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*Original Article*

# Intracranial ganglioglioma co-existing with breast cancer

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**Abstract:** In the central nervous system one of the most common origins of metastatic lesions is breast cancer. Many patients with a concurrent brain tumor(s) and breast cancer were remedied to have a lesions and metastatic in the brain, rooted specially on their picture results with no progressive pathologic verification, and including foremost brain malignancy, which in fact guarantees a detailed modality of treatment, might happen in such patients with an almost known malignancy. We, herein, documented a female patient at 47-year-old, in the left-side basal ganglion region, she suffered from a ganglioglioma (WHO I grade) 1.5 year after her diagnosis of a breast lump which was identified as breast cancer subsequently. Characteristic imaging findings, demographic data, treatment, and outcome of the patient were expounded. Related literatures were also studied.

**Keywords:** Ganglioglioma, glioma, breast cancer, differential diagnosis

## Introduction

As the most common type of cancer, Breast cancer is the second dominant cause for cancer death in women. The age-regulated occurrence rate is 124 per 100,000 women per year. In the central nervous system (CNS), Breast cancer is one of the most prevalent causes of the metastatic lesions. According to the estimated, around 10~15% of breast cancer patients suffered from the CNS metastatic lesion(s) through the whole course of treatment [1]. A lot of patients with a concurrent brain tumor(s) and breast cancer, nevertheless, do not obtain a biopsy or surgical extirpation for the CNS lesions, because characteristic radiological results including a ring-like improving multiple lesions or lesion with peritumoral edema in the magnetic resonance imaging (MRI) and computed tomography (CT) frequently have made a putative diagnosis of malignant metastatic lesion or lesions. These patients are frequently remedied with whole-brain radiotherapy (WBRT) to the brain in addition of systemic chemotherapy for local tumoral control, for most patients with metastatic lesions, in particular those with various minor lesions (less than 2 × 2 × 2 $cm^3$) that sourced from breast cancer, responding well to the radiation treatment [1, 7]. It is, whereas, probably that critical brain gliomas, in spite of extremely few in occurrence rate, might advance in patients with a mechanistic malignancy, and this patients in fact require a treatment modality almost advanced and fitted for critical CNS malignancy [14]. There are several reports in the literature describing breast cancer and glioma association [2, 6]. Mostly, the involved gliomas are high-grade, or more specifically, glioblastomas. Herein, we reported a 47-year-old female presenting with a ganglioglioma in the left basal ganglia region co-existing with a breast cancer. Demographic data, tailored treatment, final outcome of the patient, characteristic imaging findings, as well as related literatures were reviewed and discussed.

## Case report

A Chinese woman at 47-year-old was admitted to our hospital and she complained of an intermittent bitemporal headache, remote memory

