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Cancer metastases to meningioma: apropos two cases

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Abstract

Tumour-to-tumour metastasis (TTTM) is the uncommon phenomenon in the systemic and central nervous system neoplasia. We report on two new cases of metastases to meningioma. The first case concerned a patient with renal cancer and synchronous asymptomatic meningioma followed up radiologically. In the fifth year of observation, he developed acute neurological symptoms. Neuroimaging showed meningioma enlargement with irregular surrounding oedema. On gross exam, the tumour had two different components, which histopathologically comprised atypical meningioma and renal cancer deposits. The patient's postoperative course was complicated with a subdural hematoma. The second TTTM case concerned a patient with a two-year history of colorectal cancer treatment with recent severe headaches. Radiologically the temporal lobe metastatic focus was detected. During cerebral metastasectomy, small meningeal incidentaloma was resected, histologically being meningioma with adenocarcinoma metastasis. Tumour metastasis to meningioma can be the only one or one of the places of cancer dissemination. TTTM can cause postoperative complications. Our cases prove the importance of the careful sampling of tumours and necessity of immunohistochemistry in differential diagnosis between meningioma subtypes and metastatic focus.

Key words: *tumour-to-tumour metastasis, meningeal tumours, meningioma, cancer metastasis.*

Introduction

The coexistence of two histologically different neoplasms in one patient has become more often observed in oncologic patients [7,21]. However, the phenomenon of tumour-to-tumour metastasis (TTTM), where one type of neoplasm gives secondary foci to another tumour is very rare. Less than 200 cases of TTTM have been reported in the literature [6,23]. Usually the donor tumour is disseminated in such cases [6,30]. In the case of TTTM, tumour recipients are usually slow-growing neoplasms. Interactions of tumour cells with each other, surrounding normal cells and extracellular matrix or basement membrane are pivotal to all stages of cancer progression [7]. The important element in cancer cell homing during blood-borne dissemination is specific vascularization and perivascular niche in host tissue [8,27]. Metastases constitute up to 30% of all intracranial neoplasms and can be located in the brain and the meninges [8,24,27]. In CNS TTTM, the tumours harbouring metastases are most commonly meningiomas [20,30].

CNS TTTM are most often unexpected clinically and radiologically. In some instances, meningioma

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is detected in pathological examination of radiologically-described metastatic lesion [12,22]. Some of the metastatic lesions are the incidental findings within meningioma tissue and can be even the first sign of malignancy [17,25,31]. Some metastases cause significant oedema, necessitating rapid surgical resection [31]. In correct diagnosis of TTTM, it is necessary to differentiate with a rare phenomenon of collision or fusion of primary separate growth of "host" tumour and metastatic focus [2]. The role of modern neuroimaging, like functional imaging and MR spectroscopy may be helpful in preoperative diagnosis of TTTM lesions [3,18,23].

Here we present two new cases of tumour-to-tumour metastases with a short review of the literature.

Material and methods

The tumour sections were formalin fixed, paraffin embedded and HE stained for the routine diagnostic procedures. The immunostaining was performed manually on representative sections with DAKO (Denmark) routine protocol and reagents. Ready-to-use antibodies raised against: cytokeratin (CK) AE1/AE3, 7 and 20 (CK7, CK20), epithelial membrane antigen (EMA), S100, vimentin, CD10, progesterone receptor (PR), CD44, E-cadherin and CDX2 were used. Appropriate positive and negative controls (omission of the primary antibody) were carried out for every antibody. Diaminobenzidine was the chromogen in all reactions, En Vision technology was used for visualization.

Case 1

A 70-year-old man was admitted to the neurosurgery department in October 2009 with a two-week history of increasing motor aphasia and right hemiparesis. His oncologic history started in 2003 with a right radical nephrectomy due to a renal clear cell cancer (RCC) (pT1bN0M0, Fuhrman G2). Synchronously, on radiological screening, the left fronto-parietal clinically silent tumour 30 × 20 × × 20 mm was detected. The computed tomography (CT) picture was typical of meningioma, with dural tail and homogenous contrast enhancement. The patient refused to undergo the craniotomy. Moreover, in 2006, due to newly diagnosed prostate cancer (Gleason score 7), he was put on the hormonal therapy with a good response. The patient remained neurologically asymptomatic with regular follow-up of meningioma which was growing slowly, and in 2008 measured 45 × 35 × 20 mm.

