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Abstract. – Breast cancer is the most common cancer in women. Multicentric gliomas are uncommon lesions of the central nervous system (CNS) with an unprecise rate of occurrence that diffusely infiltrate large portions of the brain. High grade astrocytoma is the most agressive form of gliomas and often has a distinct neuroimaging pattern with a poor prognosis.

We report a case of a 29-year-old woman patient with primary breast carcinoma and high grade astrocytoma subsequently developed.

The woman was treated by mastectomy and 20 months post-diagnosis of the cancer she exhibited a transient facial paralysis. Magnetic resonance imaging (MRI) revealed two cranial masses suspicious of metastasis. A complete tumor removal from the brain was performed. On histological examination, this tumor was a high grade astrocytoma.

Key Words:

Invasive breast carcinoma, Multicentric high grade astrocytoma.

Introduction

Breast cancer is the most common cancer (21%) among women and the second leading cause of cancer deaths. Annual breast cancer deaths are exceeded only by those from lung cancer[1]. On the contrary, brain tumors are relatively rare and are found at autopsy with a prevalence between 1 and 2%[2].

Half of the newly discovered brain tumors are metastatic lesions, and breast cancer appears to be the second leading cause of brain metastases[3].

Anaplastic astrocytoma and glioblastoma account for approximately 38% of primary brain tumors, meningiomas and other mesenchymal tumors approximately for 27%[4].

Malignant astrocytoma and high-grade astrocytoma may arise from a diffuse astrocytoma or may arise *de novo* without indication of a less malignant precursor[5]. Anaplastic astrocytomas possess an intrinsic tendency to progress to glioblastoma. The mean age at biopsy is approximately 41 years. This tumor primarily affects the cerebral hemispheres. Chromosomal abnormalities are nonspecific. There is a consistently observed male predominance in glioblastoma and anaplastic astrocytoma, with a male to female ratio between 1.5 and 2.0[6-8].

According to the literature, the association between breast cancer and high grade astrocytoma is not as common as the association between breast cancer and other primary malignant tumors or intracranial tumors as well as meningiomas[9].

A prior history of meningioma is associated with a higher incidence of ductal breast carcinomas[10-12]. Recently, Piccirilli et al.[12] recently described the occurrence of glioblastoma multiforme (GBM) in 11 Italian patients previously treated for breast cancer.

An association between breast and brain cancers is possible, especially in the rare autosomal dominant Li-Fraumeni syndrome[13], but otherwise such an association is rare.

We report here the case of a 29 year-old woman previously diagnosed with ductal carcinoma of breast and subsequently developed anaplastic astrocytoma.

Case Report

A 29-year-old woman with a right primary breast carcinoma (T1N0M0: stage IA) was re-

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ferred to our hospital. She had no past or family history of malignancies. The tumor size was 2 cm in diameter at the first consultation. As for the diagnostic procedures, mammography (Alpha RT, Instrumentarium, Helsinki, Finland) revealed an ill-defined, spiculated tumor shadow with diffuse microcalcifications in the right breast. An irregular hypoechoic-tumorous lesion could be detected in the upper-outer quadrant of the right breast by ultrasonography (Sonoline G40 Ultrasound Unit, Siemens™, Erlangen, Germany). A modified radical mastectomy of the right breast was carried out in december 2006. Histological examination revealed that the right breast tumor was a predominantly intraductal carcinoma, histological grade 2, with negative lymph node metastasis (0/14) (Figure 1). Estrogen receptor (ER) and progesterone receptor (PR) of this tumor was positive by immunohistochemistry. Whereas the size of the invasive component was only 1 × 1 cm in diameter (50%), the size of the intraductal component was 1 × 1 cm in diameter (50%). Lymphatic invasion by tumor cells was positive but vascular invasion by tumor cells was negative. Weakly positive HER-2 overexpression (Dako Japan, Tokyo, Japan) by immunohistochemical staining were observed in this tumor. The patient was received adjuvant chemotherapy with endoxan and epirubicin followed by methotrexate and fluorouracil.

A 2 cm diameter mass detected in liver by abdominal ultrasonography suspected of liver hemangioma. No other metastatic lesion was detected by abdominal ultrasonography and chest X-ray. Bone X-ray of the skull revealed no abnormalities.