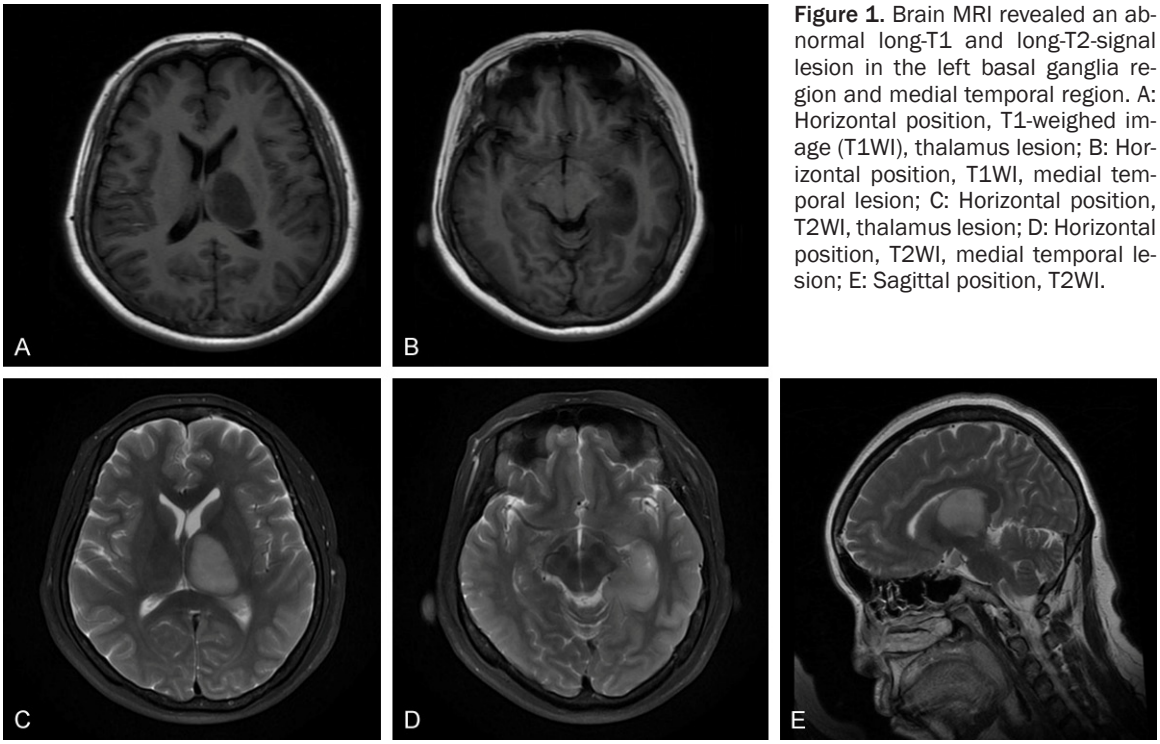


**Figure 1.** Brain MRI revealed an abnormal long-T1 and long-T2-signal lesion in the left basal ganglia region and medial temporal region. A: Horizontal position, T1-weighed image (T1WI), thalamus lesion; B: Horizontal position, T1WI, medial temporal lesion; C: Horizontal position, T2WI, thalamus lesion; D: Horizontal position, T2WI, medial temporal lesion; E: Sagittal position, T2WI.

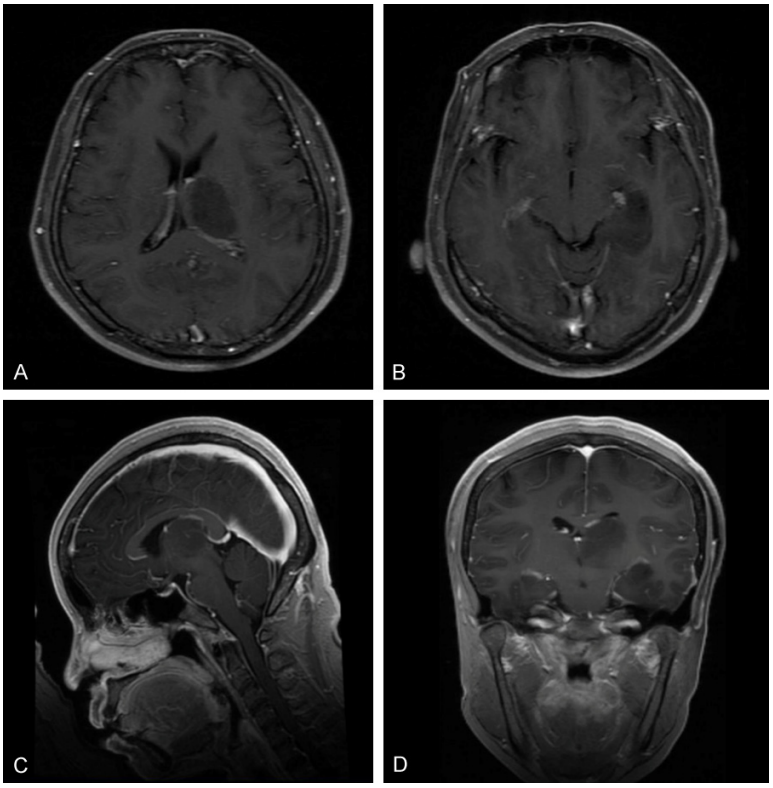


**Figure 2.** Contrast-enhanced imaging of the brain. No obvious enhancement was observed after the administration of Gd-DTPA. A: Horizontal position, thalamus lesion; B: Horizontal position, medial temporal lesion; C: Sagital position; D: Coronal position.

and progressive recent impairment and slight vertigo. She had no symptoms of convulsion, unconsciousness, cognitive disorder or epilepsy and did not take any medications. She noted a small weight loss in spite of a normal appetite. According to neurological test, the patient was detected to have hypoalgesia of the right lower limb and slight weakness (motor grade 4/5) of the right upper and lower limbs. No evident conversions in surface and profound tendon reflexes were watched. Pathological signs were absent. Babinski marks at the right side was positive. Cranial performances and other neurologic tests were not unusual MRI of her head (**Figure 1**): bilateral cerebral hemispheres were symmetrical; a long-T1 and long-T2-signal mass was present in the left basal ganglia region

