-125 when the primary tumor appeared was not detected at recurrence. This suggests that the tumor became more malignant and grew rapidly to develop paraplegia. It may be useful to have a periodical systemic checkup even if the patient was histologically diagnosed as borderline BT and no metastatic lesion was seen on initial imaging.

There are various regimens after recurrence, and favorable responses have been reported with the addition of docetaxel, topotecan, doxorubicin, gemcitabine, and bevacizumab, as well as radiation in patients with recurrent disease (Gezginç et al., 2012; Han et al., 2015; Lang et al., 2017). Furthermore, Zhang reported the use of eribulin in 3 patients with progressive renal impairment and history of severe taxane-induced neuropathy (Zhang et al., 2019). Although they progressed after 5 cycles of treatment, Zhang concluded that eribulin should not be exclude from the discussion of secondary and tertiary regimens for recurrent metastatic disease. We tried gemcitabine, etoposide, and carboplatin/paclitaxel, but it was difficult to select a suitable drug because of many side effects. The choice of a regimen for recurrent or metastatic Brenner tumors warrants further research.

4. Conclusion

Herein, we describe the first case of thoracic metastasis as recurrent borderline BT without local recurrence. The prognosis of borderline BT is generally good; however, local recurrence and metastasis may occur after some time has passed. In addition, the properties of the tumor may change to become more malignant. Thus, local examination and checking of serum levels of tumor markers may be insufficient. BT is a rare entity and very little is known about it. Accumulation of cases is essential.

Author Contributions:

T. F. wrote the manuscript in consultation with A. T., H. M., F. N., Y. F., Y. E. and T. F. Y. N., T. N. and S. F. supervised the project. All authors reviewed the manuscript draft and revised it critically on intellectual content. All authors approved the final version of the manuscript to be published.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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