On admission in 2009, cranial CT disclosed tumour enlargement to 60 × 45 × 25 mm and higher contrast enhancement (Fig. 1A). The superior part of the tumour enclosed the oval fraction which enhanced a stronger (than the rest) part of the tumour (Fig. 1B). Segmental peritumoral oedema, especially in the region of the above fraction was also present (Fig. 1C). The progression of meningioma with atypical features was suggested radiologically. CT results of the lungs and abdomen were normal.

The patient underwent a total microsurgical resection of the well-vascularized bleeding meningeal mass. The postoperative course was complicated with a hematoma in the operative area on the third day. Hematoma was removed surgically and drained, but hemiparesis persisted. The patient was discharged to the hospice care unit and died six months later due to pneumonia.

No clinical information about patients' oncologic history was written on the referral card for histopathology. Grossly, the resected tumour was gray and firm, with a soft yellow area up of to 15 mm. Histologically, the majority of the tumour mass was made up of whorled clusters of spindle cells with few necrotic foci and mitotic index of 6/10 HPF. The separating area was composed of clear polygonal neoplastic cells with dense delicate vasculature (Fig. 2A-B). The immunophenotyping disclosed differences between both areas. The predominant meningioma component was positive for vimentin, EMA, S-100, PR, CD44, and E-cadherin, and was CK AE1/AE3 negative. The second clear cell component showed a expression of cytokeratin, vimentin, CD10 and E-cadherin, being negative for S-100, PR, and CD44 (Fig. 2C-D). The final histopathological diagnosis of atypical meningioma (II WHO) with the metastasis of renal cell carcinoma was established.

Case 2

A 57-year-old man with a two-year history of a colorectal cancer (T3N1M0 at the diagnosis) was admitted in 2009 to the hospital due to severe headaches. His previous oncologic therapy included right hemicolectomy and adjuvant chemotherapy. On admission, CT revealed a contrast enhancing intracerebral temporal lobe tumour of 25 × 32 × 30 mm