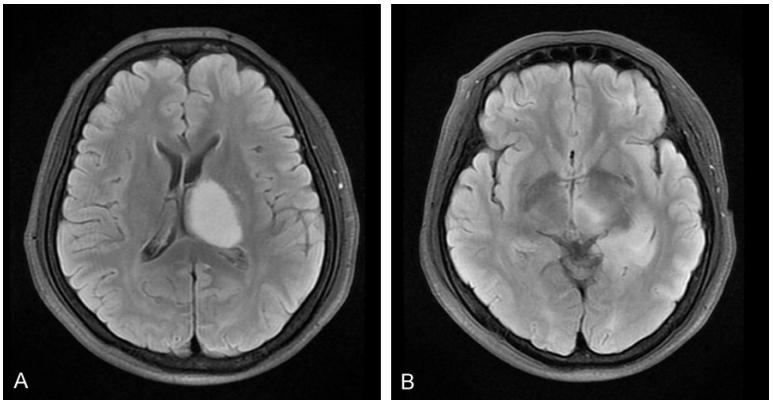


**Figure 3.** Flair image. The mass present with high signal with relatively clear border. A: Horizontal position, thalamus lesion; B: Horizontal position, medial temporal lesion.

and medial temporal region. No obvious enhancement was observed after the administration of Gd-DTPA (**Figure 2**). On flair image, the mass present with high signal with relatively clear border (**Figure 3**). In the abnormal areas of the left thalamus, basal ganglia region and medial temporal region on perfusion-weighted image (PWI), the relative cerebral blood volume (rCBV) increased compared with normal regions. The maximum value of rCBV is around 2.3 (**Figure 4**). These radiological features alone suggested a possible high-grade neuroepithelial tumor.

A year and a half earlier, the patient was found to have a lump at the left-sided breast. The lump, with some ulcers and scars on its surface, was painless and protrudes from the skin with a retraction of the nipple. The breast ultrasound test detected a hypoechoic irregular mass measuring 4.7 × 4.3 × 2.5 $cm^3$ with internal calcifications, and enlarged axillary lymph nodes. And the mammogram test found an irregular spiculated mass about the size of 4.6 cm × 4.4 cm, clustered micro-calcifications, and linear branching calcifications, suggesting malignancy (**Figure 5**). The doctors working in a local hospital advised the patient to undergo a mastectomy then. However, the patient refused, partly because of her worry about the postoperative outlook of her breast. Over the course of a year and a half, the size of the lump seemed to have increased somewhat. The patient did not have breast cancer family history.

Given breast lump's medical history in the past time, the diagnosis of breast cancer brain metastases should be considered. However, as the brain lesion seen on MRI was relatively infiltrative and invasive, not a typical appearance of metastatic brain tumors, we were more inclined to make a diagnosis of a primary brain malignancy rather than a secondary metastasis. In order to design the most reasonable and tailored regimens for treatments and relieve the symptoms, she consequently went through a stereotactic biopsy (**Figure 6**). The surgery went smoothly. A little unexpectedly, pathologic test expounded the tumor as a ganglioglioma (WHO I grade) with vascular proliferation, neoplastic glial cells and ganglion cells which were disorganized, variably cellular, and non-infiltrative. Progressive immunohistochemical (IHC) inspections indicated that the tumor was positive for glial fibrillary acidic protein (GFAP), CD34, Nestin, Neuronal Nuclei (NeuN), synaptophysin, oligodendrocyte transcription factor 2 (oligo-2), S-100, vimentin, but was negative for AE1/AE3. In addition, the Ki-67 labeling index was discovered to be around 10%, showing a mitotic movement, which matches WHO I grade (**Figure 7**).

By we doctors' persuasion, three days after the biopsy, the patient underwent a corrected radical mastectomy with left axillary lymph node dissection. The surgery was successful. Postoperative pathological test confirmed the diagnosis of a breast infiltrating ductal carcinoma with lymphatic metastasis (poorly differentiated; size 5 cm × 4.5 cm × 3.2 cm; involved axillary lymph nodes: 12/24) (**Figure 8**). Microscopically, cancer embolus in vessels and ducts could be observed to have invaded the nipple and adjacent skin tissue. The IHC test showed that the cancer was strongly positive for estrogen receptor alpha (ER-α) (90%), progestin receptor (PR) (90%), CD34, Anti-D240 antibody (D2-40) and E-Cadherin, while was unhelpful for people epidermal growth factor receptor 2 (Her-2), P53, P63, CD10, Cytokeratin 14 (CK14), CK5/6 and epidermal growth factor receptor (EGFR). The Ki-67 labeling index was found as around 40%, showing an extremely high mitotic movement (**Figure 8**).

