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Review

Tumor-to-Tumor Metastasis of the Central Nervous System

Santral Sinir Sisteminde Tümörden Tümöre Metastaz

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ABSTRACT

Tumor-to-tumor metastasis is a well recognized phenomenon. Although any tumor may be potential recipient of metastasis, renal cell carcinoma and meningioma are the most common malignant and benign recipients, respectively, whereas the lung and breast are the most common metastatic donors respectively, in both settings. Patients with hereditary cancer syndromes may be at higher risk for the development of tumor-to-tumor metastases. The most common pattern of tumor-to-tumor metastasis for intracranial neoplasms is the type in which an aggressive high-grade malignancy serves as the source of tumor and a more indolent neoplasm serves as the recipient tumor. The development of tumor metastasis from a second primary malignancy is uncommon and remains biologically puzzling. Its low incidence has made its full biological characterization evasive. Although rare, neurosurgeons should be aware of the entity of tumor-to-tumor metastasis.

KEYWORDS: Tumor, Metastasis, Central nervous system

ÖZ

Tümörden tümöre metastaz, iyi bilinen bir fenomendir. Herhangi bir tümör, metastazlar için potansiyel hedef olsa da en sık yayıldıkları malign ve benign tümörler sırasıyla renal hücreli karsinom ve menenjiyomlardır, en sık kaynaklandıkları bölgeler ise akciğer ve memedir. Herediter kanser sendromlarına sahip olan hastalar tümörden tümöre metastaz gelişimi açısından daha fazla risk taşıyabilirler. İntrakranial neoplazilerde tümörden tümöre metastazların en sık görülen şekli, saldırgan ve yüksek evreli bir tümörün daha iyi huylu bir tümöre metastazı ile olandır. Tümör metastazının ikinci bir primer malign tümörden gelişmesi az görülür ve biyolojik olarak halen şaşırtıcıdır. Bu durumun insidansının düşük olması biyolojik tanımlamanın tam olarak yapılmasını da zorlaştırmaktadır. Nadir olsa bile nöroşirürjiyenler, bir antite olarak tümörden tümöre metastaz hakkında bilgi sahibi olmalıdırlar.

ANAHTAR SÖZCÜKLER: Tümör, Metastaz, Santral sinir sistemi

INTRODUCTION

Tumor-to-tumor metastasis is a well-documented phenomenon since the first documented case of bronchogenic carcinoma metastatic to a meningioma (50). However, this phenomenon remains fairly uncommon and less than 100 cases have been published so far in the medical literature (94).

We mean different entities with the terms "tumor-to-tumor metastasis" and "collision tumor". However, they may be confused with one another. Two neighboring neoplasms must invade one another to be called "collision tumors". Extending this definition, collision lesions refer to histologically different pathological conditions found in combination and may include neoplastic, vascular, congenital, or infectious/inflammatory lesions (75). However, according to Campbell et al, tumor-to-tumor metastasis should include certain strict criteria. These are as follows: 1) More than one primary tumor exists; 2) The recipient tumor must be a true neoplasm; 3) The donor tumor must be the source of a true metastasis. Direct contagious spread is not acceptable as metastasis; and 4) Tumors that have metastasized to the lymphatic system where lymphoreticular malignant tumors already exist are excluded (25). Interestingly, in the majority of the cases, the metastatic lesions are occult and only discovered during autopsy (14). Although any tumor may be the potential recipient of metastasis, renal cell carcinoma is by far the most common recipient among the malignant tumors (121), and lung cancer metastasis to renal cell carcinoma represents the most common combination (116).

The most common pattern of tumor-to-tumor metastasis for intracranial neoplasms is the type in which an aggressive high-grade malignancy serves as the source of tumor and a more indolent neoplasm serves as the recipient tumor. However, a unique case characterized with secondary lymphoma involving metastatic follicular thyroid carcinoma of the skull has been reported (85). This case represents an unusual presentation of a patient with metastatic follicular thyroid carcinoma to the skull (recipient tumor), who then developed a diffuse large B-cell lymphoma (donor tumor) that secondarily infiltrated the skull metastasis (85).

