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Association of Breast Cancer and Meningioma

Report of 12 New Cases and Review of the Literature

Di Bonito, L. Giarelli, G. Falconieri, D. Bonifacio-Gori, G. Tomasic and P. Vielh[1]

Department of Anatomic Pathology, University of Trieste, Italy, and [1]Department of Clinical Cytopathology, Institute Curie, Paris, France

SUMMARY

We report 12 new cases of female breast cancer associated with intracranial meningiomas, inclusive of autopsy study. At the time of death the patients' age ranged from 52 to 95 years (average 70.6 years). Breast carcinomas were documented ante mortem in 11 cases and at autopsy in 1. Meningiomas were diagnosed at autopsy (10 cases) or in vivo (2 cases). The diagnosis of meningioma antedated that of mammary carcinoma in only one patient. Histologically, the cancers were of ductal (11 cases) and lobular infiltrating (1 case) types and showed a variable malignancy grade. Widespread extracranial metastases were present at autopsy in 7 cases. Brain metastases were seen in 1 case. Neurologic signs were referred in 4 subjects. Four breast cancers and one meningioma showed immunoreactivity for progesterone receptors, whereas all the cases were negative for estrogen receptors.

In one case, metastatic breast carcinoma tissue was present within a psammomatous meningioma.

A brief review of the literature, which includes 14 similar observations, is reported. Although the association of breast cancer and meningioma is still difficult to explain, its clinical implications are important and deserve proper attention. A proper work up in patients with suspected intracranial metastases is recommended so that resectable meningiomas are not mistaken for metastases.

Introduction

In 1977 and 1980 we documented at our Institute a few cases of carcinoma of the female breast associated with meningioma of the cranial dura mater[7, 11]. On the basis of clinical and autopsy data available at that time we suggested that more than a casual relationship, most likely on endocrine basis, existed between these two apparently unrelated lesions although no definite proof could be brought in order to substantiate our initial impression.

In the last decade numerous cases of this unusual association have been added to the already published ones. In most instances the meningiomas, discovered either ante mortem or at autopsy, had followed the breast tumor at a variable interval. In a few cases, the meningeal tumor contained metastatic cells from the breast cancer. Meanwhile, studies on functional as well as biochemical features of meningiomas, supported also by steroid receptor assays, have indicated possible molecular mechanisms, to explain the simultaneous occurrence of the two neoplasms in the same patient as well as the rare phenomenon of tumor-in-tumor growth.

In view of these new insights, we have reviewed all the new cases thereafter documented at our Department, including autopsy and surgical observations of breast cancer and meningioma.

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Material and Methods

For the present study we have reviewed the cases of female breast cancer in which a meningioma had been found before or after the mammary tumor. For this purpose we retrieved all the cases seen between 1980 and 1989 at the Department of Anatomic Pathology either in life or at autopsy, using our computerized archive implemented since 1980. Clinical charts were also reviewed in order to obtain proper information on symptoms, signs, therapy and survival. Tissues from autopsy and surgical specimens included hematoxylin-eosin stained sections from routinely processed material initially fixed in 10 % neutral buffered formalin, with final embedding in paraffin.

Breast cancers were classified and graded according to the WHO scheme using sections from surgical material obtained during operating room consultation[2].

Meningiomas were classified morphologically following the criteria of Rubinstein[31].

Estrogen receptor (ER) and progesteron receptor (PR) assays were carried out on routine sections of breast and meningeal tumors cut from filed paraffin blocks, selected among those showing better cell preservation. Sections of breast cancer and meningioma were rehydrated and initially digested using DNAase (10 U/ml) for 30 min at 37 °C, followed by incubation with primary monoclonal antibodies directed against ER and PR. The DNAase has been donated by the "Area" Research Laboratory, Trieste; prediluted anti-ER and PR antibodies were purchased from Abbott. Treatment with secondary antimouse antibody followed after repeated washings in phosphate buffered saline. The peroxidase antiperoxidase method was used as a revealing system with diaminobenzidine as chromogen and Harris' hematoxylin for nuclear counterstain.

Known positive cases from snap frozen and formalin-fixed tissues were used as controls.