20 months after the diagnosis of breast cancer, patient developed epilepsy,left lower limp and right upper limp paresis. Magnetic resonance imaging (MRI) of the brain demonstrated two lesions, including a 50 × 45 mm well circumscribed mildly heterogenous mass with faint contrast enhancement in superficial left frontoparietal region and another smaller (19 × 11 mm) non – enhancing mass lesion with homogenous
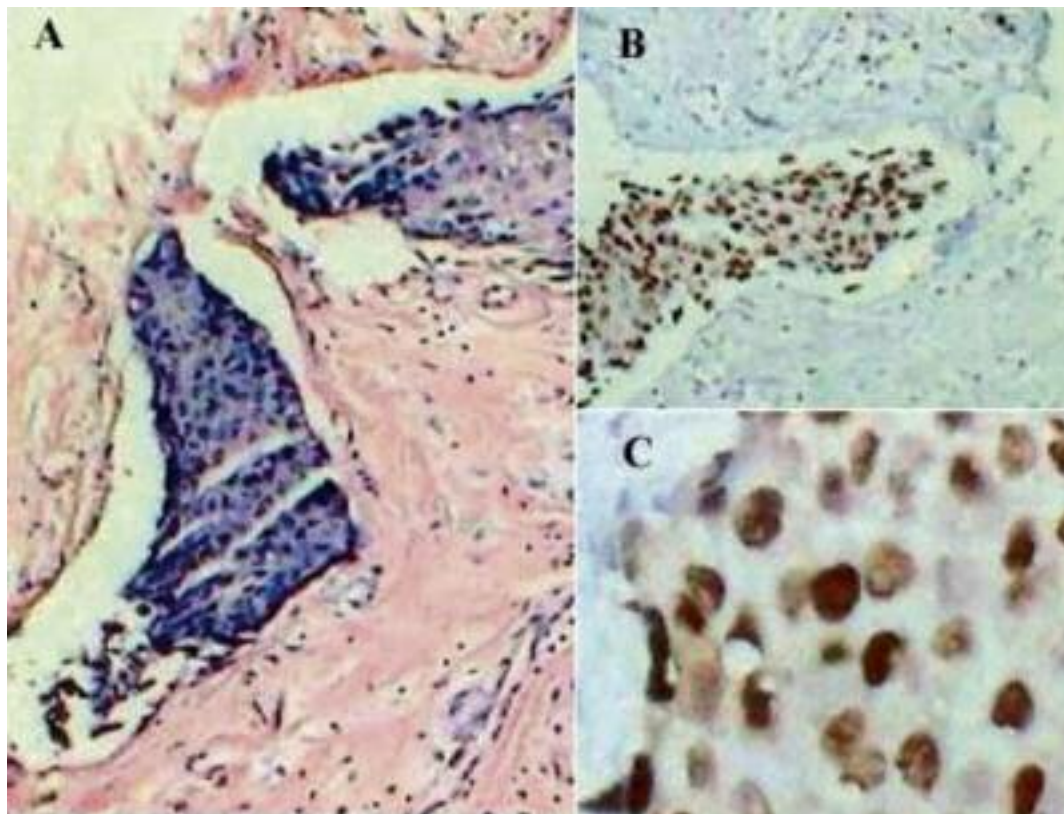

Figure 1. Photomicrographs illustrating histologic analysis of the patient's breast tumor. **A,** Right breast ductal carcinoma (hematoxylin-eosin ×100). **B,** Immunohistochemical examination of the right breast cancer by progesterone receptor (PR) ×100. **C,** PR ×400.

signal intensity in right frontal lobe suspicious for metastatic disease associated with her breast cancer (Figure 2). The patient underwent a craniotomy and gross total resection of the larger frontoparietal lobe lesion.

The tumor was firm and had a white color. The postoperative course was smooth and the patient remained neurologically intact. No other possible metastatic lesion could be determined during a detailed survey of the systems.

Histopathologic analysis demonstrated a high-grade glial neoplasm with moderate mitotic activity, characteristic of high grade astrocytoma (Figure 3) Immunohistochemically, tumor cells showed glial fibrillary acidic protein (GFAP) and Ki-67 positivity. The Ki-67 labeling index was 2-3%.

Tumor markers (CEA, CA125) were within the normal rangesand and CA 15-3 level was above normal.

The patient received external beam radiation to 5000 cGy with low-dose daily temozolomide and dexamethasone. Following radiation, she continued temozolomide for several weeks. The patient was discharged and continued the oral use of tamoxifen and phenytoin.

