Transitional meningioma malignant transformation and rib metastases following surgery: A case report

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Received January 12, 2023; Accepted July 13, 2023

DOI: 10.3892/ol.2023.13985

Abstract. The majority of benign meningiomas exhibit a slow growth rate and are associated with a good prognosis. The recurrence and extracranial metastases of meningioma are rare. The present report describes the case of a patient with recurrence of transitional meningioma for which total resection had been performed 8 years prior. Furthermore, the transitional meningioma transformed into atypical meningioma, and metastasized to the ribs. The present report aimed to describe the clinical features and pathological findings of a case of malignant transformation and distant metastasis of benign meningioma. A review of the literature was also performed.

Introduction

Meningioma is one of the most common and frequent primary tumors of the central nervous system, and it originates from either arachnoid or meningothelial cells in the central nervous system (1). Recurrence and extracranial metastases of meningioma are rare, and these have previously been considered to only be associated with malignant meningiomas, which are aggressive and associated with a poor prognosis (1,2). Due to the increased understanding of benign meningioma obtained from previous studies, it is now known that benign meningioma also has malignant potential (3-6). Nakasu *et al* (7) calculated that the incidence rate of malignant transformation following surgery for benign meningioma was 2.98/1,000 person-years by meta-analysis; 10-year survival after malignant transformation was 50.1%; extent of removal, location and gender were the potential risk factors associated with benign meningioma malignant transformation (7). Some researchers suggest that asymptomatic small-sized tumors can be followed up with close observation, symptomatic lesions and those with accelerated growth are primarily treated with maximum gross total surgical resection, external beam radiotherapy, brachytherapy or stereotactic radiosurgery (SRS) after surgical resection can be used in grade 2 and 3 meningiomas and adjuvant therapies might be required to reduce the recurrence rate in incompletely removed meningiomas and atypical or malignant meningiomas (8,9). However, available data on the malignant transformation of transitional meningioma, a subtype of benign meningioma, are limited. Ma *et al* (10) retrospectively assessed the surgical outcomes of 298 patients who was diagnosed as transitional meningioma, after a median follow-up of 61.8 months, 23 patients (8.6%) had developed recurrence and two patients (0.8%) had died; TM represent an unexpectedly high recurrence rate (10).

The present report describes the case of a patient with transitional meningioma, for which total resection was performed 8 years prior, and transformation to a higher grade and metastases to the ribs occurred. After a 1-year follow-up, the recurrent meningioma was slightly larger (1.3 cm mass) than before (a 1 cm mass). Gamma knife radiosurgery could be an option for the patient; however, the patient did not consent to radiotherapy, she still considered conservative treatment.

Case report

A 57-year-old female patient was hospitalized at Weihai Central Hospital (Weihai, China) in September 2021 due to right chest pain. Following admission, a computed tomography (CT) scan of the chest in September 2021 revealed bone destruction of the right fifth rib, indicating a soft tissue mass (size, 5x3x2 cm) (Fig. 1A), with a clear margin and expansion of the bone cortex. A contrast-enhanced CT scan of the chest in September 2021 revealed that the soft tissue mass of the right rib was evenly enhanced and clearly demarcated from the lung tissue (Fig. 1B). Rib reconstruction shows bone destruction of the right fifth rib (Fig. 1C). The CT scan of the chest suggested a metastatic tumor in the rib. Subsequently, emission CT also revealed that the right rib exhibited high levels of the radioactive tracer Technetium-99m (Fig. 1D). The pre-operative magnetic resonance imaging (MRI) scan of the patient in September 2013 revealed a 'mushroom'-like

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Key words: gross total resection, transitional meningioma, malignant transformation, recurrence, rib metastasis