Literature Review Methods

In this review, we intended to direct the attention of neurosurgeons to this well-recognized but rarely encountered entity by performing a PubMed search to identify all cases published up to now. Articles that were referenced by reviewed articles were also evaluated. Data were extracted from articles after a search for the words "tumor", "metastasis" and "central nervous system". Exclusion criteria included collision tumors reported as tumor-to-tumor metastasis, and doubtful cases reported with insufficient surgical or post-mortem evidence.

Metastasis to Meningiomas

In the central nervous system, meningiomas have been found to be the most common intracranial benign tumors to host a metastatic cancer (59), the majority of which arise from lung or breast carcinomas (81). Certain similarities between meningioma and breast cancer exist. They each occur more frequently in women in the fifth and sixth decade, and pregnancy accelerates the symptoms of both entities. Since metastases to leptomeninges commonly occurs, a leptomeningeal metastatic focus can grow adjacent to the meningioma followed by successive fusion of both tumors (collision tumors). These cases should be eliminated from tumor-to-tumor metastasis, and for this purpose, Pamphlett proposed basic criteria for the diagnosis of true tumor-to-meningioma metastasis: 1) The metastatic focus must at least be partially enclosed by a rim of histologically distinct host tumor tissue; and 2) The existence of metastasizing primary carcinoma must be proven and compatible with the metastasis (105). Furthermore an increase in the estrogen and progesterone receptor proteins has been noted.

According to Barz, 88 meningiomas (0.9%), were found among 8371 autopsies. 29 meningiomas (0.3%) were associated with extraneural primary malignancies. In 4 cases (0.04%), a carcinoma metastasized into a meningioma (8). Less common primary sites of genitourinary system yielding to such metastasis have been reported, including the kidneys and prostate (96). A higher predisposition to metastasize to meningiomas has been reported for breast carcinoma (82).

A review of 20 cases of metastatic carcinoma disclosed several interesting facts; 1) metastasis to an intracranial meningioma or neurilemmoma was twice as frequent in autopsy material as in surgical material, 2) this phenomenon was twice as common in females, 3) adenocarcinoma of the lung in males and of the breast in females were the most commonly encountered donor tumors, 4)the metastasizing tumor was always found to be widely disseminated in autopsy studies, 5) despite the presence of widespread metastases, the existence of the primary carcinoma was known prior to autopsy in only about 60% of cases, 6) CNS symptoms were present in 2/3 of the patients, however, additional metastases to organs outside the CNS were more common in those without symptoms (30).

The predisposing factors are predisposing factors:

- The loss of a tumor-suppressor gene associated with syndromes of multiple primary tumors (often including meningiomas), increasing the likelihood of two or more tumors coexisting in the same patient, a hormonal relationship between meningioma and breast cancer, also increasing the likelihood of both tumors, E-cadherin expression by both meningiomas and breast cancer (3).
- The low metabolic rate and indolent growth of these tumors (55).
- The rich vascular supply that may act as a vascular filter or the low flow rate within the cranial venous system that may increase the likelihood of tumor cell adherence (118).
- Absence of the host immune response within the meningiomas rendering these tumors as immunological havens for metastases.
- The high collagen and lipid content of meningiomas that can provide a "fertile soil" for the seeding of malignant cells (47).

Surely, disruption of the blood-brain barrier should be considered as a possible route of invasion since the metastatic spread is almost certainly hematogeneous (111). Most of the cases with metastases to meningioma were intracranially located except three cases that were spinal meningiomas (3, 63, 102).

There is no reliable radiological imaging technique to detect the presence of metastasis within meningioma at present. It is supposed that computed tomography may show a hyperdense area or, when associated with necrotic component, a hypodense area (71, 115). A case of metastatic malignant melanoma within meningioma with intratumoral infarct that caused hypodensity was reported (104). There are some other cases of focal hypodensity within meningioma (30, 81). However, this appearance usually reflects the presence of calcification, necrotic foci, cystic degeneration or haemorrhage. Also, atypical signal characteristics were reported after intravenous administration of gadolinium on MRI in a few cases in the literature (27, 43, 81) without particular features. Since the physiological features of the tumor change after metastasis, neuroimaging methods such as perfusion MR and MR spectroscopy may be useful in differentiating tumor histology (23, 72). Even so, the correct diagnosis might be made by histological examination. However, the clinical picture may provide a clue about metastasis. Acute deterioration in the consciousness level and rapid onset of neurological symptoms should keep the surgeon aware of changes due to perilesional edema and increased mass effect.