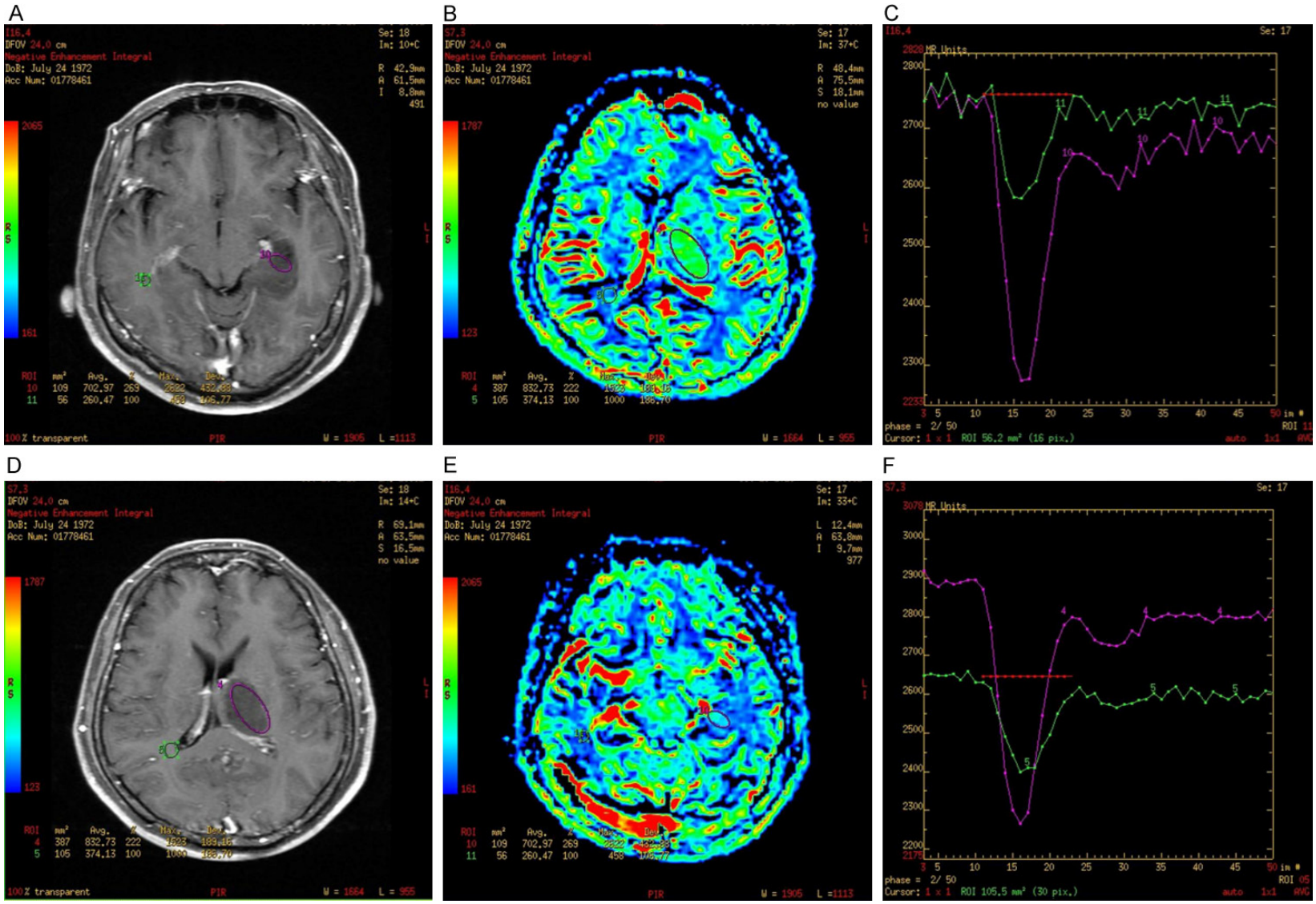


**Figure 4.** Perfusion-weighted image (PWI) of the abnormal lesions in the left thalamus region (A-C) and medial temporal region (D-F). The relative cerebral blood volume (rCBV) increased compared with normal regions.