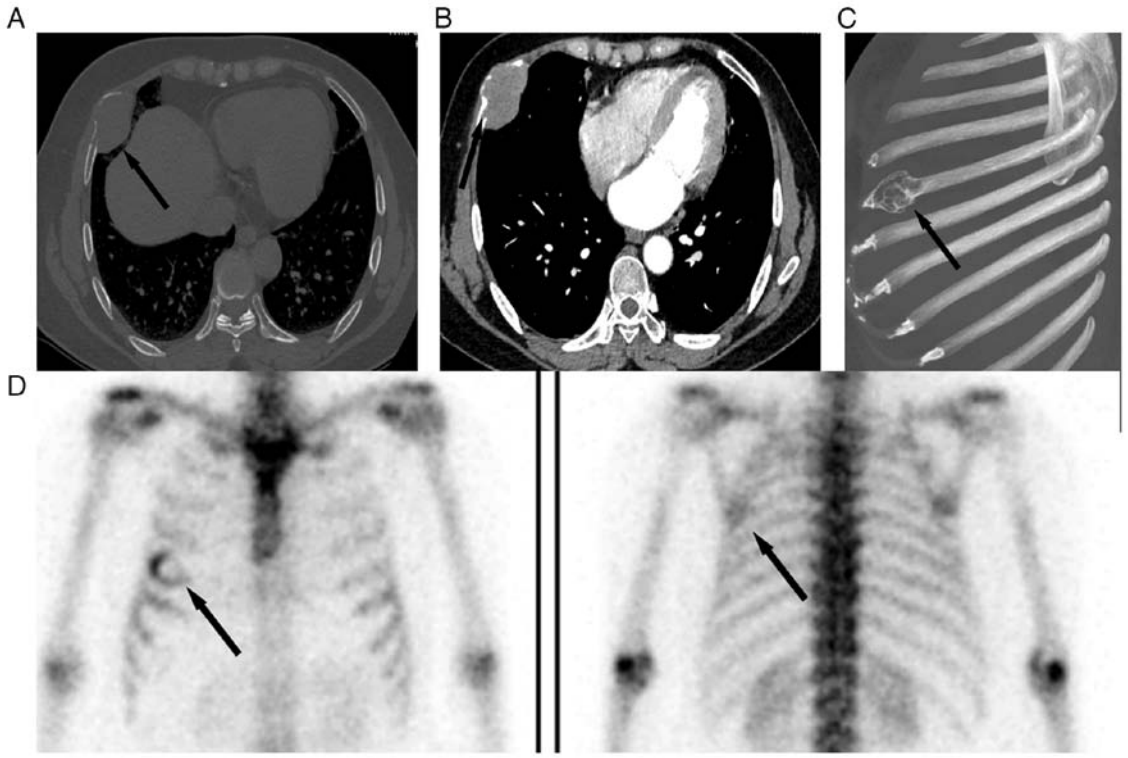

Figure 1. Metastatic tumors of the rib. (A) Bone window of the chest CT scan in September 2021 revealed the destruction of the right rib bone (black arrow). (B) Enhanced scan of the chest CT in September 2021 revealed the homogenous enhancement of the soft tissue mass in the right rib (black arrow). (C) Rib reconstruction in September 2021 (black arrow). (D) Emission CT illustrating the abnormal uptake (Technetium-99m) of the right rib (black arrow). CT, computed tomography.