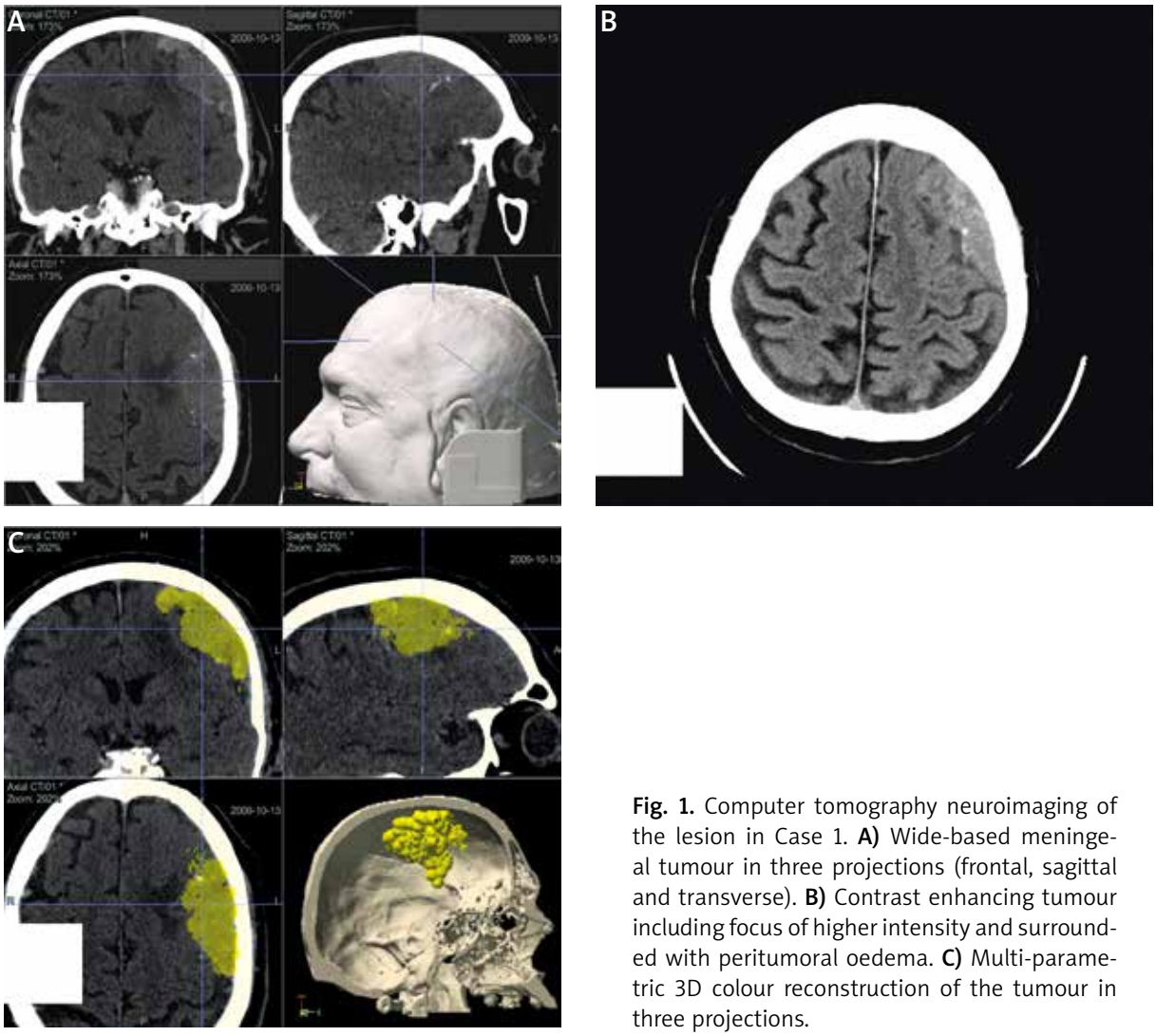

Fig. 1. Computer tomography neuroimaging of the lesion in Case 1. **A)** Wide-based meningeal tumour in three projections (frontal, sagittal and transverse). **B)** Contrast enhancing tumour including focus of higher intensity and surrounded with peritumoral oedema. **C)** Multi-parametric 3D colour reconstruction of the tumour in three projections.

surrounded with prominent oedema. He was qualified for the resection. The neurosurgeon removed brain metastasis totally and another, radiologically not described meningeal tumorlet with a diameter of 9 × 5 mm in the parietal region. The postoperative course was uncomplicated. The patient died one year later due to cancer dissemination to the liver and lungs.

Grossly, the resected brain tumour consisted of several fragments of greyish tissue. The meningeal tumorlet was beige and oval. Histologically, in the cerebral tumour samples, necrotizing metastatic colonic tubular adenocarcinoma was diagnosed. The meningeal incidentaloma was a meningothelial meningioma (I WHO) bearing typical immunophenotype (S100 +, EMA +, cytokeratins-negative, E-cadherin ++), including a 4 mm focus of a metastasis of tubular adenocarcinoma (Fig. 2E-F). The metastasis, consistent with colonic cancer, was positive for cytokeratins CKAE1/3 and CK20, also expressed CDX2 and E-cadherin.

Discussion

Tumour-to-tumour metastases are very rare in systemic and CNS neoplasia [2,6,23]. The tumours – recipients are usually benign, as thyroid adenoma, lipoma and schwannoma, and rarely malignant – bronchoalveolar lung carcinoma, thyroid carcinoma and renal cell carcinoma [23,29]. The intracranial host tumours for metastases are most commonly meningiomas. The second most frequent type of TTTM is renal cancer metastatic to hemangioblas-