Analysis of Table I discloses the biggest numbers in the literature for metastasis to meningioma. There are 114 cases of tumor-to-meningioma metastasis that have been reported. Similar to previous reviews, most primary tumors were of the breast (54 cases), lung (23 cases) and kidney (10 cases). In contrast, breast and prostate metastases (8 cases) were much more common than previous studies. This increase may be explained by routine screening and early diagnosis.

Table I: Summary of Meningiomas Containing Metastases Reported in the Literature

Donor site	Tumor type of donor site	Recipient site	Tumor type of recipient site	# of cases	References
Breast	Carcinoma	Brain	Meningioma	1	Bernstein, 1933 (11)
	Carcinoma	Brain	Meningioma	1	Lapresle et al., 1952 (78)
	Carcinoma	Brain	Meningioma	2	Osterberg, 1957 (101)
	Carcinoma	Brain	Meningioma	1	Helpap, 1965 (60)
	Carcinoma	Brain	Meningioma	1	Buge et al., 1966 (22)
	Carcinoma	Brain	Meningioma	1	Anlyan et al., 1970 (5)
	Carcinoma	Brain	Meningioma	1	Theologides et al., 1972 (133)
	Carcinoma	Spine	Meningioma	1	Hockley, 1975 (63)
	Carcinoma	Brain	Meningioma	1	Di Bonito et al., 1978 (39)
	Carcinoma	Brain	Meningioma	1	Chambers et al., 1980 (30)
	Carcinoma	Brain	Meningioma	1	Nunnery et al., 1980 (100)
	Carcinoma	Brain	Meningioma	1	Savoiardo et al., 1980 (115)
	Carcinoma	Brain	Meningioma	1	Joglekar et al., 1981 (70)
	Carcinoma	Brain	Meningioma	2	Lodrini et al., 1981 (84)
	Carcinoma	Brain	Meningioma	2	Barz, 1983 (8)
	Carcinoma	Brain	Meningioma	1	Schmitt, 1984 (118)
	Carcinoma	Brain	Meningioma	1	Doron et al., 1987 (40)
	Carcinoma	Brain	Meningioma	1	Zon et al., 1989 (155)
	Carcinoma	Brain	Meningioma	1	Fabaron et al., 1990 (45)
	Carcinoma	Brain	Meningioma	1	Bucciero et al., 1992 (21)
	Carcinoma	Brain	Meningioma	1	Chou et al., 1992 (32)
	Carcinoma	Brain	Meningioma	1	Chow et al., 1992 (33)
	Carcinoma	Brain	Meningioma	1	Bonito et al., 1993 (15)
	Carcinoma	Brain	Meningioma	1	Völker et al., 1993 (139)
	Carcinoma	Brain	Meningioma	1	Cervoni et al., 1994 (28)
	Carcinoma	Brain	Meningioma	2	Fornelli et al., 1995 (48)
	Carcinoma	Brain	Meningioma	9	Salvati et al., 1996 (114)
	Carcinoma	Brain	Meningioma	1	Lee et al., 1998 (81)
	Carcinoma	Brain	Meningioma	1	Elmaci et al., 2001 (43)
	Carcinoma	Brain	Meningioma	1	Maiuri et al., 2002 (89)
	Carcinoma	Brain	Meningioma	1	Watanabe et al., 2002 (141)
	Carcinoma	Brain	Meningioma	1	Baratelli et al., 2004 (7)
	Carcinoma	Spine	Meningioma	1	Aghi et al., 2005 (3)
	Carcinoma	Brain	Meningioma	3	Caroli et al., 2006 (27)
	Carcinoma	Brain	Meningioma	1	Jun et al., 2006 (72)
	Carcinoma	Brain	Meningioma	1	Seckin et al., 2006 (120)
	Carcinoma	Brain	Meningioma	1	Miyagi et al., 2007 (92)
	Carcinoma	Brain	Meningioma	1	Lanotte et al., 2009 (77)
	Carcinoma	Brain	Meningioma	1	Lin et al., 2009 (83)
	Carcinoma	Spine	Meningioma	1	Pablo et al., 2009 (102)
Lung	Bronchogenic carcinoma	Brain	Meningioma	1	Fried et al., 1930 (50)
	Bronchial carcinoma	Brain	Meningioma	1	Osterberg, 1957 (101)
	Carcinoma	Brain	Meningioma	1	Best, 1963 (12)
	Carcinoma	Brain	Meningioma	1	Wilson et al., 1967 (146)
	Carcinoma	Brain	Sphenoid ridge meningioma	1	Wolintz et al., 1970 (147)
	Carcinoma	Brain	Meningioma	1	Zoos, 1970 (156)
	Adenocarcinoma	Brain	Parasagittal meningioma	1	Gyori, 1976 (57)
	Bronchial carcinoma	Brain	Meningioma	1	Weems et al., 1977 (142)
	Bronchial carcinoma	Brain	Sphenoid ridge meningiom	1	Hope et al., 1978 (65)
	Carcinoma	Brain	Meningioma	1	Chambers et al., 1980 (30)