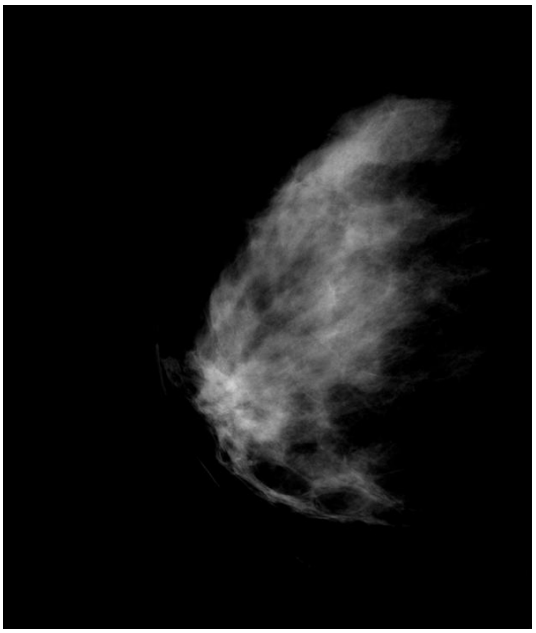

**Figure 5.** Mammogram test found an irregular spiculated mass about the size of 4.6 cm × 4.4 cm, with clustered micro-calcifications, and linear branching calcifications, suggesting malignancy.

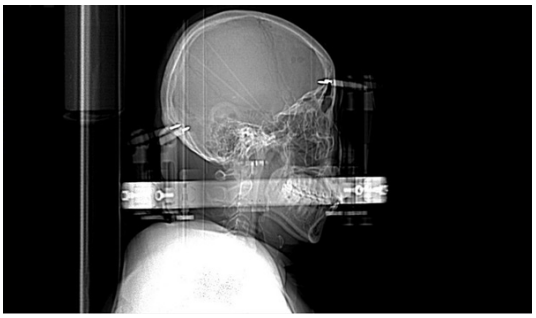

**Figure 6.** The CT image for the stereotactic biopsy.

The patient was further treated with local radiotherapy (60 Gy for ganglioglioma, 50 Gy for left chest wall and 50 Gy for left supraclavicular lymph nodes) and a combined anthracycline- plus taxane-based chemotherapy, without notable adverse effects. The patient's headache was relieved a lot. Upon follow-up, she remained progression free and did not have notable intracranial tumor enlargement and breast cancer recurrence up to 6 months after the surgery.

## Discussion

Critical brain tumors might emerge in patients who are with systemic malignancies, in particular, at the stage with enhanced surgical methods for tumoral extirpation, pursued by well-advanced chemotherapy and radiotherapy, or even target therapy [10, 11]. In a retrospective research, Maluf et al have confirmed 21 patients with a histologic treatment of coexisting high-grade glioma after a previous treatment of a hematological or solid malignancy [10]. Particularly, the most common cancer in women is breast cancer, which has been predicted that around 10~15% of breast cancer patients are likely to suffer from the CNS metastatic lesion(s) through whole the course of the treatment [1]. By comparison, in the general population, an yearly occurrence rate of coexisting critical brain malignancy in patients with other mechanistic cancers could be predicted to be much lower than 1 per million, merely on the basis of the yearly occurrence rates of 10~15 cases per 100,000 who advance critical brain tumors [2]. Hence, it is obvious that in patients with a familiarized systemic malignancy including breast cancer, the incidence of metastatic brain lesion(s) is much more prevailing than that of the coexisting critical brain malignancy.

There are several reports in the literature describing breast carcinoma and glioma association. **Table 1** showed the clinical features and treatments of previously published cases of gliomas co-existing with breast cancers. Among the 21 cases in Maluf et al's study, 5 had breast cancer. An Italian group reported on 11 cases of breast cancer and glioblastoma multiforme (GBM) [10]. Hanalioglu et al reported 2 case of breast cancer with GBM, and one case with anaplastic oligodendroglioma (WHO grade III) [6]. And Elmariah reported one case of multicentric GBM in a patient with breast cancer [4]. A timeline of the relevant publications each year is available as **Figure 9**, showed a normal tendency to add up over time. Based on a world map with the international distribution of relevant publications on the basis of the analysis of their geolocational data, the countries that the publications are from are mainly centralized in Europe, East Asia and North America (**Figure 10**). In the present case, the pathological pattern of the glioma was ganglioglioma, which is a rare, slow-growing primary CNS tumors which most frequently occurs in the temporal lobes of children (our case is a middle-aged women) [3, 12]. Gangliogliomas are generally benign WHO grade I tumors con-

