Resolution of Pulmonary Metastases after Surgical Removal of Clear Cell Meningioma

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ABSTRACT

We report a rare instance of complete resolution of pulmonary metastatic lesions after gross total resection of a clear cell meningioma. This case showed that clear cell meningioma could metastasise to the lungs and that complete excision of the primary tumour resulted in resolution of the metastatic lesions, which is a phenomenon that has never been reported in the literature. A 25-year-old man presented with clear cell meningioma involving right parasagittal area. After incomplete resection of the primary tumour, he developed multiple bilateral pulmonary metastases and the anaemia of chronic disease. The metastatic lesions were confirmed by open biopsy to be from the clear cell meningioma. Following complete excision of the primary brain lesion, all the pulmonary metastatic lesions underwent spontaneous resolution and the patient has been free of disease for the last five years. Systemic spread of the tumour and later spontaneous resolution of metastatic lesions after complete removal of the primary suggests that aggressive local control of primary lesions should be attempted whenever possible.

Key Words: Lung neoplasms; Meningeal neoplasms; Meningioma; Tomography, X-ray computed

中文摘要

手術移除透明細胞型腦膜瘤後肺轉移癌的自動緩解

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本文報告一宗完全切除透明細胞型腦膜瘤術後肺轉移癌徹底緩解的罕見病例。這病例顯示透明細胞型腦膜瘤可向肺部轉移，原發腫瘤完全切除後會令轉移病變徹底消失。文獻中未有發表類似的病例報告。一名25歲男性的右矢狀竇旁發現透明細胞型腦膜瘤，他曾接受切開手術但未有把腫瘤完全切除，其後病人出現雙肺多發轉移癌和慢性貧血。病人切開活組織檢查確定轉移病灶來自透明細胞型腦膜瘤。其後把原發腦腫瘤完全切除後，發現其肺部轉移癌隨即自動消失。病人術後五年內未有復發。本病例腫瘤系統性轉移因切除原發腫瘤而誘發轉移癌自行消失，提示可能的話應盡量控制局部原發腫瘤。
CASE REPORT

We report a case of a 25-year-old man who presented with a history of twitching in the left leg for one year and subsequently suffered a generalised seizure while driving in February 1999. This prompted him to attend local emergency room services. Computed tomography (CT) in February 1999 showed a dural mass involving the posterior-superior right parasagittal area (Figure 1). No other abnormality was noted, nor was there any vasogenic oedema or mass effect. He underwent a stereotactic frameless biopsy and subsequently the mass was excised. However, the meningioma was incompletely excised as it was tightly adherent to the patient’s sagittal sinus. At that time the surgeon felt that sagittal sinus could not be resected, and opted to leave behind some residual tumour. The final pathology revealed large fields of monotonous cells with clear cytoplasm and showed positivity for epithelial membrane antigen but not for glial fibrillary acidic protein (Figure 2). The periodic acid-Schiff reaction in the neoplastic cells was strong, and there was no evidence of necrosis or significant mitotic activity. Ultra-structural study revealed abundant cytoplasmic glycogen, a few cytoplasmic lumina, intermediate filaments, interdigitation of cell membranes, and desmosomal junctions. Overall picture was compatible with clear cell meningioma (CCM).

In the postoperative period, the patient continued to suffer from repeated focal seizures despite intensive anticonvulsant therapy. In September 2000 he started having night sweats, weight loss and was noted to have hypochromic microcytic anaemia. Bone marrow aspiration and biopsy were consistent with the anaemia of chronic disease. Routine chest X-ray revealed multiple bilateral pulmonary nodules suggestive of metastases, and a CT thorax (Figure 3) was also consistent with such a diagnosis. No mediastinal or hilar nodes were noted, and no other disease was evident in the lungs. An abdominal CT yielded nil abnormal, as were the findings of bone scans. Colonoscopy and gastroscopy did not reveal any abnormality. Broncoscopy and a CT-guided biopsy failed to produce a diagnosis. In December 2000 a thoracotomy was performed, whereupon lung biopsy showed the presence of metastatic CCM.

Nine months after the diagnosis of pulmonary metastases was established, his clinical condition deteriorated, there being worsening of seizure activity. Brain CT showed enlargement of the residual tumour, with a dural-based mass involving the posterior-superior right parasagittal area. The patient underwent a second craniotomy in September 2001. A gross total resection of meningioma was performed along with part

![Figure 1.](image-url)
of the longitudinal sinus, which by this time was totally occluded by the tumour and secondary venous drainage had become established. The patient did well in the postoperative period. Six months after the second cranial surgery, the patient was seizure-free. His anaemia resolved and he started to put on weight. Overall, his quality of life improved substantially. Follow-up CT of the lungs showed complete resolution of the known metastatic disease at one year after the surgery (Figure 4). The patient remains clinically and radiologically free of any disease at the nine-year follow-up since his first presentation.