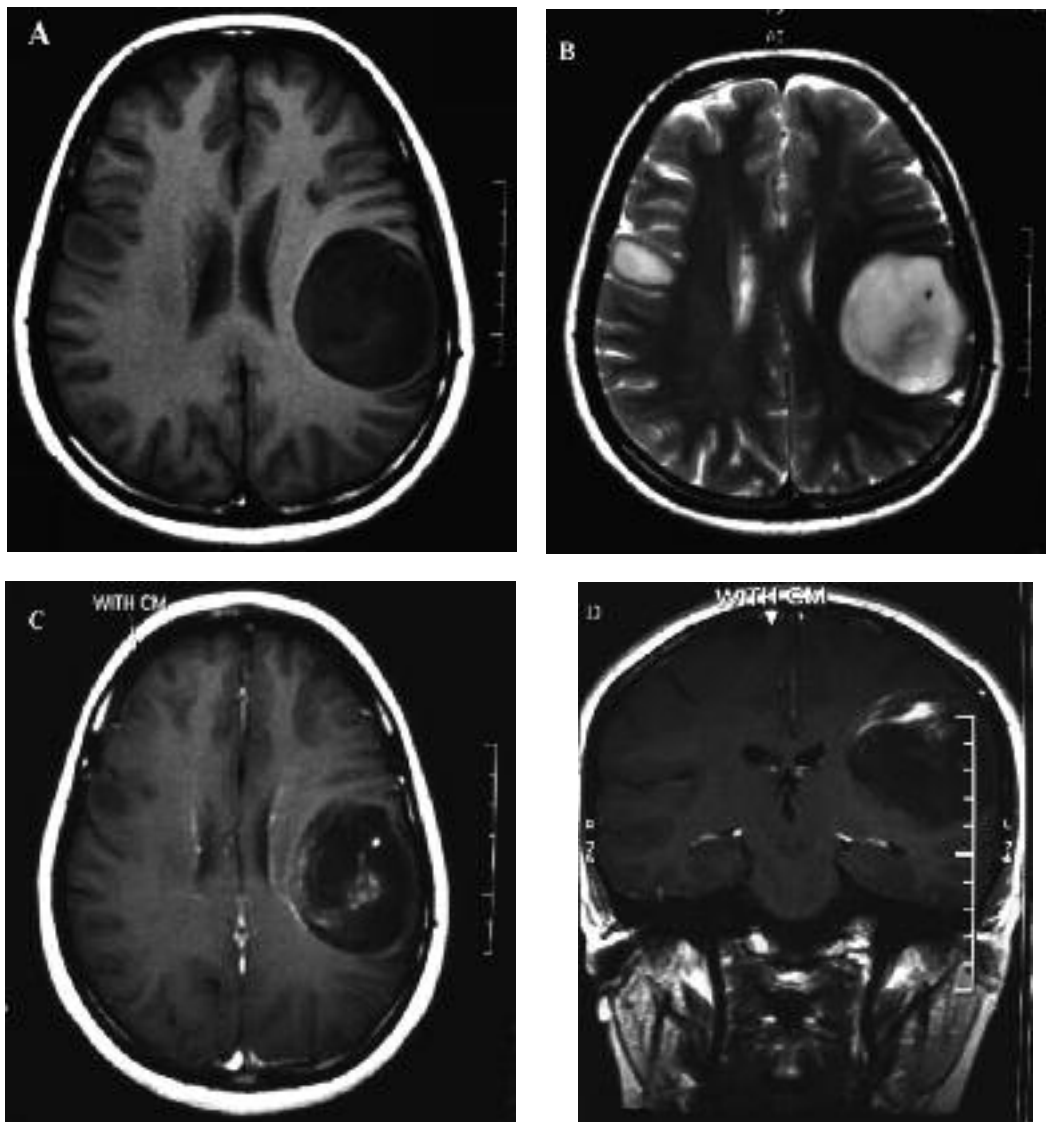The patient is currently well 4 years after the initial surgery for breast cancer.