Table I: Cont.

Lung	Carcinoid tumor	Brain	Fibroblastic meningioma	1	Smith et al., 1981 (124)
	Carcinoma	Brain	Meningioma	1	Jomin et al., 1982 (71)
	Carcinoma	Brain	Meningioma	1	Barz, 1983 (8)
	Carcinoma	Brain	Meningioma	1	Pamphlett, 1984 (105)
	Carcinoma	Brain	Meningioma	1	Schmitt, 1984 (118)
	Adenocarcinoma	Brain	Meningioma	1	Conzen et al., 1986 (36)
	Adenocarcinoma	Brain	Optic nerve sheath meningioma	1	Arnold et al., 1995 (6)
	Bronchogenic carcinoma	Brain	Meningioma	1	Gardiman et al., 1996 (53)
	Carcinoma	Brain	Meningioma	1	Bhargava et al., 1999 (13)
	Carcinoma	Brain	Meningioma	1	Bori et al., 2002 (16)
	Pulmonary adenocarcinoma	Brain	Secretory meningioma	1	Cserni et al., 2002 (38)
	Carcinoma	Brain	Meningioma	1	Duprez et al., 2009 (42)
	Adenocarcinoma	Brain	Microcycstic meningioma	1	Takei et al., 2009 (130)
Renal	Adenocarcinoma	Brain	Meningioma	1	Stortebecker, 1951 (126)
	Renal cell ca	Brain	Meningioma	1	Gutierrez Morales et al., 1957 (56)
	Renal cell ca (with doubt)	Brain	Meningioma	1	Osterberg, 1957 (101)
	Carcinoma	Brain	Meningioma	1	Barz, 1983, (8)
	Renal cell ca	Brain	Meningioma	1	Breadmore et al., 1994 (17)
	Renal cell ca	Brain	Meningioma	1	Han et al., 2000 (59)
	Renal cell ca	Brain	Meningioma	1	Kimiwada et al., 2004 (74)
	Renal cell ca	Brain	Meningioma	1	Chahlavi et al., 2005 (29)
	Renal cell ca	Brain	Meningioma	1	Lanotte et al., 2009 (77)
	Renal cell ca	Brain	Meningioma	1	Tsunoo et al., 2010 (135)
Prostate	Carcinoma	Brain	Meningioma	1	Döring, 1975 (41)
	Carsinoma	Brain	Meningioma	1	Chambers et al., 1980 (30)
	Carcinoma	Brain	Meningioma	1	Bernstein et al., 1983 (10)
	Carcinoma	Brain	Meningioma	1	Cluroe, 2006 (34)
	Adenocarcinoma	Brain	Meningioma	1	Pugsley et al., 2009 (111)
	Adenocarcinoma	Brain	Meningioma	1	Mitchell et al., 2011 (90)
	Carcinoma	Brain	Meningioma	2	Moody et al., 2012 (94)
Skin (MM)	Malignant melanoma	Brain	Meningioma	1	Wong et al., 1999 (148)
	Malignant melanoma	Brain	Meningioma	1	Shariff et al., 2009 (122)
	Malignant melanoma of vulva	Brain	Fibroblastic meningioma	1	Takei et al., 2009 (130)
	Malignant melanoma	Brain	Sphenoid wing meningioma	1	Pal et al., 2010 (104)
Colorectal	Carcinoma	Brain	Meningioma	1	Benedetto et al., 2007 (9)
	Carcinoma	Brain	Meningioma	1	Moody et al., 2012 (94)
Stomach	Gastric carcinoma	Brain	Meningioma	1	Honma et al., 1989 (64)
Esophagus	Carcinoma	Brain	Meningioma	1	Kepes et al., 1982 (73)
Gallbladder	Adenocarcinoma	Brain	Suprasellar meningioma	1	Peison et al., 1961 (106)
Cervix	Carcinoma	brain	Meningioma	1	Wu et al., 1977 (150)
Unknown	Carcinoma	Brain	Meningioma	1	Cappabianca et al., 1985 (26)
Salivary gl.	Parotid adenocarcinoma	Brain	Meningioma	1	Van Zandijcke et al., 1996 (138)