DISCUSSION

In 1995, Zorludemir et al\textsuperscript{1} were the first group to describe CCM and since then, less than 50 cases have been reported in the English literature. Thus, CCM is a rare meningioma variant. Although it has bland cytological features, it has a higher rate of recurrence (61\%) than benign meningiomas (7-20\%) and atypical meningiomas (29-38\%).\textsuperscript{2} Most commonly, CCMs arise in spinal (lumbar and thoracic) and posterior fossa (cerebellopontine angle) intradural locations; very few arise in the fourth ventricle, tentorium-clinoid processes, skull base, and foramen magnum.\textsuperscript{3} Moreover, supratentorial and intraparenchymal locations are rare.\textsuperscript{4}

Intraparenchymal meningioma without any dural attachment generally arises from arachnoid cap cells in the Virchow-Robin spaces along the cerebral vasculature or from the pia mater within the brain sulcus.\textsuperscript{5} Most intraparenchymal meningiomas tend to be supratentorial in location, with a predilection for the frontotemporal and brainstem regions.\textsuperscript{6} Other uncommon sites include the deep sylvian, subcortical, pineal, and suprasellar areas.\textsuperscript{7} Except for those that are intraventricular, most intraparenchymal meningiomas are fibroblastic, and more often affect males, and the mean age of onset is about 20 years earlier than usual meningiomas.\textsuperscript{8} The differential diagnosis of CCM includes: microcystic meningioma, haemangioblastoma, and clear cell ependymoma.

Extracranial metastases are reported to occur in less than one in 1000 cases.\textsuperscript{9} The most frequent extracranial sites for metastases are the lungs; the reported frequency is only 0.1%.\textsuperscript{10} Pulmonary metastases could be explained by haematogenous spread via the caval circulation. In our patient, the tumour was attached to the longitudinal sinus and manipulation at the initial surgery could have
caused haematogenous tumour cell dissemination to visceral sites.

In the past, most intraparenchymal tumours with clear cell morphology were reported as metastatic renal cell carcinomas, oligodendrogliomas, haemangioioblastomas and clear cell ependymomas; that impression being based purely on histomorphology. The absence of immunohistochemistry (IHC) facility in the late 1990s and lack of sufficient data most probably attributed to misinterpretation of initial tumours as oligodendrogliomas. This reiterates the importance of IHC in the diagnostic workup of neurosurgical specimens.

In 2000, the World Health Organization (WHO) designated meningiomas as a distinct group in the classification of brain tumours. According to WHO, meningiomas were classified into benign (grade I), atypical (grade II), or anaplastic (grade III), which was associated with a stepwise change in the genetic characteristic of benign tumours, as these become anaplastic. Overall 90% of meningiomas are slowly growing and benign tumours, and histologically correspond to grade I. About 6 to 8% are designated as atypical meningiomas (WHO grade II) and show a tendency for local recurrence even after complete resection. The remaining 2 to 3% of meningiomas exhibit histological signs of malignancy and are classified as anaplastic (WHO grade III) and have a high risk for local recurrence and metastasising.

Most patients with CCMs are usually young (aged <30 years), but they have been reported in older patients (usually women). Biologically CCMs are aggressive, despite their benign histological appearance, and may display inconsistent correlation with MIB-1 proliferation. Yamada et al. noted high MIB-1 labelling index (LI) [range, 3.3-25.7%; mean, 13.3%] with a 61% recurrence rate. The authors failed to note any definite correlation between tumour recurrence and factors such as mitotic activity, proliferating cell nuclear antigen proliferation indices, percent S-phase determination, or DNA ploidy status. In Jain et al’s series, 22% recurred despite low MIB-1 LI status. Pimentel et al., however, noted that CCMs usually recurred intracranially, especially if patients had endured subtotal resection.

Currently, molecular genetics and karyotype studies have shown a consistent correlation between meningioma recurrence and loss of heterozygosity 22q, 1p, and 14q. Other mutations at 18p11 and 1p35 were also found in benign meningiomas. To gain insight into the pathophysiology of their aggressive behaviour, detailed cytogenetic evaluation is necessary, especially in a large series, and prior to attributing their aggressiveness to any definitive factor.