Figure 2. Precontrast Axial Brain MRI T1 *(A)* and T2 images *(B)*, and axial *(C)* and coronal *(D)* post- gadolinium images revealing a dominant lesion located in the left frontoparietal lobe, and a second smaller lesion located in the right frontal lobe.
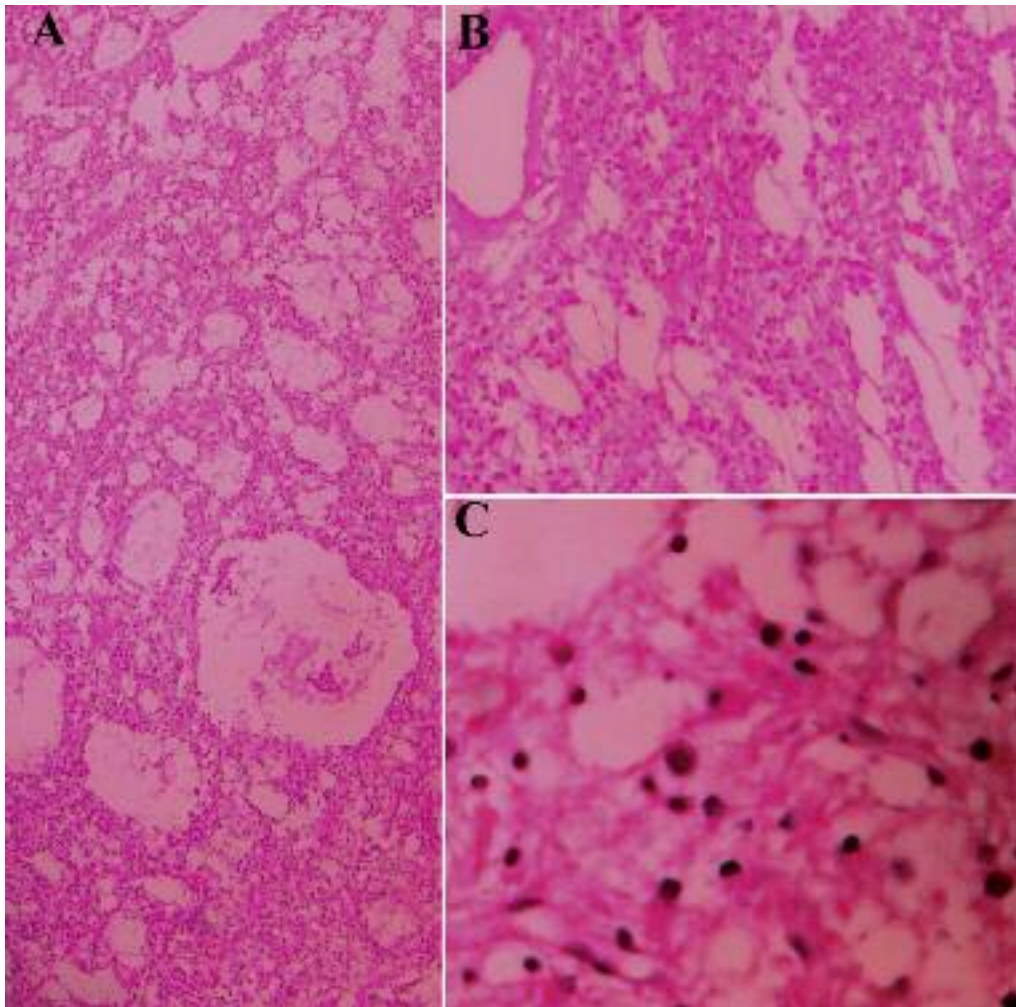
Figure 3. Histopathological examination of the brain tumor. H+E staining, showing fragments of highly cellular astrocytic tumor with areas of moderate nuclear atipia and numerous interspersed gemistocytes. ×10. *(A)* ×40 *(B)* and ×100 *(C)*.

Her latest examination was performed in the two months ago and she was still neurologically intact with no evidence of recurrence on MRI, or metastasis.

Discussion

It has been reported that breast cancer is the second most common cause of intracranial metastases[14]. A personal or family history of breast cancer is not currently considered a risk factor for developing malignant glial tumors and there are only a few reports in the literature about the association between breast cancer and brain glial tumor[15,16]. In contrast, there are several clinical reports on patients who have had breast cancer and meningioma[9].

Multiple tumors in the brain usually indicate metastatic disease. Primary brain tumors are typically seen in a single region, but some brain tumors like lymphomas, multicentric glioblastomas and gliomatosis cerebri can be multifocal. Roughly one-third of CNS tumors are metastatic lesions, one third are gliomas and one-third is of non-glial origin.