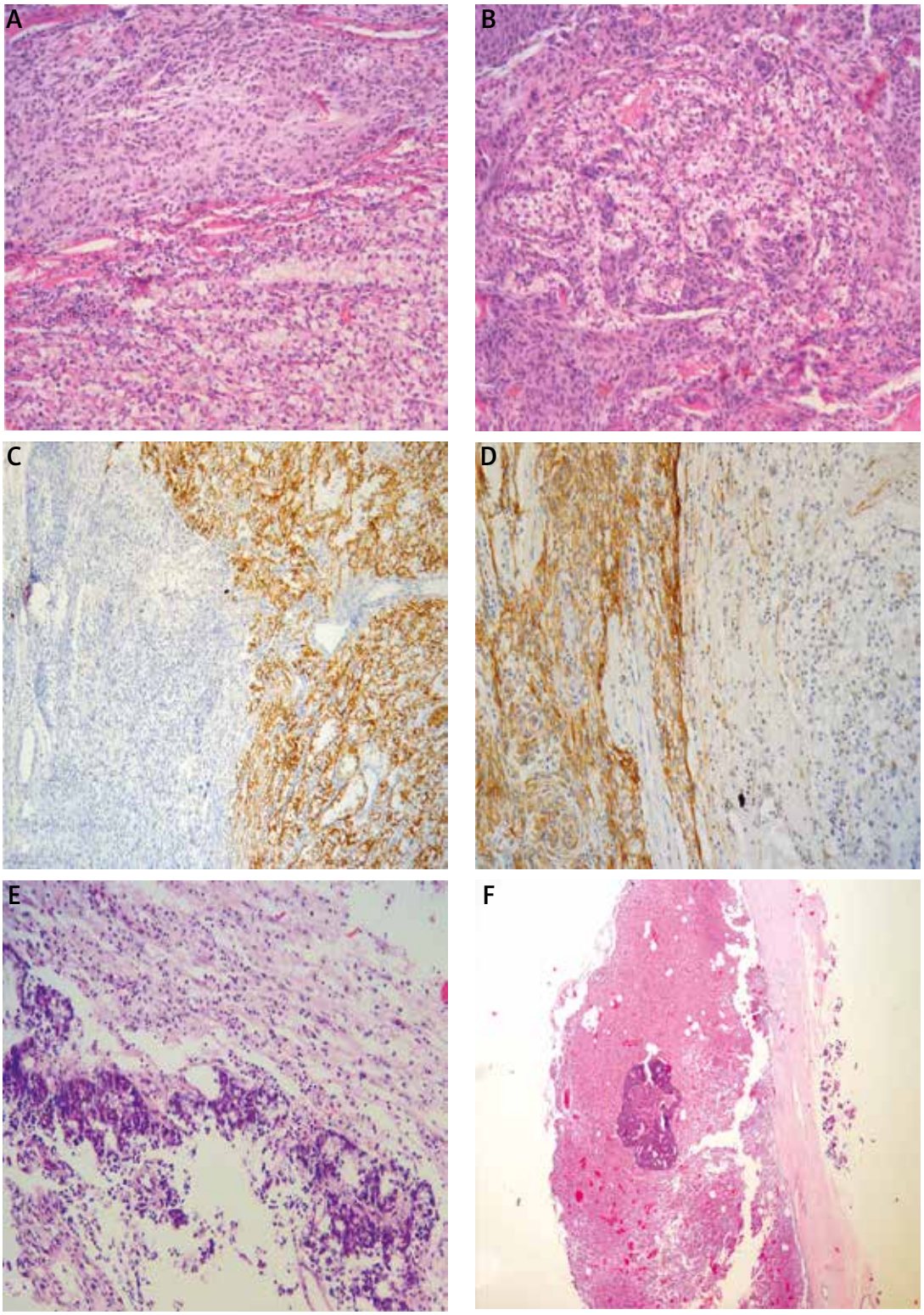

Fig. 2. Histopathology of the tumours (**A-D** Case 1; **E-F** Case 2). **A)** Histology of the renal cancer metastasis to meningioma – sharp interface between two neoplastic populations (HE, 100×). **B)** Clear cell cancer focus surrounded with host meningioma component (HE, 200×). **C)** CD10 expression in metastatic renal clear cell carcinoma (CD10, 100×). **D)** S100 positivity in host meningioma tissue (S100, 200×). **E)** Brain metastasis of necrotizing colonic adenocarcinoma (HE, 200×). **F)** Tubular adenocarcinoma metastasis within meningioma (HE, 40×).

toma in patients with von Hippel-Lindau syndrome [17,20]. Pamphlett and Campbell *et al.* found the criteria to assess a true TTTM, underlining that the metastatic focus must be enclosed by a rim of histologically distinct host tumour tissue to exclude a collision process. Moreover, the existence of two primary tumours must be proven and histologically ascertained [6,25]. Both cases presented here fulfil these criteria.