The treatment of choice for patients with CCM is surgical resection, radiosurgery, and radiotherapy being reserved for recurrences. With due care, meningioma can be surgically resected if they are superficial to the dural surface and easily accessible. Transarterial embolisation with polyvinyl alcohol, alcohol, gelatin foam, coils/microcoils, and Avitene (Davol, Inc., Cranston [RI], US), and other agents have been used as an adjunct to surgery, in order to minimise blood loss, decrease tumour volume, and aid excision. This is not always possible however; depending on their size and location, some meningioma cannot be totally removed if they are too close to or involve with important parts of the brain or blood vessels. The probability of tumour recurrence or growth after surgical resection can be estimated by the tumour’s WHO grade and by the extent of surgery (based on Simpson criteria). If the tumour is not excised completely, adjuvant radiation therapy is often recommended with a view to reduce the risk of regrowth. Radiation doses of 54 Gy for grade I and 60 Gy for grade II-III have been widely used. Recently there have been reports regarding the safe use of stereotactic radiosurgery (SRS). In one retrospective study, 368 patients were treated with SRS, using a median margin dose of 12.5 Gy at 50% isodose (6.5-24 Gy). With a median follow-up of five years, tumour volume had decreased in 70%, were stable in 28%, and had increased in 2%; with actuarial local control of 98%. The results were worse in men and when the radiation dose was <12 Gy. The authors concluded that SRS is a safe and effective treatment for meningiomas. The University of Pittsburgh group also described 99 consecutive patients with benign meningiomas treated by SRS with a median marginal dose of 9 to 25 Gy. They reported an 88% tumour reduction rate of 8 to 10 years after treatment, and a failure rate of approximately 5% at 53 to 120 months. This is the longest reported follow-up in the literature, but only pertains to benign meningiomas. Intensity modulated radiation therapy (IMRT) is an advanced mode of high-precision radiation that utilises computer-controlled linear accelerators to
deliver precise doses to a malignant tumour or specific areas within the tumour. It allows for the radiation dose to conform more precisely to the three-dimensional (3D) shape of the tumour by modulating — or controlling — the intensity of the radiation beam in multiple small volumes. It also allows higher radiation doses to be focused to regions within the tumour while minimising the dose to surrounding critical structures. When compared with conformal radiotherapy, IMRT improves target conformity and coverage by 10 and 36%, respectively. Pirzkall et al.27 employed IMRT to treat recurrent, residual, or untreated skull-base benign meningiomas. After a median follow-up of 36 months, no tumour growth was observed. Since IMRT can achieve high target doses with reduced risks to adjacent structures, this treatment modality is uniquely suitable for treating meningiomas in spinal locations.

The European Organization for Research and Treatment of Cancer (EORTC) completed accrual on a phase III study (EORTC 26021), which essentially compared observation versus conventional-fractionated radiotherapy or radiosurgery after non-radical surgery for benign intracranial meningiomas, but results are still awaited. However, when the meningioma is unresectable and / or all other previous local treatments have failed, immunotherapy or chemotherapy may be an option for malignant tumours, and immunotherapy and hormone therapy if they are benign. Various chemotherapy regimens have shown some efficacy, including: combinations of doxorubicin and dacarbazine or ifosfamide and mesna.26 The most effective immunotherapy appears to be interferon-alpha, which is relatively non-toxic and well-tolerated.27 However, more studies are needed to define the roles of these agents in the management of recurrent, unresectable, or malignant meningiomas. Antiprogestin agents have been used, but with variable results.28 Hydroxyurea has recently been shown to shrink unresectable or recurrent meningiomas to some extent, but needs further evaluation.29

Resolution of pulmonary metastasis after complete resection of the primary tumour is unique. This phenomenon has never been reported previously in the literature. Similar phenomena have been observed in patients with renal cell carcinoma, whereby spontaneous metastatic tumour regression ensues after nephrectomy.30 However most of the latter regressions are short-lived.31 Among the various hypotheses to explain this phenomenon, an immunological response (activation of lymphocytes leading to release of cytotoxic mediators such as interferon and interleukins which cause regression) is the most favoured. Other postulated mechanisms include decreases in angiogenic factors entering the circulation due to removal of the primary tumour.32

CONCLUSIONS

Our case report indicates that CCM can result in systemic spread, especially if the tumour is located close to the vasculature. Complete excision of the primary tumour should be attempted whenever possible, if metastatic disease is encountered. Our patient also highlights the need for incorporating IHC to supplement conventional histomorphology in the routine diagnostic workup of intraparenchymal clear cell tumours. The latter include a wide spectrum of conditions often with distinctive features, and range from oligodendroglioma, haemangioblastoma, clear cell ependymoma, extraventricular neurocytoma, CCMs, and metastatic tumours.

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