Table I: Cont.

NE	Pituitary carcinoma	Brain	Meningioma	1	Zhou et al., 2012 (154)
Leukemia	Chronic myeloid leukemia	Brain	Meningioma	1	Sonet et al., 2001 (125)
Genitourinary	Endometrial carcinoma	Brain	Meningioma	1	Ho, 1980 (62)
Hematopoietic	Testicular lymphoma	Brain	Meningioma	1	Kepes et al., 1982 (73)
	Lymphoma	Brain	Meningioma	1	Takakura et al., 1982 (129)
	Lymphoma	Brain	Meningioma	1	Widdel et al., 2010 (144)
	Multiple myeloma	Brain	Meningioma	1	Widdel et al., 2010 (144)

Metastasis to Other Benign CNS Tumors

Patients with hereditary cancer syndromes may be at increased risk for the development of tumor-to-tumor metastases. Among the von Hippel-Lindau (VHL) disease cases with CNS hemangioblastomas, Jarrel et al. found six cases characterized with metastasis to CNS hemangioblastoma (69). The primary site of metastatic disease was the kidney in five patients (renal cell carcinoma) and the pancreas in one (a pancreatic neuroendocrine tumor). Two patients (including one who was also in the surgical group) were found at autopsy to have CNS metastases exclusively to spinal hemangioblastomas. Hemangioblastomas are usually an early and preferred site for metastasis in VHL cases (69). Altinoz et al. revealed that renal cell carcinoma-to-CNS hemangioblastoma is the most common donor-recipient tumor association among tumor-to-tumor metastasis cases (4) (Table II).

Similar to meningiomas, schwannomas have also been mostly metastasized by carcinomas of the breast and lung. Although there are only 11 reported cases of metastasis to schwannoma, similar mechanisms with meningiomas can be suggested except for hormonal tendency. Fukushima et al. have suggested that [(18)F]-fluorodeoxyglucose positron emission tomography might play an effective role in the preoperative diagnosis of tumor-to-tumor metastasis in schwannomas preoperatively (51) (Table II). This could be another difference with meningiomas.

Hypotheses regarding a high collagen or lipid content that have been proposed for meningiomas seem unlikely in pituitary tumors (18). On the contrary, it was suggested that the organized trombi in cavernomas may play the same role with lipid aggregation and provide metastasis a fertile soil for seeding and growth (31). Alterations of vasculature have been thought to be another reason for development of metastases in pituitary adenomas. Direct arterial supply from the carotid and meningeal systems may give rise to metastases by bypassing portal vessels. Likewise, the architecture of cavernomas may increase the chances of hematogenous metastases by slowing the flow within the lesion and increasing the likelihood of adherence to vessel wall by the metastatic emboli (31). According to our review, there are two exceptional cases among all others of benign CNS tumours. They were included in our study due to their histological origin although the location was the skin for both (31, 54).