Results

During the 10-year interval a total number of 25,055 autopsies were performed. In the same period 1,413 new cases of breast cancers (nearly all diagnosed on surgical material) and 64 meningiomas were accessioned. The association between breast cancer and meningioma has been documented in 12 patients (Table 1). The age of the patients at the time of death averaged 70.6 years, ranging from 56 to 95 years.

In 11 patients the breast tumor was diagnosed in life: in these subjects the age ranged from 51 to 80 years and survival after surgery lasted from 1 to 8 years. One patient (case 10) underwent bilateral mastectomy. In most cases, breast carcinomas belonged to the ductal infiltrating category with a variable histological grade. In one patient the histological material was not available for review.

The testing for ER was negative in all cases, whereas PR assay was positive in 4 breast tumors and dubious in one.

All the meningeal tumors were intracranial. They were found incidentally at autopsy in 10 cases. In 2 patients, however, they were documented in life following one and 2 years respectively after the breast operation. Histologically, they were psammomatous in 7 cases, transitional in 3, mixed in 2.

Table 1. Case series of breast cancers associated with meningioma reported in the present article

Case No.	Age, Y	Breast cancer type and grade	Meningioma type and site	CNS symptoms	Autopsy features	Other remarks
1	85	IDC,2	Psammomatous, vault	–	Metastatic IDC to lymph nodes	Also RT for cancer of uterine cervix
2	73	ILC	Transitional, left parietal	–	Pulmonary embolism	–
3	85	IDC,2	Transitional, middle cranial fossa	–	Cerebral infarction	–
4	82	IDC,2	Psammomatous, unknown	Hemiparesis, confusion	Metastatic diffuse IDC Cerebral infarction	–
5	85	IDC,1	Meningotheliomatous, unknown	Hemiparesis	Metastatic diffuse IDC Cerebral infarction Pulmonary embolism	Also cancer of renal pelvis
6	74	IDC,2	Psammomatous, vault	–	Metastatic diffuse IDC	–
7	84	ILC,3	Transitional, vault	–	Bone ILC metastasis	RT for breast cancer
8	56	IDC,3	Psammomatous, with IDC, vault	Vertigo	Bone and pleural IDC metastasis	–
9	95	NOS	Psammomatous, vault	Confusion	Pneumonia	Breast surgery 25y before
10	66	IDC,2	Psammomatous, parasellar	–	Brain and bone IDC metastasis	bilateral mastectomy
11	62	IDC,2	Transitional, temporo-parietal	–	Metastatic diffuse IDC	CT for breast cancer
12	52	IDC,3	Psammomatous, vault	–	Metastatic diffuse IDC	CT for breast cancer

IDC – infiltrating ductal carcinoma; ILC – infiltrating lobular carcinoma; NOS – not otherwise specified; CT – chemotherapy; RT – radiotherapy; CNS – central nervous system. – *Note:* Breast cancers discovered in vivo in all patients, except case 5. – Meningiomas found incidentally at autopsy in all cases, except patients 2 and 11. – ER/PR: all the cases negative for ER; cases 3, 6, 8, 12 had PR positive breast cancer tissue; case 11 had meningioma positive for PR. See text for further details.