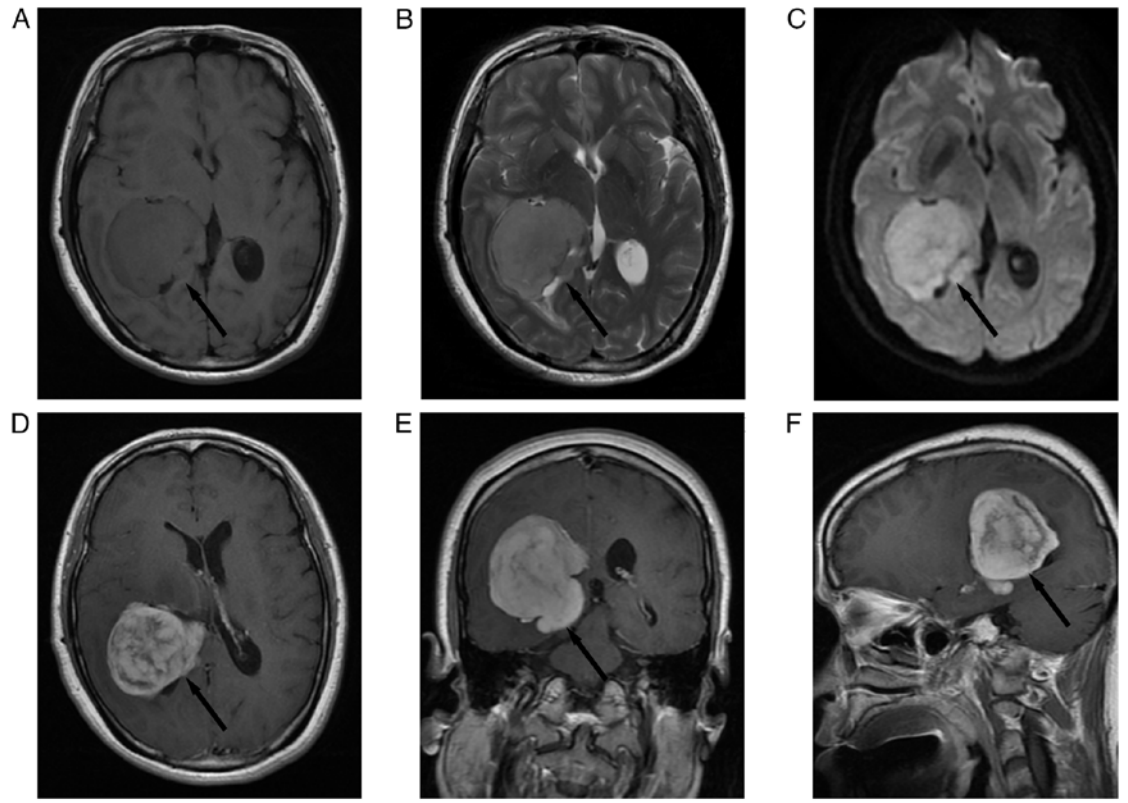

Figure 2. Pre-operative MRI in September 2013 illustrating a large irregular and lobulated meningioma in the right lateral ventricle. (A) Axial T1-weighted MRI indicating an isointense mass of 5x4x6 cm in size (black arrow). (B) Axial T2-weighted MRI illustrating a hyperintense signal with minimal peritumoral edema (black arrow). (C) Diffusion-weighted imaging illustrating a hyperintense signal (black arrow). (D) Axial, (E) coronal and (F) sagittal T1-weighted gadolinium-enhanced MRI illustrating heterogeneous contrast enhancement without a dural tail sign and no metastatic lesions (black arrow). MRI, magnetic resonance imaging.