Glioma is a non-specific term indicating that the tumor originates from glial cells like astrocytes, oligodendrocytes, ependymal and choroid plexus cells. Gliomas are the most common primary brain tumors, and about three quarters of them are aggressive. The true frequency of

glioma in adults, as compared with the frequency of other intracranial neoplasms, is uncertain because of the difficulty in identifying indolent tumors, the frequency of which would be underestimated in epidemiologic and most autopsy studies. All the subtypes of glioma can present as very slowly expanding, calcified masses. However, consideration of this patient's age and the location of the mass, suggests the most likely subtype.

Astrocytomas are the most common subtypes of glioma and are usually lobar in adults. Most astrocytomas are high-grade tumors, producing rapidly progressive neurologic deficits, but about 10 percent of them are low grade and can be asymptomatic for years[17]. However, it is unusual for symptoms to begin after the age of 40 years and in nearly half the cases of low-grade astrocytoma, the tumor eventually becomes high grade[18]. Astrocytomas tend to infiltrate the white matter diffusely before showing evidence of cortical involvement. Calcification is found on CT images in only 15 to 20 percent of cases[19].

Glioblastoma and anaplastic astrocytoma respectively account for 54% and 8% of all gliomas in adults[20]. Astrocytomas occur at any age, but glioblastoma multiforme is mostly seen in older people.

The median age at diagnosis of glioblastoma is 58 to 63 years of age, and it is 43 to 52 years of age for anaplastic astrocytoma[6,20].

All brain tumors manifest symptoms based upon a combination of the tumor size and location. Astrocytomas have a tendency to become progressively anaplastic if left untreated. This transformation may be heralded by a rapid clinical deterioration.

Multicentric gliomas are well-separated lesions, localized in different lobes or hemispheres, which cannot be ascribed to dissemination through commissural pathways, cerebrospinal-fluid (CSF), blood or local extension. Despite of advances in neuroradiological techniques, in case of multicentric cerebral lesions, differential diagnosis may require cerebral biopsy[21-23].

Multicentric gliomas are uncommon lesions of the central nervous system with an unprecise rate of occurrence that diffusely infiltrate large portions of brain. Various incidences ranging from 2.3 to 9%[24-25] have been reported. Radiological features separate this group of brain tumours and patients have a very short life expectancy even after surgical excision, radiotherapy and chemotherapy.

Multicentric gliomas are fascinating lesions of the brain. Making the differential diagnosis and choosing the management strategy are the main difficulties encountered with this rare entity. Multiple cerebral masses should be thoroughly evaluated and not always presumed to be of metastatic origin[26]. Although multicentric gliomas can mimic metastatic diseases, the treatment of these two lesions is considerably different with respect to adjuvant radiotherapy and chemotherapy[27-30].

Furthermore, multicentric glioma associated with other primary cancers is extremely rare. To date, reports have been limited to patients with prostate, lung or colorectal cancers[31]. To our knowledge, multicentric anaplastic astrocytoma have not yet been described in the setting of breast cancer. Anaplastic astrocytoma rarely occurs in the presence of other primary tumors in the general population. Until recently, only isolated reports describing one or two patients have documented glioblastomas that develop in patients with a previous history of breast cancer[17,32-34].

A small proportion (less than 5%) of persons with malignant astrocytoma has a definite or suspected hereditary predisposition. High grade astrocytomas are associated with several hereditary tumor disorders that also predispose toward the development of breast cancer, including Li-Fraumeni and Cowden syndromes. Malignant astrocytomas occur in approximately 10% of persons with Li-Fraumeni syndrome, an autosomal dominant disorder of susceptibility to a specific group of tumors, including breast carcinoma, osteosarcoma, soft tissue sarcomas, adrenocortical carcinoma, leukemia, and brain tumors[13,35]. Penetrance is approximately 50% by 30 years of age and 90% by 60 years of age. Affected individuals may have multiple primary tumors. The vast majority of gliomas associated with Li-Fraumeni syndrome occur prior to 40 years of age. A germline mutation in the *p53* gene located on chromosome band 17p13, which encodes a nuclear transcription factor that regulates DNA repair processes and the cell cycle is present in affected persons from approximately 80% of families with "classic" Li-Fraumeni syndrome[36].