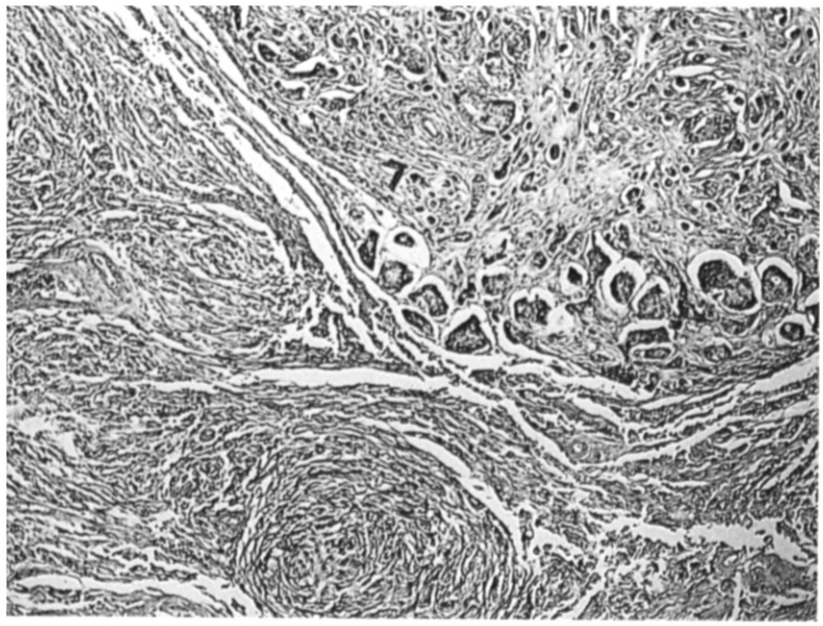

Fig. 1. Psammomatous meningioma containing metastatic carcinoma, consistent with ductal infiltrating primary in breast (H.E., 32 ×).

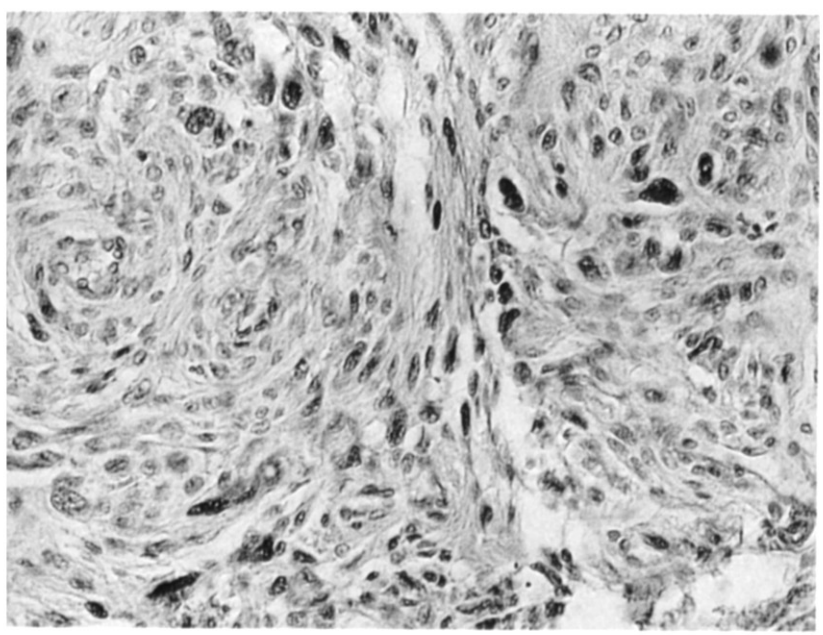

Fig. 2. Transitional meningioma exhibiting nuclear positivity for progesterone receptors (Anti-PR serum, 80 ×).

In one patient the meningeal tumor contained metastatic tissue from the breast cancer (Fig. 1). All the meningiomas were negative for ER and PR, except one case in which a slight nuclear positivity was found for PR: this corresponded to a transitional meningioma with nuclear pleomorphism (Figs. 2 and 3).

Discussion

The simultaneous occurrence of multiple distinct tumors in the intracranial cavity and in other body sites is rare although not exceptional, being reported with an incidence of 2–8 % in patients suffering from malignancy[25,26].

The association of carcinoma of the breast, the most frequent malignant tumors in females, and meningioma, a common neoplasm of the central nervous system, has been pointed out by Schoenberg (1965) in a large series drawn from the Connecticut Tumor Registry and, later on, by other authors in individual reported cases[7,8,17,19,24,25,26,30,33,35]. Most of these articles have dealt with meningiomas occurring in the cranial cavity, but exceptionally a few spinal cord cases have been reported[16,19].

In a limited number of articles the intimate association of breast carcinoma metastatic to a meningioma has been documented, sometimes supported by autopsy investigations (Table 2).