The pathomechanism of TTTM is still unresolved, however several ideas exist including: metabolic, vascular, hormonal, immunologic and molecular [2,6,26]. TTTM to meningiomas can also represent a special type of meningeal metastasis. In the case of metastases to meningioma, the rich vascular network of a meningioma provides a particularly susceptible medium to receive a hematogenous metastasis [19,23]. The possible role of chemokine receptor CXCR4 cooperating with CXCL12 is suggested [26]. Certain chemokines serve as tissue-specific attractant molecules for tumour cells, promoting cell migration to a particular site. Chemokine expression is involved in cancer metastasis by modulating neoplastic cell movement, migration and homing [7,26]. The molecular recognition theory is exemplified by HER2-positive breast cancer and its higher rate of metastases to the brain where HER2 is expressed [27]. A similar theory, used in TTTM, concerns breast cancer with E-cadherin expression and its affinity to homing within meningioma tissue with E-cadherin positivity. Interestingly, E-cadherin expression is frequently higher in distant metastases than in primary tumours and often these secondary tumours are better differentiated than primary ones [10,28]. This can be a manifestation of mesenchymal-epithelial transition (MET), a process of reacquisition of epithelial features by metastatic cells [10].

Our Case 1 is the first reported TTTM to meningioma with a long radiologic observation, in a patient with three different tumour types. There was probably a genetic background of neoplasia in this patient, but the molecular analyses were not carried out. Meningiomas show a naturally slow growth rate, especially in older patients, allowing for wait-and-see approach in selected patients [15,19,32]. Rapid exacerbation of clinical symptoms in long standing meningioma patients is most probably connected with the phenomenon of progression of its grade [1,13]. Perhaps in our patient, antiandrogenic therapy in the course of the prostatic cancer could influence meningioma biologic progression. Finally, blood-born RCC metastasis caused mass effect, hypervascularization, vasogenic oedema and acute neurologic symptoms. Moreover, well-vascularized TTTM caused intense postoperative bleeding. The immunophenotyping was pivotal for differentiation of RCC focus from a clear cell meningioma component, especially because no clinical information about oncologic history of the patient was added.

Metastases from renal cancer to meningioma are rare and only seven cases have been described so far [5,11,12,16,17]. The patients' age ranged from 45 to 82 years. The time span between nephrectomy and different neurological symptoms due to TTTM render from several days to 7 years [12,23]. Five cases were subtyped into: three meningothelial, one lipomatous and one anaplastic. Interestingly, the diagnosis of RCC was based at first on the meningioma with TTTM investigation in three cases [5,11,16].

The other types of cancer metastasis to meningioma include lung, breast, prostate and single cases of other malignancies [4,22,30]. The second of our TTTM cases – the incidentaloma is one of extremely rare cases, where TTTM accompanied synchronous cancer metastases to the brain. This is also one of few examples of colon cancer deposits within meningioma. Our TTTM was small, localized outside the vascularization region of big cerebral adenocarcinoma metastasis. In this patient, CNS metastases preceded generalized cancer systemic dissemination.