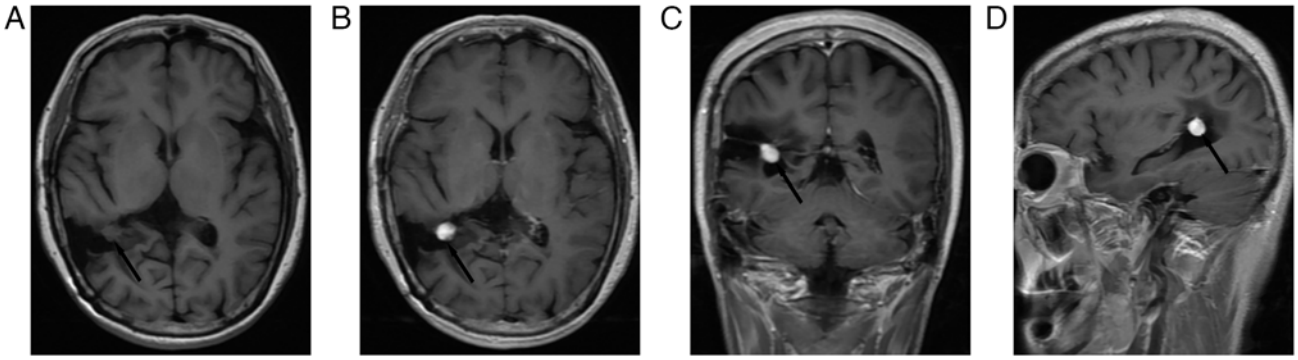

Figure 3. Postoperative T1-weighted gadolinium-enhanced MRI in September 2021 indicating a recurrent meningioma. (A) Axial T1-weighted MRI scan revealed a mass of 1 cm in diameter in the area of previous surgical resection (black arrow). (B) Axial, (C) coronal and (D) sagittal T1-weighted gadolinium-enhanced MRI illustrating a mass with homogeneous contrast enhancement (black arrow). MRI, magnetic resonance imaging.

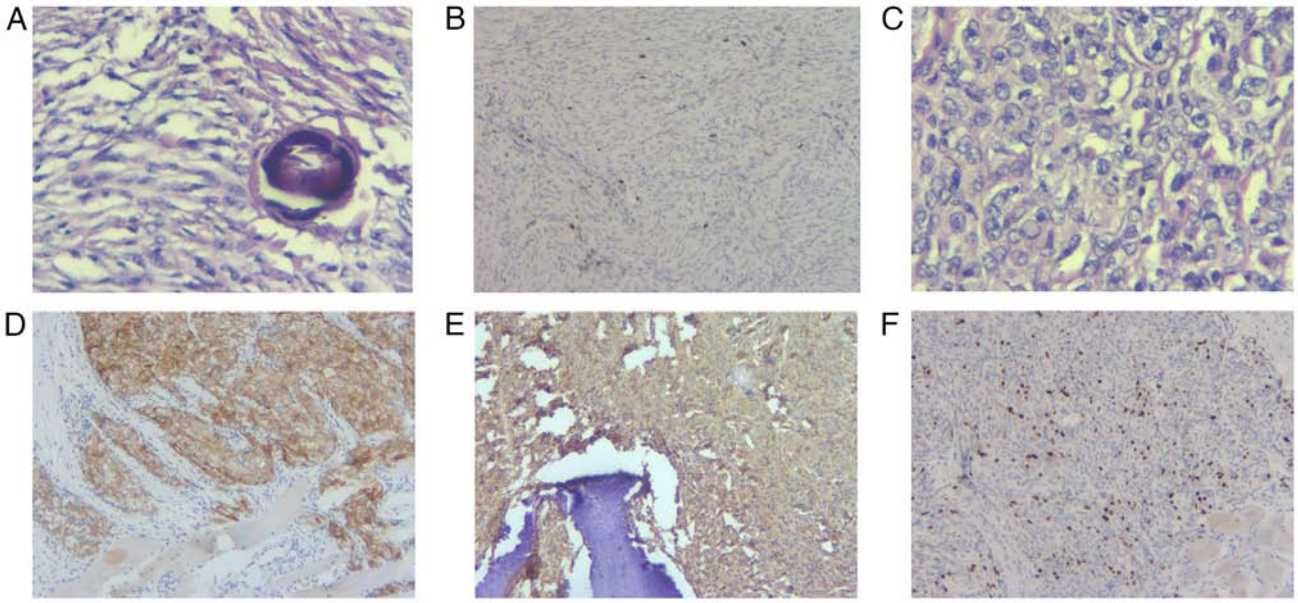

Figure 4. Histopathological analysis of the meningioma in September 2013 and the rib metastatic tumor in September 2021. (A) H&E-stained slide of the intracranial meningioma illustrating a transitional meningioma (original magnification, x400). (B) The Ki-67 index of intracranial meningioma was ~3% (original magnification, x40). (C) H&E-stained slide from the metastatic tumor of the rib illustrating atypical features with the diffuse arrangement of cells, focal necrosis (original magnification, x400). (D) Positive immunohistochemical staining for epithelial membrane antigen (original magnification, x40). (E) Positive immunohistochemical staining for vimentin (original magnification, x40). (F) The Ki-67 labeling index of the rib metastatic tumor was ~15% (original magnification, x40). H&E, hematoxylin and eosin.