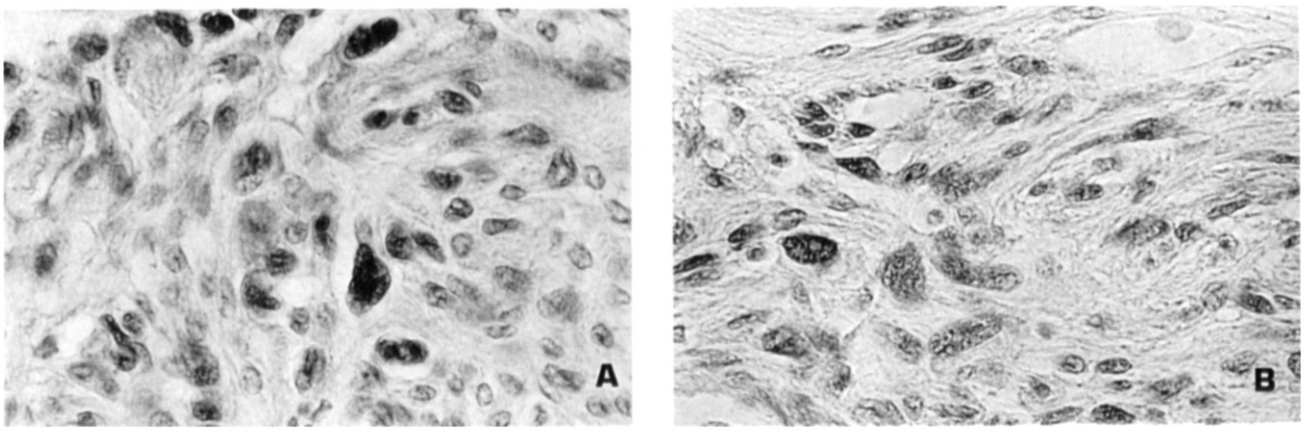

Fig. 3. Section of meningioma showing different immunostaining intensity: bizarre cells (A) feature stronger reactivity than typical cells (B) (Anti-PR serum, 118 ×).

Table 2. Breast cancer metastatic to meningioma. Review of literature cases

Authors	Age,Y	Breast Cancer site and type	Meningioma type and site	CNS Symptoms	Autopsy features	Other remarks
Bernstein, (1933)[5]	72	Lt, NOS	Rt middle fossa	–	Metastases, NOS	–
Lapresle et al, (1952)[20]	45	NOS	Psammomatous, cerebral convexity	–	Diffuse intracranic metastasis	–
Helpap, (1965)[15]	42	NOS	Dura mater	–	Peritoneum, lymph nodes metastasis	–
Anlyan et al, (1970)[1]	42	NOS	Frontal parasagittal SP	NOS	–	Breast surgery 18m before
Theologides & Lee, (1972)[36]	74	Rt, scirrous	Psammomatous, rt temporal fossa	–	Diffuse metastasis	Breast surgery 2m before
Hockley, (1975)[16]	72	Lt, NOS	Psammomatous, cervical spinal cord	Spastic tetraparesis	–	Breast surgery 6y before, RT
Kepes, (1976)[18]	49	Lt, NOS	Meningothelial, lt parietal, SP	–	–	Breast surgery 2.5y before
Di Bonito & Bianchi, (1978)[11]	68	Lt, IDC	Transitional, frontal	–	Diffuse metastasis	Breast surgery 2y before, RT, CT
Chambers et al, (1980)[10]	66	IDC	Psammomatous, lt frontal	Numerous, NOS	Diffuse metastasis	Meningioma diagnosed ante mortem
Nunnery et al, (1980)[27]	53	Rt, NOS	Anterior fossa, SP	Frontal headache, memory loss, personality changes		Breast surgery 4y before, RT
Lodrini & Savoiardo, (1981)[21]	53	Rt, NOS	Endotheliomatous, anterior fossa	Headache, confusion, anosmia	Alive at ly follow-up	Breast surgery 1y before, CT
Barz, (1983)[3]	56	NOS	Meningotheliomatous	–	Skin metastasis	Breast surgery 2y before
Doron & Gruszkiewicz, (1987)[13]	64	Lt, NOS	Meningotheliomatous, frontal pole with bone invasion, SP	Frontal pain	–	Breast surgery 2y before, RT
Zon et al, (1989)[40]	57	Rt, ILC	Meningotheliomatous, SP	Memory loss, emotional lability, limb tremor	–	Breast surgery 5y before, CT

NOS – not otherwise specified; IDC – infiltrating ductal carcinoma; ILC – infiltrating lobular carcinoma; SP – surgical pathology specimen; RT – radiotherapy; CT – chemotherapy; Lt – left; Rt – right; m – months; y – years; CNS – central nervous system.