It is difficult to diagnose TTTM based on imaging and intraoperative gross clinical picture. In our Case 1, the oval stronger enhancing component in the upper part of the meningioma was a metastatic focus, but CT exam was interpreted as focal malignant transformation. Radiologically, there are some features of atypical meningioma on CT scanning: heterogeneous appearance, homogeneous dense enhancement after contrast injection, bone destruction and peritumoral oedema [9,14,18]. RCC and its metastases are hypervascular lesions and a high enhancement after contrast medium administration is typically noted. However, the same enhancement pattern is observed in meningioma with necrotic changes and cystic degeneration [3,18]. It is extremely difficult to distinguish two different tumours in one pathological mass without histological examination, especially in the case of a similar type of vasculature [14]. In Case 2, a radiologic report focused on a cerebral

metastasis and signs of peritumoral oedema, whilst small meningeal tumour was not described at all. MR spectroscopy can be a helpful diagnostic tool in differential diagnosis of dural metastases *versus* meningioma and even TTTM. Moreover, diffusion and perfusion MRI techniques will enable diagnostic efficacy. However, despite modern neuroimaging, pathological examination is crucial for correct diagnosis [3,18,30].

Cancer metastasis to meningioma can be the first manifestation of the metastatic stage of disease or can arise during neoplastic hematogenous dissemination. Often there are limited clinical consequences of TTTM, but high vascularization of these tumours can cause peritumoral oedema and the postoperative haemorrhage. Metastasis to meningioma should be included into histopathological diagnosis scope of meningeal masses in patients with systemic malignancies. Our cases prove the importance of the careful gross inspection and sampling of tumours and necessity of immunohistochemistry in differential diagnosis between multiple meningioma subtypes and possible metastatic focus.