appearance mass of 5x4x6 cm in size which in the right lateral ventricle, characterized by an isointense signal on Axial T1-weighted image (T1WI) (Fig. 2A), a hyperintense signal with minimal peritumoral edema on T2-weighted image (T2-WI) (Fig. 2B), diffusion-weighted imaging (DWI) illustrating a hyperintense signal (Fig. 2C). Axial (Fig. 2D), coronal (Fig. 2E) and sagittal (Fig. 2F) T1-WI gadolinium-enhanced MRI illustrating heterogeneous contrast enhancement without a dural tail sign and no metastatic lesions. Complete resection of the tumor was performed in September 2013. During surgery, it found the meningioma originated from the choroid plexus tissue. In addition, the texture of the tumor observed was uneven, surrounded by nodules. The tumor was surgically removed and electrocoagulation of the choroid plexus was performed. Subsequent to this hospitalization, a brain MRI scan in September 2021 revealed a well-circumscribed mass (diameter, 1 cm) in the area of previous surgical resection, characterized by an isointense signal on Axial T1-WI (Fig. 3A), a homogenous contrast enhancement signal on Axial (Fig. 3B), coronal (Fig. 3C) and sagittal T1-WI (Fig. 3D). We carry out the immunohistochemical analysis of the meningioma pathological section which was resected in September 2013, revealed meningothelial and fibroblastic features, meanwhile, contained a large amount of psammoma (Fig. 4A), the patient was diagnosed with transitional meningioma of World Health Organization (WHO) grade 1 (11), and the Ki-67 index was ~3% (Fig. 4B). The patient had no neurological symptoms apart from right chest pain. Therefore, it was decided to use a minimally invasive surgical approach to remove the metastatic tumor of the rib. During the surgery, it was found that the tumor did not invade the lung. The whole procedure was completed successfully with no complications.

Tumor tissue samples were fixed with 10% buffered formalin for 24 h at room temperature, paraffin-infiltrated overnight. Tissue blocks were sectioned at 3 μm, dewaxed, and stained with hematoxylin (~5%) for 5 min, followed by eosin (~1%) staining for 2 min at room. Hematoxylin and eosin staining were examined using an Olympus BX53 light microscope. The rib metastatic tumor revealed atypical features with the diffuse arrangement of cells, focal necrosis and there were mitotic figures up to five figures/10 points (Fig. 4C). The results of immunohistochemistry (Fixed with 10% buffered formalin for 24 h at room temperature, paraffin-infiltrated overnight. Tissue blocks were sectioned at 3 μm. Heated at 70˚C for 30 min in an electric thermostatic drying oven (Shanghai Yiheng Scientific Instrument Co., Ltd.), dewaxed with xylene at room temperature, rehydrated in a descending alcohol series at room temperature, and endogenous peroxidase activity was blocked using 3% H_2O_2 at room temperature for 10 min, followed by blocking with 10% normal goat serum (ab7481; Abcam) at 37˚C for 30 min. Anti EMA (E29) (prediluted by the manufacturer; cat. no. Z2048MP; Thermo Fisher Scientific, Inc.), Ki 67 (SP6) (prediluted by the manufacturer; cat. no. PIMA514520; Invitrogen™; Thermo Fisher Scientific, Inc.), Anti Vimentin (v9) (prediluted by the manufacturer; cat. no. MA1102; Boster Biological Technology). Incubation Time/Temperature: Anti EMA (E29) 13 min/room temperature; Ki 67 (SP6) 30-60 min/room temperature and Anti Vimentin (v9) 5-10 min/room temperature. The secondary antibody was obtained from the EnVision FLEX/HRP (prediluted; cat. no. K8000; Agilent Technologies, Inc.) and was used to treat sections at room temperature for 25 min. Subsequently, a chromogen detection reagent was applied (EnVision FLEX DAB+ Chromogen; cat. no. K8000, Agilent Technologies, Inc.). Using an Olympus BX53 light microscope (Olympus Corporation) revealed the positive expression of epithelial membrane antigen (EMA; Fig. 4D), vimentin (Fig. 4E) and progesterone receptor, and the negative expression of S-100 protein, cytokeratin(P), glial fibrillary acidic protein, CD34, smooth muscle actin and desmin. The Ki-67 positive index was ~15% (Fig. 4F). Vimentin and EMA exhibited positive staining, and these are the critical markers supporting the diagnosis of meningioma (6,12). Thus, the metastatic tumor in the rib was diagnosed as atypical meningioma (WHO grade 2). As the patient had no symptoms in September 2021, the patient selected conservative treatment. After 1-year follow-up, the patient's brain MRI scan in August 2022 revealed the recurrent meningioma was slightly larger (a 1.3 cm mass) than before (a 1 cm mass). Here, the gamma knife radiosurgery could be an option for the patient, however, the patient did not consent to radiotherapy, she still considered conservative treatment.