Metastasis to Gliomas

As can be seen from Table III, metastasis to gliomas has been reported 16 times previously. Similar to meningiomas, gliomas were metastasized by lung and breast carcinomas. The mechanisms of metastasis to gliomas remains obscure due to the fact that there are few cases and a remarkable number are from necropsy studies. Mörk et al. have suggested that no casual relationship can be invoked in these cases and the concomitance of a primary glioma and metastatic carcinoma should be regarded as coincidental (96). It is important to mention the studies of gliomas mimicking metastatic carcinomas (52, 73) as they can give an idea about the process in metastasis or differentiation. However, it can be said that the behavioral characteristics of tumor cells are the determining factors for tumor-to-tumor metastasis. Aggressive and malignant tumors usually act as donors, not recipients. Slow-growing characteristic of the host provides a longer period for metastases. This might explain the limited number of gliomas acting as the host lesions.

DISCUSSION

Although rare, neurosurgeons should be aware of the entity of tumor-to-tumor metastasis. Meningiomas are the third and pituitary adenomas are the fifth most frequent tumor types in large series, probably reflecting their rich vascularity (144). Metastasis to a meningioma usually results in rapid enlargement of the long-standing meningioma, and leads to the first clinical manifestation of the donor malignancy. The donor tumor is usually found to be widely disseminated (30). These predisposing factors of meningiomas may render these tumors particularly susceptible to receiving seeds from extracranial malignancies. The low metabolic rate acts as a noncompeting metabolic environment conductive to cell growth. The high lipid and collagen content of meningiomas provides a fertile soil not only for the seeding of malignant cells, but also for hematogenous spread of bacterial infections (123). This is consistent with Paget's "seed and soil theory", which postulates that tumor development is a consequence of the supply of fertile environment (the soil) in which tumor cells (the seed) can proliferate (103). Two theories have been developed to explain the relationship between primary

Table II: Summary of Other Benign CNS Tumors Containing Metastases Reported in the Literature

Donor site	Tumor type of donor site	Recipient site	Tumor type of recipient site	# of cases	References
Breast	Carcinoma	Brain	Schwannoma	1	Wallach et al., 1959 (140)
	Carcinoma	Brain	Schwannoma	1	Wong et al., 1962 (149)
	Carcinoma	Pituitary gland	Pituitary adenoma	1	Richardson et al., 1971 (113)
	Carcinoma	Pituitary gland	Pituitary adenoma	1	Van Der Zwan et al., 1971(136)
	Carcinoma	Brain	Schwannoma	1	Wessel et al., 1973 (143)
	Carcinoma	Pituitary gland	Pituitary adenoma	1	Zager et al., 1987 (153)
	Carcinoma	Pituitary gland	Pituitary adenoma	1	Bret et al., 2001 (18)
	Carcinoma	Skin	Schwannoma	1	Gazic et al., 2011 (54)
	Carcinoma	Brain	Schwannoma	1	Lua et al., 2012 (87)
Lung	Carcinoma	Pituitary gland	Pituitary adenoma	1	Kovacs, 1973 (76)
	Carcinoma	Brain	Schwannoma	1	LeBlanc, 1974 (80)
	Bronchial Carcinoma	Cerebellum	Cavernoma	1	Hirtzler et al., 1975 (61)
	Carcinoma	Brain	Schwannoma	2	Chambers et al., 1980 (30)
	Carcinoma	Pituitary gland	Pituitary adenoma	1	Scheithauer, 1984 (117)
	Carcinoma	Pituitary gland	Pituitary adenoma	1	Molinatti et al., 1985 (93)
	Carcinoma	Pituitary gland	Pituitary adenoma	1	Post et al., 1988 (110)
	Bronchial Carcinoma	Brain	Cavernoma	1	Trapella et al., 1993 (134)
	Carcinoma	Brain	Schwannoma	1	Tang et al., 2007 (132)
	Carcinoma	Brain	Schwannoma	1	Fukushima et al., 2011 (51)
Renal	Transitional cell ca	Pituitary gland	Pituitary adenoma	1	Burns et al., 1973 (24)
	Renal cell ca	Pituitary gland	Pituitary adenoma	1	James et al., 1984 (67)
	Renal cell ca	Cerebellum	Hemangioblastoma	1	Jamjoom et al., 1992 (68)
	Renal cell ca	Cerebellum	Hemangioblastoma	1	Bret et al., 1999 (19)
	Renal cell ca	Spinal cord	Hemangioblastoma	1	Hamazaki et al., 2001 (58)
	Renal cell ca	Cerebellum	Hemangioblastoma	1	Hamazaki et al., 2001 (58)
	Renal cell ca	Cerebellum	Hemangioblastoma	1	Mottolese et al., 2001 (95)
	Renal cell ca	Spinal cord	Hemangioblastoma	1	Abou-Hamden et al., 2003 (2)
	Renal cell ca	Spinal cord	Hemangioblastoma	1	Altinoz et al., 2005 (4)
	Renal cell ca	Cns	Hemangioblastoma	5	Jarrell et al., 2006 (69)
	Renal cell ca	Cns	Hemangioblastoma	1	Polydorides et al., 2007 (108)
	Renal cell ca	Cns	Hemangioblastoma	1	Xiong et al., 2010 (152)
Prostate	Carcinoma	Cerebellum	Hemangioblastoma	1	Crockard et al., 1988 (37)
	Carcinoma	Pituitary gland	Pituitary adenoma	1	Ramsay et al., 1988 (112)
Colorectal	Carcinoma	Pituitary gland	Pituitary adenoma	1	Noga et al., 2001 (99)
Stomach	Carcinoma	Brain	Schwannoma	1	Schwesinger et al., 1974 (119)
	Carcinoma	Pituitary gland	Pituitary adenoma	1	Molinatti et al., 1985 (93)
	Carcinoma	Pituitary gland	Pituitary adenoma	1	Van Seters et al., 1985 (137)
Oesophagus	Carcinoma	Brain	Paraganglioma	1	Lu et al., 2009 (86)
Salivary gl.	Acinic cell carcinoma	Scalp	Neurofibroma	1	Cohn et al., 2005 (35)
NE	Pancreatic ne tumor	Pituitary gland	Pituitary adenoma	1	Ramsay et al., 1988 (112)
	Pancreatic ne tumor	Cns	Hemangioblastoma	1	Jarrell et al., 2006 (69)
Unknown	Carcinoma	Pituitary gland	Pituitary adenoma	1	Post et al., 1988 (110)
	Carcinoma	Pituitary gland	Pituitary adenoma	1	Bret et al., 2001 (18)
Kidney or lung	Carcinoma	Pituitary gland	Pituitary adenoma	1	Hurley et al., 1992 (66)