The general interest of the association between breast cancer and meningioma is, of course, raised by the clinical relevance of an intracranial mass discovered in a patient with history of breast cancer and the need of differentiating it from a metastasis[17,21,24,30].

Several explanations have been claimed to elucidate the relationship between these two apparently distinct lesions. Although none is fully satisfactory, interesting observations have come from retrospective epidemiological surveys indicating that both cancer of the breast and meningeal tumors occur in the same adult female population, usually in the 5th–6th decade. Thus, a response to a common hormonal influence has been suggested, as indirectly supported by the meningioma size fluctuation in conditions with high blood levels of estrogens and progestins, such as pregnancy[38].

It is important to note that besides the well-established existence of ER and PR in breast carcinoma, many authors have recently documented, using various special techniques, that meningiomas may have steroid receptors[9,12,23,29,32,37]. ER had been detected initially, but PR were later documented in higher tissue concentration[12]. In fact, quantitative assessment of these hormone receptors usually yielded twice as much PR than ER in meningiomas[9,29,37]. From the qualitative standpoint, noteworthily, the ER/PR profile of meningiomas substantially differ from that customarily seen in breast cancer tissue: this might explain the rarity of the breast cancer-meningioma association as well as the uncertain role of hormone therapy for meningiomas[9,12,29,32,37]. In vitro demonstration of androgen receptors in meningiomas has also been published[28].

Of interest in explaining this association are data obtained from molecular investigations focusing on the role of certain oncogenes in the development of breast cancer[14,22,23]. Whether the established enhancement of oncogene expression by estrogens in cell lines from breast cancer is paralleled by an analogous amplification in meningeal cells, is not known at the moment, and could represent a source of valuable information for future studies.

Our data pertaining to the ER/PR assay are not comparable with those reported in the literature since most of the tested meningiomas were from an autopsy file. Therefore, no definite conclusions can be drawn, even though – besides total negativity for ER – significant positivity was observed for PR in 4 breast cancers and one meningioma. However, positive meningeal tumor cells were not paralleled by analogous positivity in the correspondent breast cancer. Interestingly this unique PR positive meningioma was characterized by conspicuous bizarre nuclearity, in this confirming a phenomenon previously observed[9,29].

Clinical stage and grade of breast cancer as well as histology type did not correlate significantly with the development of the meningeal neoplasm. Likewise, the histology of meningioma appeared to be another independent variable.

In one of our patients a psammomatous meningioma harbored metastatic tissue from a ductal infiltrating carcinoma of the breast. The intracranial tumor was incidently discovered at autopsy in a 56-year-old woman treated with surgery for mammary cancer 5 years prior to death. She also received radio- and chemotherapy.

To the best of our knowledge this is the 15th reported case of meningioma serving as a recipient for metastatic tumor implant. As in most previously published reports, widespread metastases were present in other sites (Table 2).

Several speculations have been claimed to explain the metastasis of a cancer in another primary tumor. Historically, renal carcinoma is a typical example of tumor host, most likely because it provides an optimal environment to blood-borne malignant cells[4]. In addition, a highly developed microcirculation may increase the chance of accepting tumor cells from a different "donor" tumor. In the case of meningioma and breast cancer the association is still difficult to explain.

Some authors believe that the association between the two entities is fortuitous, since meningioma may occasionally be involved with other primary tumors such as cancer of the lung or testis[8]. The limited number of 15 cases seen during a 20-year interval at our Institute, where the autopsy rate of in-hospital deaths approaches 100 %, would lend some support to this view. Other investigators favor the hypothesis of a "low metastatic threshold" of meningioma due to its rich microcirculation or biochemical composition (high lipidic content, especially of angioblastic forms)[6,39]. It is also possible that precise molecular factors, such as sex hormone affinity, account for a more specific cell-to-cell interaction and ultimately the tumor-in-tumor growth. Whether antitumoral therapy might play a "permissive" role remains to be established.