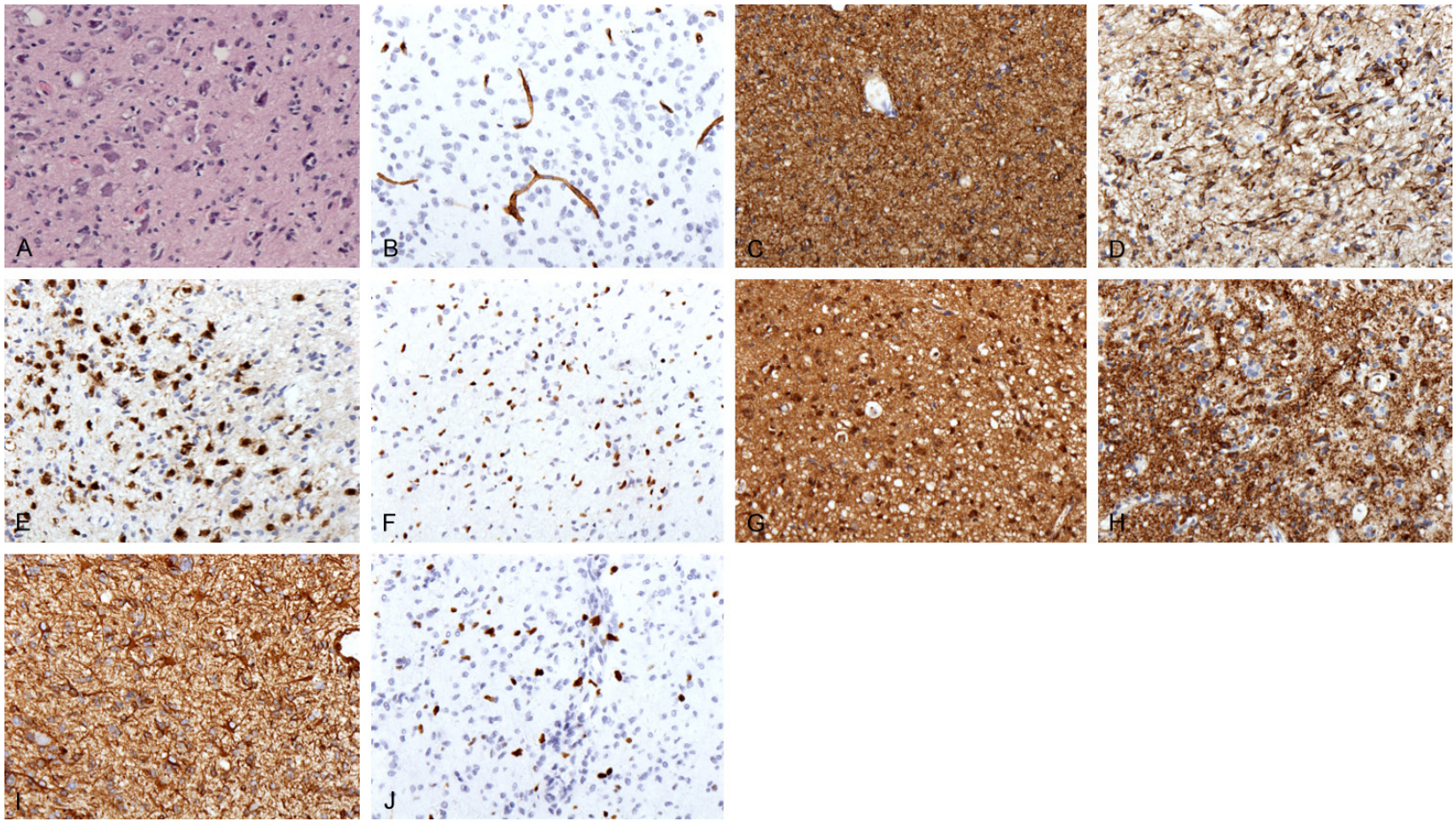


**Figure 7.** Pathologic examination demonstrated the tumor to be a ganglioglioma (WHO I grade) (A, H&E staining, × 200). Further immunohistochemical (IHC) examinations showed that the tumor was positive for glial fibrillary acidic protein (GFAP) (B, × 200), CD34 (C, × 200), Nestin (D, × 200), Neuronal Nuclei (NeuN) (E, × 200), synaptophysin (F, × 200), oligodendrocyte transcription factor 2 (oligo-2) (G, × 200), S-100 (H, × 200), vimentin (I, × 200). The Ki-67 labeling index was found to be approximately 10% (J, × 200).