References

1. Al-Mefty O, Kadri PA, Pravdenkova S, Sawyer JR, Stangeby C, Husain M. Malignant progression in meningioma: documentation of a series and analysis of cytogenetic findings. J Neurosurg 2004; 101: 210-218.
2. Anlyan FH, Heinzen BR, Carras R. Metastasis of tumor to second different tumor: collision tumors. JAMA 1970; 212: 2124.
3. Bendszus M, Warmuth-Metz M, Burger R, Klein R, Tonn JC, Solymosi L. Diagnosing dural metastases: the value of 1H magnetic resonance spectroscopy. Neuroradiology 2001; 43: 285-289.
4. Benedetto N, Perrini P, Scollato A, Buccoliero AM, Di Lorenzo N. Intracranial meningioma containing metastatic colon carcinoma. Acta Neurochir (Wien) 2007; 149: 799-803.
5. Breadmore R, House R, Gonzales M. Metastasis of renal cell carcinoma to a meningioma. Australas Radiol 1994; 38: 144-143.
6. Campbell LV, Jr., Gilbert E, Chamberlain CR, Jr., Watne AL. Metastases of cancer to cancer. Cancer 1968; 22: 635-643.
7. Eccles SA, Welch DR. Metastasis: recent discoveries and novel treatment strategies. Lancet 2007; 369: 1742-1757.
8. Gavrilovic IT, Posner JB. Brain metastases: epidemiology and pathophysiology. J Neurooncol 2005; 75: 5-14.
9. Goyal LK, Suh JH, Mohan DS, Prayson RA, Lee J, Barnett GH. Local control and overall survival in atypical meningioma: a retrospective study. Int J Radiat Oncol Biol Phys 2000; 46: 57-61.
10. Gunasinghe NP, Wells A, Thompson EW, Hugo HJ. Mesenchymal-epithelial transition (MET) as a mechanism for metastatic colonisation in breast cancer. Cancer Metastasis Rev 2012; 31: 469-478.
11. Gutierrez Morales JC, Gutierrez Morales SE, Astudillo Gonzalez A. 72 year-old man with new seizure while dancing. Brain Pathol 2009; 19: 347-348.
12. Han HS, Kim EY, Han JY, Kim YB, Hwang TS, Chu YC. Metastatic renal cell carcinoma in a meningioma: a case report. J Korean Med Sci 2000; 15: 593-597.
13. Izycka-Swieszewska E, Rzepko R, Borowska-Lehman J, Baranowska E, Warzocha D. Recurrent meningiomas – the immunohistochemical analysis of angiogenesis and cellular proliferation. Preliminary study. Folia Neuropathol 1999; 37: 179-184.
14. Jaskólski D, Fortuniak J, Stefańczyk L, Majos A, Gajewicz W, Papierz W, Liberski PP, Sikorska B. Differential diagnosis of intracranial meningiomas based on magnetic resonance spectroscopy. Neurol Neurochir Pol 2013; 47: 247-255.
15. Jaskólski D, Papierz T, Liberski PP, Sikorska B. Ultrastructure of meningiomas: autophagy is involved in the pathogenesis of "intranuclear vacuoles". Folia Neuropathol 2012; 50: 187-193.
16. Kimiwada T, Motohashi O, Kumabe T, Watanabe M, Tominaga T. Lipomatous meningioma of the brain harboring metastatic renal-cell carcinoma: a case report. Brain Tumor Pathol 2004; 21: 47-52.
17. Lanotte M, Benech F, Panciani PP, Cassoni P, Ducati A. Systemic cancer metastasis in a meningioma: report of two cases and review of the literature. Clin Neurol Neurosurg 2009; 111: 87-93.
18. Lee EK, Lee EJ, Kim MS, Park HJ, Park NH, Park S, 2nd, Lee YS. Intracranial metastases: spectrum of MR imaging findings. Acta Radiol 2012; 53: 1173-1185.
19. Marosi C, Hassler M, Roessler K, Reni M, Sant M, Mazza E, Vecht C. Meningioma. Crit Rev Oncol Hematol 2008; 67: 153-171.
20. Martin SE, Al-Khatib SM, Turner MS, Douglas-Akinwande AC, Hattab EM. A 41-year-old woman with von Hippel-Lindau and a cerebellar lesion. Brain Pathol 2010; 20: 511-514.
21. Matyja E, Kunert P, Grajkowska W, Marchel A. Coexistence of meningioma and schwannoma in the same cerebellopontine angle in a patients with NF2. Folia Neuropathol 2012; 50: 166-172.
22. Mitchell RA, Dimou J, Tsui A, Kavar B. Metastatic prostate adenocarcinoma invading an atypical meningioma. J Clin Neurosci 2011; 18: 1723-1725.
23. Moody P, Murtagh K, Piduru S, Brem S, Murtagh R, Rojiani AM. Tumor-to-tumor metastasis: pathology and neuroimaging considerations. Int J Clin Exp Pathol 2012; 5: 367-373.
24. Nayak L, Abrey LE, Iwamoto FM. Intracranial dural metastases. Cancer 2009; 115: 1947-1953.
25. Pamphlett R. Carcinoma metastasis to meningioma. J Neurol Neurosurg Psychiatry 1984; 47: 561-563.
26. Peguero JS, Camacho LH, Kemp B, Campos LT. Chemokine expression in tumor-to-tumor metastasis. Oncol Lett 2010; 1: 449-452.
27. Preusser M, Capper D, Ilhan-Mutlu A, Berghoff AS, Birner P, Bartsch R, Marosi C, Zielinski C, Mehta MP, Winkler F, Wick W, von Deimling A. Brain metastases: pathobiology and emerging targeted therapies. Acta Neuropathol 2012; 123: 205-222.
28. Prudkin L, Liu DD, Ozburn NC, Sun M, Behrens C, Tang X, Brown KC, Bekele BN, Moran C, Wistuba, II. Epithelial-to-mesenchymal transition in the development and progression of

adenocarcinoma and squamous cell carcinoma of the lung. Mod Pathol 2009; 22: 668-678.
29. Stevens TM, Richards AT, Bewtra C, Sharma P. Tumors metastatic to thyroid neoplasms: a case report and review of the literature. Patholog Res Int 2011; 2011: 238693; doi: 10.4061/2011/238693.
30. Takei H, Powell SZ. Tumor-to-tumor metastasis to the central nervous system. Neuropathology 2009; 29: 303-308.
31. Widdel L, Kleinschmidt-DeMasters BK, Kindt G. Tumor-to-tumor metastasis from hematopoietic neoplasms to meningiomas: report of two patients with significant cerebral edema. World Neurosurg 2010; 74: 165-171.
32. Yoneoka Y, Fujii Y, Tanaka R. Growth of incidental meningiomas. Acta Neurochir (Wien) 2000; 142: 507-511.