Discussion

According to the 2021 WHO tumor classification, >80% of meningiomas are benign meningiomas (grade 1), 15-20% are atypical meningiomas (grade 2) and 1-3% are malignant meningiomas (grade 3), depending on the mitotic rate, brain invasion or specific histological features, such as rhabdoid and papillary morphology qualified for CNS WHO grade 3 irrespective of any other indications for malignancy (11,13). Transitional meningioma is an uncommon subtype of benign meningioma, which is characterized by a transitional morphological appearance between endothelial meningiomas and fibrous meningiomas (10). The histological tumor grade of the meningioma is the most crucial predictor for recurrence or metastasis (11). Thus, it was previously considered that benign meningiomas rarely metastasize or recur and can be cured through surgical resection (8). By contrast with benign meningioma, atypical and anaplastic meningiomas often exhibit a more aggressive biological potential of malignant tumors, such as an abnormal proliferative activity and aggressive growth patterns and have a higher risk of recurrence and poorer progression than benign meningiomas (8,14). Studies found that the recurrence rate of WHO grade I meningiomas is 7-23%, WHO grade II meningiomas is 50-55%, and WHO grade III meningiomas is 72-78% in 5 years after total resection (8,14). It has previously been considered rare for atypical and anaplastic meningiomas to exhibit an increased risk of extracranial metastasis (6,15). Similarly, reported cases of extracranial metastasis of benign meningiomas are limited (4,5,7). Some studies have reported that the lungs are the most common site for seeding, followed by the liver, bone, skin, lymph nodes and mediastinum (4,6,16). The routes of metastasis are blood and the lymphatic vessels, as well as the cerebrospinal fluid, hematogenous spread is the most common route of metastasis (4,6,15). Furthermore, metastasis mostly occurs in postoperative patients, and the spread of tumor cells following surgery also may lead to tumor metastasis (14). Based on aforementioned previous research reports, for the patient described in the present report, it was hypothesized that rib metastasis occurred through the vertebral venous plexus, as surgery was considered to have led to the release of neoplastic cells into torn veins, allowing tumor cells to access the blood circulation and to travel from there to the vertebral venous plexus. These vertebral veins have extensive communication links with the veins of the intercostal veins of the thoracic-abdominal wall anatomically. Through these connections, tumor cells can spread from the brain to the ribs (16). It is considered reasonable to relate isolated rib metastatic involvement to the existence of the vertebral venous system.