In conclusion, the occurrence of breast cancer and meningioma, simultaneously or at different times in patients with breast cancer, does not seem to be negligible although the intimate growth of the two neoplastic lesions is very rare. As breast cancer has the propensity to metastatize to the intracranial cavity, focal lesions detected in women with known mammary carcinoma should be properly evaluated to rule out a meningioma which is potentially resectable[35].

References

[1] Anlyan FH, Heinzen BR, Carras R (1970) Metastasis of tumor to second different tumor: collision tumors. JAMA *212:* 2124

[2] Azzopardi JG, Chepick OF, Hartmann WH, Jafarey NA, Llombart-Bosch A, Ozzello L, Rilke F, Sasano N, Sobin LH, Sommers SC, Stalsberg H, Sugar J, Williams AO (1982): The World Health Organization histological typing of breast tumors. Second edition. Am J Clin Pathol *78:* 806–813

[3] Barz H (1983) Zur Häufigkeit der Metastasierung maligner Tumoren in Meningiome. Zentralbl Allg Pathol *127:* 367–374

[4] Berent W (1902) Seltene Metastasenbildung. Zentralbl Allg Pathol *13:* 401–410

[5] Bernstein SA (1933) Über Karzinommetastase in einen Duraendotheliom. Zentralbl Allg Pathol *58:* 163–166

[6] Best PV (1963) Metastatic carcinoma in a meningioma. J Neurosurg. *20:* 892–894

[7] Bianchi C, Vassallo A, Di Bonito L, Giammusso V (1980) Association cancer du sein-méningiome. A propos de deux observation. Sem Hop Paris *56:* 488–489

[8] Burns PE, Jha N, Bain GO (1986) Association of breast cancer with meningioma. Cancer *58:* 1537–1539

[9] Cahill DW, Bashirelahi N, Solomon LW, Dalton T, Salcman M, Ducker TB (1984) Estrogen and progesterone receptors in meningiomas. J Neurosurg *60:* 985–993

[10] Chambers PW, Davis RL, Blanding JD, Buck FS (1980) Metastases to primary intracranial meningiomas and neurilemomas. Arch Pathol Lab Med *104:* 350–354

[11] Di Bonito L, Bianchi C (1978) Métastase d'un cancer mammaire dans un méningiome. Arch Anat Cytol Pathol *26:* 175–176

[12] Donnell MS, Meyer GA, Donegan WL (1979) Estrogen-receptor protein in intracranial meningiomas. J Neurosurg 50: 499–502

[13] Doron Y, Gruszkiewicz J (1987) Metastasis of invasive carcinoma of the breast to an extradural meningioma of the cranial vault. Cancer *60:* 1081–1084

[14] Dumanski JP, Carlbom E, Collins VP, Nordenkjold M (1987) Deletion mapping of a locus on chromosome 22 involved in the oncogenesis of meningioma. Proc Natl Acad Sci USA *84:* 9275–9279

[15] Helpap B (1965) Mammakarzinom Metastase in einem Meningiom. Zentralbl Allg Pathol *1965:* 242–245

[16] Hockley AD (1975) Metastatic carcinoma in a spinal meningioma. J Neurol Neurosurg Psychiatry *38:* 695–697

[17] Jacobs DH, McFarlane MJ, Holmes FF (1987) Female patients with meningioma of the sphenoid ridge and additional primary neoplasms of the breast and genital tract. Cancer *60:* 3080–3082

[18] Kepes JJ (1976) Cellular whorls in brain tumors other than meningiomas. Cancer *37:* 2232–2237

[19] Knuckey NW, Stoll JJr, Epstein MH (1989) Intracranial and spinal meningiomas in patients with breast carcinoma: case report. Neurosurgery *25:* 112–117