Table II: Cont.

Hematopoietic	Lymphoma	Infundibulum	İnfundibular choristoma	1	Takakura et al., 1982 (129)
Mediastinum	Carcinoid tumor	Pituitary gland	Pituitary adenoma	1	Abe, 1997 (1)
Skin (MM)	Melanoma	Brain	Cavernoma	1	Chan et al., 2006 (31)

Table III: Summary of Gliomas Containing Metastases Reported in the Literature

Donor site	Tumor type of donor site	Recipient site	Tumor type of recipient site	# of cases	references
Breast	Carcinoma	Brain	Oligodendroglioma	1	Strang, 1965 (127)
	Carcinoma	Brain	Oligodendroglioma	1	Tally et al., 1988 (131)
	Carcinoma	Brain	Oligodendroglioma	1	Wurm et al., 1994 (151)
	Carcinoma	Brain	Pilocytic Astrocytoma	1	Muller et al., 1999 (98)
Lung	Bronchial carcinoma	Brain	Astrocytoma	2	Mörk et al., 1988 (96)
	Bronchial carcinoma	Brain	Fourth ventricle ependymoma	1	Mörk et al., 1988 (96)
	Bronchial carcinoma	Brain	Astrocytoma	1	Tajika et al., 1990 (128)
Skin (MM)	Melanoma	Brain	Glioma	1	Zulch, 1965 (157)
	Melanoma	Brain	Oligodendroglioma	1	Farnsworth, 1972 (46)
	Melanoma	Brain	Glioma	1	Takakura et al., 1982 (129)
	Melanoma	Brain	Neurocytoma	1	Brown et al., 2003 (20)
Renal	Carcinoma	Brain	Glioblastoma	1	Franke et al., 1990 (49)
Thyroid	Carcinoma	Brain	Glioblastoma	1	Posnikoff et al., 1960 (109)
Colorectal	Carcinoma	brain	Oligodendroglioma	1	Mizutani et al., 1987 (91)
Unknown	Carcinoma	Brain	Glioma	1	Joglekar et al., 1981 (70)

tumor and metastasis. These are "The Mechanical Theory" of Ewing and "The Soil and Seed Theory" of Paget (44, 103).