In the present case, despite the histopathological confirmation of transitional meningioma (WHO grade 1) during the initial surgery, the histopathological examination of the rib metastatic tumor led to a diagnosis of atypical meningioma (WHO grade 2). Atypical and malignant transformation is a recognized phenomenon, and it has been reported that 2-10% of benign tumors exhibit malignant potential (6). A previous study determined that despite the gross total resection of benign meningioma, the recurrence rate was ~9.5% (3). Furthermore, it has been demonstrated that the probability of a recurrent benign meningioma progressing to an atypical or anaplastic pathology was as high as 28.5% (15). Recurrent or malignant transformation usually begins with excessive cell proliferation (12). Ki-67 is a nuclear antigen expressed during the active phases of the cell cycle. A higher Ki-67 proliferative index indicates shorter cell cycle times and more rapid tumor growth (12). It has been demonstrated that, in meningioma, the Ki-67 proliferative index increases with recurrence or malignant progression to grade 3 anaplastic meningioma (11). Generally, Ki-67 proliferative index of 4% indicates benign meningioma, while a Ki67 proliferative index of 10-15% is

indicative of aggressive meningioma (6). In the present case, the Ki-67 index was ~3% in the primary benign meningioma; however, the Ki-67 index increased to 15% in the recurrent meningioma. The patient exhibited recurrence of benign meningioma with a worsened tumor grade (WHO grade 2) based on the immunohistochemical analysis of the metastatic tumors. Furthermore, the Ki-67 proliferative index was high in the resected specimen. Thus, Ki-67 may be used as a marker of tumor cell proliferation to help predict the malignant potential of meningioma.

In the present case, the meningioma originated from choroid plexus tissue. During the surgery, the tumor was surgically removed section by section, and electrocoagulation of the choroid plexus was performed. Although the tumor was completely resected, tumor cells may still have been present at the surgical margin, leading to postoperative tumor recurrence. In addition, the texture of the tumor observed during surgery was uneven, surrounded by nodules. The combined MRI revealed a 'mushroom'-like appearance and a heterogeneous enhancement of the mass. This may have provided critical indications of the malignancy or aggressiveness of the tumor. Although the texture of the tumor was uneven during surgery and magnetic resonance imaging, indicating a malignancy, histopathological analysis is considered the gold standard for the diagnosis of benign meningioma.

The majority of primary meningiomas are diagnosed and resected prior to the occurrence of distant metastases, which supports the hypothesis that surgical resection may increase the risk of iatrogenic metastasis in meningiomas (16). Some cases of metastasis have been observed even without prior surgery (16). Theoretically, a craniotomy may lead to the release of tumor cells from a normally cohesive state into the bloodstream or cerebrospinal fluid. In particular, neoplastic cells enter the torn vein, and subsequently spread to the heart, and are released to various organs (16).

With an increasing number of studies reporting the malignant transformation of meningioma, researchers have found that chromosomal instability with recurrent cytogenetic alterations is often associated with the malignant progression of meningioma, including chromosomal aberrations at 1p, 6q, 9q, 10q, 12q, 14q,15q, 17q, 18q, 20q and 22q (13,14). A previous study reported that a meningioma with telomerase reverse transcriptase promoter mutations harbors a higher risk of malignant transformation and a more aggressive clinical course compared to meningioma without (TERT) promoter mutations (17). Furthermore, another study demonstrated that a neurofibromatosis type 2 mutation activated the Hippo, Notch, PI3K/AKT, mTOR and RAS/MAPK signaling pathways, with an ensuing increase in cell proliferation (18). In addition, some studies have found that stereotactic radiosurgery (19), surgical stress (16) and viral infection (4) can induce the malignant transformation of intracranial meningioma. These findings provide theoretical support for the recurrence of benign meningioma and the malignant progression of transformation into atypical or anaplastic meningioma.