[20] Lapresle J, Netsky MG, Zimmerman HM (1952) The pathology of meningiomas. A study of 121 cases. Am J Pathol *28:* 757–791

[21] Lodrini S, Savoiardo M (1981) Metastases of carcinoma to intracranial meningioma: report of two cases and review of the literature. Cancer *48:* 2668–2673

[22] Lundberg C, Skoog L, Cavenee W, Nordenskjold M (1987) Loss of heterozygosity in human ductal breast tumors indicates a recessive mutation on chromosome 13. Proc Natl Acad Sci USA *84:* 2372–2376

[23] Magdelenat H, Pertuiset BF, Poisson M, Martin PM, Philippon J, Pertuiset B, Buge A (1982) Progestin and oestrogen receptors in meningiomas. Biochemical characterization, clinical and pathological correlations in 422 cases. Acta Neurochir (Wien) *64:* 199–213

[24] Metha D, Khatib R, Patel S (1983) Carcinoma of the breast and meningioma. Association and management. Cancer *51:* 1937–1940

[25] Moertel CG, Dockerty MB, Baggenstoss AH (1961) Multiple primary malignant neoplasms. III. Tumors of multicentric origin. Cancer *14:* 238–248

[26] Moertel CG (1964) Incidence and significance of multiple primary malignant tumors. Ann NY Acad Sci *114:* 886–895

[27] Nunnery EJr, Kahn LB, Rudnick SA (1980) Breast carcinoma metastatic to meningioma. Arch Pathol Lab Med *104:* 392–393

[28] Olson JJ, Beck DW, MacIndoe JW, Loh PM (1988) Androgen receptors in meningiomas. Cancer *61:* 952–955

[29] Poisson M, Magdelenat H, Foncin JF, Bleibel JM, Philippon J, Pertuiset B, Buge A (1980) Récepteurs d'oestrogènes et de progestérone dans le méningiomes. Etude de 22 cas. Rev Neurol (Paris) *136:* 193–203

[30] Rubinstein AB, Schein M, Reichenthal E (1989) The association of carcinoma of the breast with meningioma. Surg Gynecol Obstet *169:* 334–336

[31] Rubinstein L (1972) Tumors of the Central Nervous System. AFIP, *Fasc. 6* Washington

[32] Schnegg JF, Gomez F, Le Marchand-Beraud T, De Tribolet N (1981) Presence of sex steroid hormone receptors in meningioma tissue. Surg Neurol *15:* 415–418

[33] Schoenberg BS, Christine BW, Whisnat JP (1975) Nervous system neoplasms and primary malignancies of other sites. The unique association between meningiomas and breast cancer. Neurology *25:* 705–712

[34] Seizinger BR, De la Monte S, Atkins L, Gusella JF, Martuza RL (1987) Molecular genetic approach to human meningioma. Loss of genes on chromosome 22. Proc Natl Acad Sci USA *84:* 5419–5423

[35] Smith FP, Slavik M, MacDonald JS (1978) Association of breast cancer with meningioma. Report of two cases and review of the literature. Cancer *42:* 1992–1994

[36] Theologides A, Lee JC (1972) Tumor to tumor metastasis. JAMA *219:* 384

[37] Tilzer LL, Plapp FV, Evans JP, Stone D, Alward K (1982) Steroid receptor proteins in human meningiomas. Cancer *49:* 633–636

[38] Weyand RD, MacCarty CS, Wilson RW (1951) The effect of pregnancy on intracranial meningiomas occurring about the optic chiasm. Surg Clin North Am *31:* 1225–1233

[39] Wolintz AH, Mastri A (1970) Metastasis of carcinoma of lung to sphenoidal ridge meningioma. NY State J Med *70:* 2592–2598

[40] Zon LI, Johns WD, Stomper PC, Kaplan WD, Connolly JL, Morris JH, Harris JR, Henderson IC, Skarin AT (1989) Breast carcinoma metastatic to a meningioma. Case report and review of the literature. Arch Intern Med *149:* 959–962

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Luigi Di Bonito, M.D., Department of Anatomic Pathology, Ospedale Maggiore, I-34125 Trieste, Italy