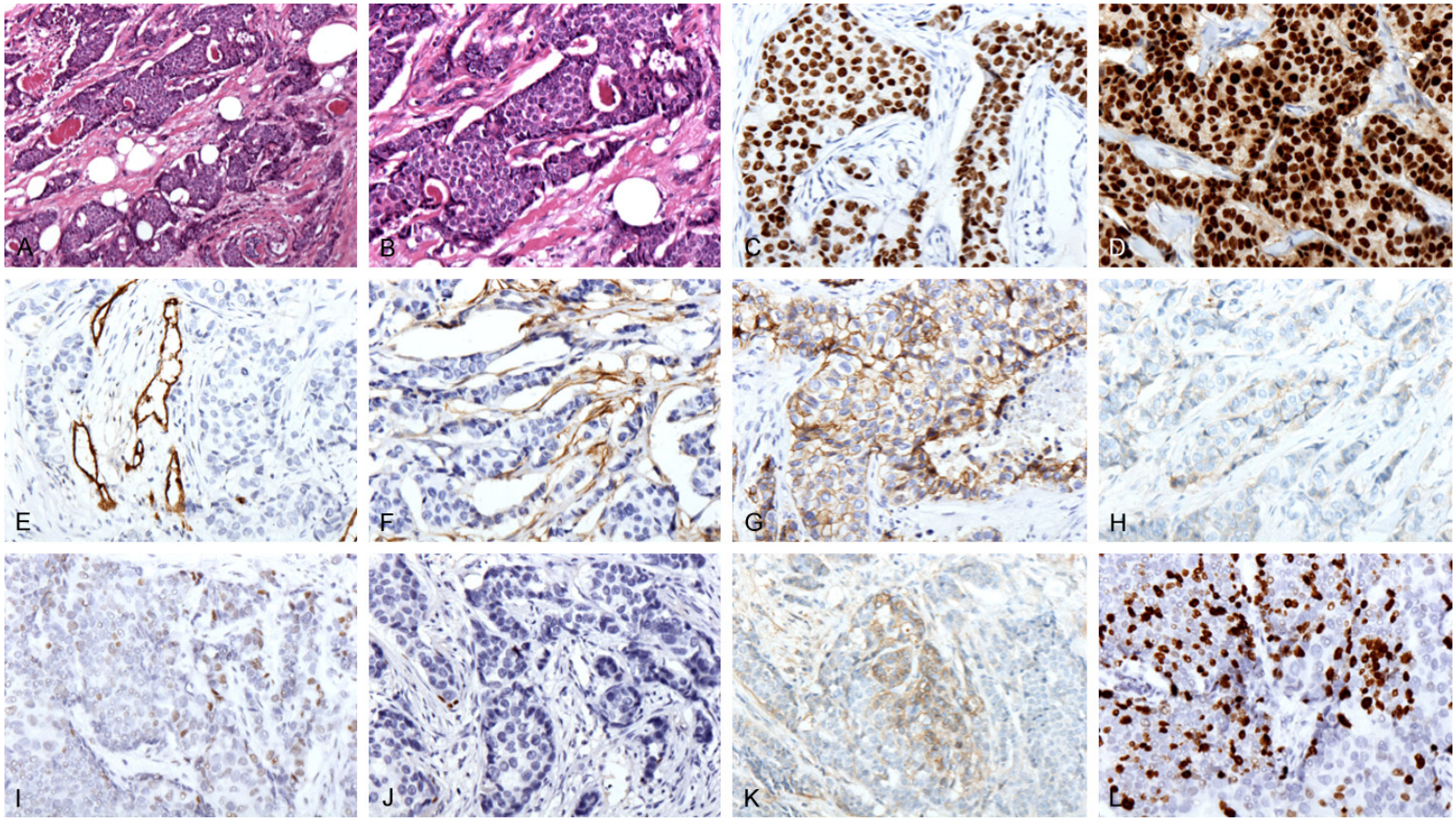


**Figure 8.** Postoperative pathological test and IHC test confirmed the diagnosis of a breast infiltrating ductal carcinoma with lymphatic metastasis (A, H&E staining, × 100; B, H&E staining, × 200). The IHC test showed that the cancer was strongly positive for estrogen receptor alpha (ER-α) (90%) (C, × 200), progestin receptor (PR) (90%) (D, × 200), CD34 (E, × 200), Anti-D2-40 antibody (D2-40) (F, × 200) and E-Cadherin (G, × 200), while was negative for human epidermal growth factor receptor 2 (Her-2) (H, × 200), P53 (I, × 200), P63 (J, × 200) and epidermal growth factor receptor (EGFR) (K, × 200). The Ki-67 labeling index was detected as approximately 40% (L, × 200), indicating a relatively high mitotic activity.