Conversely, Cowden syndrome results most commonly from a mutation in the *PTEN* tumor suppressor gene on chromosome band 10q23[37]. The *PTEN* gene encodes a protein that inhibits the PI3K signaling pathway required for regulating cell growth and survival, and thereby pro-

motes cell death. *PTEN* inactivation, as seen in Cowden syndrome, predisposes affected individuals to breast and thyroid carcinomas as well as mucocutaneous hamartomas. Similar genetic mutations have been found in malignant astrocytomas, glioblastomas, meningiomas, and medulloblastomas[38,39]. While the prevalence of these hereditary genetic syndromes is extremely low, somatic mutations in p53 and *PTEN* have been demonstrated in several human cancers and are likely to play an important role in the pathogenesis of a variety of tumors, including breast cancer and high grade astrocytoma.

Hormonal sensitivity and steroid receptor modulation may also serve as a common link in the transformation, growth, and severity of breast and glial tumors. Epidemiologic data from the United States and Europe demonstrate that the incidence of more malignant gliomas, including anaplastic astrocytoma and GBM, is approximately 1.5 times higher in males than females[8,40].

Furthermore, McKinley et al.[40] reported that the protective effects of gender peak at peri-menopausal ages and diminish when women reach postmenopausal ages. In animal studies, female nude mice implanted with human GBM lines exhibit a survival advantage over males and ovariectomized females undergoing similar treatment. Estrogen replacement can reverse the effects of ovariectomy, suggesting that estrogen may be largely responsible for the observed survival advantage in females[41]. Interestingly, higher estrogen levels, a known risk factor for developing breast cancer, may protect against developing high grade astrocytoma. In contrast, while progesterone has no observed effect on survival in animals[42], a correlation between the presence of progesterone receptors and more aggressive gliomas, including anaplastic astrocytomas and GBMs, has been observed in histologic studies[42]. These observations suggest that regulation of hormonal signaling may contribute to the pathogenesis of breast and glial tumors.

The pathogenesis of multiple primary neoplasms is unknown. While extrinsic factors such as environmental effects including irradiation or chemical exposure to the host genome might be important for heterochronous multiple primary neoplasms, intrinsic factors, age, immunity or genetic factors (for example, the rare autosomal dominant Li-Fraumeni syndrome) have been proposed as possible mechanisms in the occurrence of multiple primary neoplasms[43-44].

The relationship between sex steroid receptors and the pathogenesis and/or treatment of either breast cancer and prostatic carcinoma has previously been shown, and so in recent years[45], there has been increasing interest in the role of these receptors in brain tumors.

Progesterone receptors in astrocytic tumors were found to correlate with histologic grade and to participate in the growth of these tumors and tumor angiogenesis[46].

Androgen and glucocorticoid receptor mRNAs were detected in all astrocytic neoplasms. Progesterone receptor mRNA was observed more frequently in high grade gliomas than in low-grade gliomas[47]. Normal astrocytes were consistently negative for estrogen and progesterone receptors. The majority of glioma cases were negative for estrogen receptors while strong progesterone receptor nuclear immunopositivity was observed in 59% of glioblastomas, 45% of anaplastic astrocytomas and 8% of low-grade astrocytomas[42].

On the other hand, the antiestrogen tamoxifen has been found to be effective in decreasing glioblastoma cell proliferation[48]. Thus, the expression of estrogen receptor in U138MG glioblastoma cells was successfully demonstrated[49]. These findings might raise the question of whether the mechanism underlying this effect of tamoxifen works through the estrogen receptors of astrocytes. Khalid et al.[50] showed that an estrogen receptor-related antigen (ER-D5) was observed in the microvascular endothelial proliferations and in tumor blood vessels, suggesting its participation in the growth of the gliomas and tumor angiogenesis. Tamoxifen probably decreases cell proliferation through its effect on this antigen.

We studied estrogen and progesterone receptors on both pathologic slides of our patient. However, neither estrogen nor progesterone receptor immunoreactivity were positive in high grade astrocytoma, whereas the breast cancer cells were positive for estrogen and progesterone receptors. She still uses tamoxifen predominantly for her breast cancer and no recurrence has been detected at either site to date.

We failed to demonstrate a common hormonal or oncogenetic basis for the neoplastic growth of these 2 associate diverse primary malignancies in our patient. Further investigations including mutational analysis in such patients with mutiple primary neoplasms may help to explore the genetic and epigenetic factors influencing carcinogenesis.

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