Notably, intracranial Ewing's sarcoma (ES)/primitive neuroectodermal tumor, also known as a 'small round blue cell tumor', is a rare entity arising from bone and soft tissue, which is frequently observed among children and adolescents (20). Intracranial ES may be intra- or extra-axial with or without bone involvement, and mostly occurs as a solitary lesion associated with the dura, mimicking a meningioma in a radiological examination. Intracranial ES mostly exhibits mixed isointense-to-hypointense signals on T1WI, and isointense-to-hyperintense signals on T2WI, which is frequently accompanied by intratumoral hemorrhage or necrosis. In a post-contrast MRI, it presents as a heterogeneous enhancement. Therefore, it has been defined as a markedly enhanced solid mass accompanied by hemorrhagic and cystic components. Notably, hemorrhaging and necrosis are uncommon in meningioma, mostly presenting as isointense or hypointense signals on T1WI, and isointense or hyperintense signals on T2WI, exhibiting a homogenous contrast enhancement, which is common among in adults than in children. Furthermore, meningioma usually causes pressure onto the adjacent parenchyma, whereas parenchyma invasion is observed in ES. However, imaging may not be helpful in these situations, as both tumors may present as well-defined dural masses with contrast enhancement and exhibit bony erosion.

In the present patient, MRI of the primary meningioma revealed heterogeneous enhancement resembling ES, with isointense signals on T1WI and hyperintense signals on T2WI. However, according to the intraoperative findings, the tumor was located in the lateral ventricles and the tumor originated from the choroid, therefore, ES was not considered when the diagnosis of the meningioma was determined using MRI.

To the best of our knowledge, there is no clear guidance for the management of the malignant transformation and recurrence of benign meningioma following surgery. Some researchers have found that gamma knife radiosurgery may be an effective therapy for the first recurrence of transitional meningioma (10). Observation is another option, generally reserved for small, asymptomatic tumors and for patients that are deemed poor candidates for other therapeutic options (18). The management of these patients requires observation and serial monitoring with MRI scans. Notably, when tumor growth or symptom progression indicate that observation has failed, additional treatments are then warranted. As the patient in the present study has no symptoms in September 2021, further surgery is no longer considered to be in the best interests of the patient. The patient did not consent to radiotherapy, ultimately selecting conservative treatment. After a 1-year follow-up, the patient's brain MRI scan in August 2022 revealed the recurrent meningioma was slightly larger (a 1.3 cm mass) than before (a 1 cm mass). Here, the gamma knife radiosurgery could be an option for the patient, however, the patient did not consent to radiotherapy, she still considered conservative treatment.

In conclusion, although the majority of benign meningiomas are slow-growing and associated with a good prognosis, they can also exhibit an aggressive growth and recurrence, and can present different grades of dedifferentiation from grade 1-3, associated with different outcomes (4,6,15). Rib metastasis of meningiomas is uncommon, and meningiomas located exclusively within the ventricles are also rare (16). The present study describes the case of a patient with recurrence of transitional meningioma for which total resection had been performed 8 years prior. This case highlights the aggressive potential of transitional meningiomas and emphasizes the need to consider the metastasis of meningioma in the case

of discovered a rib mass in patients with a history of transitional meningioma. Given this finding, it may be clinically useful to evaluate annually patients with asymptomatic or small transitional meningioma by radiological imaging, after 5 years, this follow up interval can be doubled. The present study also reviewed previous research that chromosomal instability with recurrent cytogenetic alterations is often associated with recurrent and progressive meningiomas. A further understanding of the mechanisms underlying the recurrence or malignant progression of transitional meningioma may help to predict the clinical behavior of meningiomas, which may prove to be beneficial for the early recognition of high-risk meningiomas or progressive meningiomas and may lead to the timely adoption of effective treatment strategies.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

WZ and SY designed and guided the study. SY, JW, BH and JS analyzed the data and wrote the initial manuscript. WZ, BH and JS revising it critically for important intellectual content. SY, JW, JS and BH confirm the authenticity of all the raw data and analysis and interpretation of data. BH and JS obtained the images and drafted the figures. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was granted an exemption from requiring ethics approval from the Ethics Committee of Weihai Central Hospital (Weihai, China).

Patient consent for publication

The patient provided written informed consented to the data and images being obtained for research purposes and consented to their publication.

Competing interests

The authors declare that they have no competing interests.

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