It is not surprising that nearly all CNS tumor-to-tumor metastasis cases have eluded preoperative radiological diagnosis and were only discovered incidentally during postoperative pathological examination (72).

Cancer metastasis results from a multi-step cascading process that includes; 1) vascularization of the primary tumor; 2) detachment and invasion of cancer cells; 3) intravasation into lymphatic and blood vessels; 4) survival and arrest in the circulation; 5) extravasation into distant organs; and 6) colonization and growth of metastatic tumors. MicroRNAs (miRNAs) play critical roles in this multi-step process, both promoting and suppressing metastasis (79). Specific miRNA can cause cancer cells to invade and metastasize (88).

In the first step, vascularization of the primary tumor takes place. In the second and third stages the cancer cells released from the primary tumor have to penetrate to the blood or lymphatic vessels (intravasation), the road that dissemination follows. In the fourth stage, cancer cells should survive and in the fifth stage circulating cells can migrate through the walls of vessels to surrounding tissues (extravasation) where they settle, proliferate, and induce angiogenesis, creating metastases. The activation of proteolytic enzymes that are capable of degrading the extracellular matrix (ECM) surrounding the endothelium or creating the basement membrane of epithelial tissue in different organs is indispensable in the process of intra- and extravasation (145). In this stage the activation of proteolytic enzymes, such as proteinases of the plasmin system, serineproteinases, and matrix metalloproteinases (MMPs), is necessary. Simultaneously, changes occur in the expression of many superficial glycoproteins and factors responsible for cell adhesion (integrins) and intercellular communication (cadherins). Moreover, Muller et al. showed that the chemokines and their receptors have critical roles in determining the metastatic destination of tumor cells (97). Cross talk between the primary CNS tumor and the malignant tumor usually occurs by means of expressions. For example, E-cadherin expression by both meningiomas and breast cancer may affect the choice of "seed" (cancer cells) to find the "soil" (recipient CNS tumor) (3). Neoangiogenesis is connected with the expression of many markers of this process, among them vascular endothelial growth factor (VEGF), endoglin (CD105), a transmembranous glycoprotein which is a

component of the receptor for transforming growth factor beta (TGFbeta), as well as neuropilin (NRP), the co-receptor for VEGF. These molecular and cellular markers play key roles in tumor progression.

As stated above, metastasis to the brain and primary brain tumors is augmented by the activation of homologous molecules between the systemic cancer and primary CNS neoplasm tissue. These molecules are not only expressed by the primary cancers, but are also echoed in the brain parenchyma and especially in primary CNS neoplasms. These molecules may act as a "fertilizer" for cancer cells and selectively reside in the primary CNS neoplasms. These findings are also consistent with Paget's "seed and soil theory".

It is conceivable that cancer cells will metastasize to organs from similar embryological origins. Hence, malignant melanoma has a greater likelihood of forming leptomeningeal metastasis since they are both derived from neural crest cells (97).

Although these results suggest that integrins, cathedrins and chemokines play a prominent role in the dissemination of tumor cells and their subsequent invasion to a second malignancy in tumor-to-tumor metastasis cases, the development of tumor metastasis from a second primary malignancy is uncommon and remains biologically puzzling.

The collected data depends mostly on post mortem studies. This suggests a higher incidence for tumor-to-tumor metastasis. Benign tumors should undergo periodic radiologial and physical examinations just like malignant tumors. Likewise, in patients with carcinoma, lesions of the central nervous system should not be labeled as metastasis. Whenever possible, the whole tumor should be examined pathologically.

CONCLUSION

We conclude that neurosurgeons should be aware of the phenomenon of tumor-to-tumor metastasis. Knowing this potential association is important in appropriate patient management. One can say that the preoperative diagnosis of metastasis to a tumor would not change the indication for surgical removal of the lesion. However, it will surely change the technical approach and imply an en bloc removal of the lesion to avoid any intraoperative seeding of metastatic cells.

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