**Table 1.** The clinical features and treatments of previously published cases of gliomas co-existing with breast cancers

| Author | Publishing year | Age when breast cancer diagnosed | Glioma type | Glioma age (year) | Interval (month) | Glioma location | Glioma clinical featurs | Glioma treatment | Survival after the 1st surgery | Breast cancer staging | BC treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ogasawara et al | 1986 | 27 | Glioblastoma (first primary focus) | 27 | 1 | Left frontal lobe | Consciousness disturbance; Intracranial hypertension | Totally removed | - | - | Bilateral mastectomy with lymph-node dissection |
| Friedman et al | 1982 | 50 | Glioblastoma | 66 | 16 | - | - | - | - | - | - |
| Kobayashi et al | 1987 | 52 | Glioblastoma | 55 | 3 | - | - | - | 17 year; free of glioma 4 year | - | - |
| Akimoto et al | 2005 | 42 | Pilocytic astrocytoma | 43 | 1 | Right thalamus | Headache and nausea. | Gross total resection of the tumor followed by radiochemotherapy | - | - | - |
| Boukerroucha et al | 2015 | 28 (L) 36 (R) | Glioblastoma | 34 | 6 | - | - | Macroscopic surgical resection (stage IV) + temozolomide chemotherapy and radiotherapy followed by chemotherapy alone (6 cycles). | 12 | T1N0M0 stageIA (L); T2N0M0 stage IIA (R) | Radical mastectomy + FEC adjuvant chemotherapy (L); adjuvant chemotherapy targeted therapy (docetaxel and trastuzumab) for one year (R) |
| | | 56 (L) 61 (R) | Glioblastoma (stage IV) | 61 | 5 years | Fronto-insular level | mental confusion | Surgical excision + temozolomide chemotherapy and radiotherapy + surgical resection of progressive glioblastoma | 6 y | T2N0Mx stage IIA (L); pT1aN0Mx (R) | Mastectomy + 6 cures of FEC chemotherapy + palliative chemotherapy (paclitaxel) and zoledronic acid. mastectomy + |
| Noronha et al | 2011 | 64 | Anaplastic oligodendroglioma | 66 | 2 | Right temporal lobe | Mental confusion | Subtotal resection of the temporal lobe mass + adjuvant involved-field irradiation + adjuvant chemotherapy with PCV + resect | - | Early-stage | Lumpectomy and 6120 cGy of adjuvant RT |
| Pour et al | 2011 | 29 | High-grade glial high grade astrocytoma | 30 | 20 m | Superficial left frontoparietal region + right frontal lobe | Epilepsy + limp | Craniotomy and gross total resection of the larger frontoparietal lobe lesion + beam radiation + low-dose daily temozolomide and dexamethasone. | - | T1N0M0: stage IA | Modified radical mastectomy + adjuvant chemotherapy |
| Piccirilli et al | 2005 | 34 | Glioblastoma | 47 | 13 | Left frontal lobe | Seizures | Surgery Radiotherapy Chemotherapy | 13 | T1N0M0 | Quadrantectomy, radiotherapy, chemotherapy |
| | | 45 | Glioblastoma | 56 | 11 | Right frontal lobe | Seizures | Surgery Radiotherapy Chemotherapy | 11 | T1N0M0 | Quadrantectomy, radiotherapy, chemotherapy |
| | | 40 | Glioblastoma | 57 | 17 | Right frontal lobe | Endocranial hypertension | Surgery Radiotherapy Chemotherapy | 18 | N0 | Mastectomy, radiotherapy, chemotherapy |
| | | 36 | Glioblastoma | 53 | 17 | Right temporal lobe | Temporal seizures | Surgery | lost to follow-up | T2N1M0 | Mastectomy, radiotherapy, chemotherapy |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 49 | Glioblastoma | 60 | 11 | Left frontal lobe | Change in character | Surgery Radiotherapy Chemotherapy | 13 | TisN0M0 | Tumorectomy, radiotherapy |
| 52 | Glioblastoma | 71 | 19 | Posterior part left frontal lobe | Apathy, sopor, drowsiness | Biopsy | 5 | N0 | Mastectomy |
| 40 | Glioblastoma | 58 | 18 | Left occipital lobe & splenium | Drowsiness | Biopsy | 4 | T2N1M0 | Mastectomy, radiotherapy, chemotherapy |
| 55 | Glioblastoma | 77 | 22 | Right frontal lobe | Drowsiness, apathy | Surgery Radiotherapy Chemotherapy | 13 | N0 | Mastectomy, radiotherapy, chemotherapy |
| 37 | Glioblastoma | 55 | 18 | Right frontal lobe | Seizures | Surgery Radiotherapy Chemotherapy | 23 | N0 | Mastectomy, radiotherapy, chemotherapy |
| 32 | Glioblastoma | 51 | 19 | Right frontal lobe | Seizures | Surgery Radiotherapy Chemotherapy | 27 | T1N0M0 | Quadrantectomy, radiotherapy, chemotherapy |
| 52 | Glioblastoma | 56 | 34 | Thalamus | Hemiplegia, hemianesthesia | Biopsy | 4 | N0 | Mastectomy |

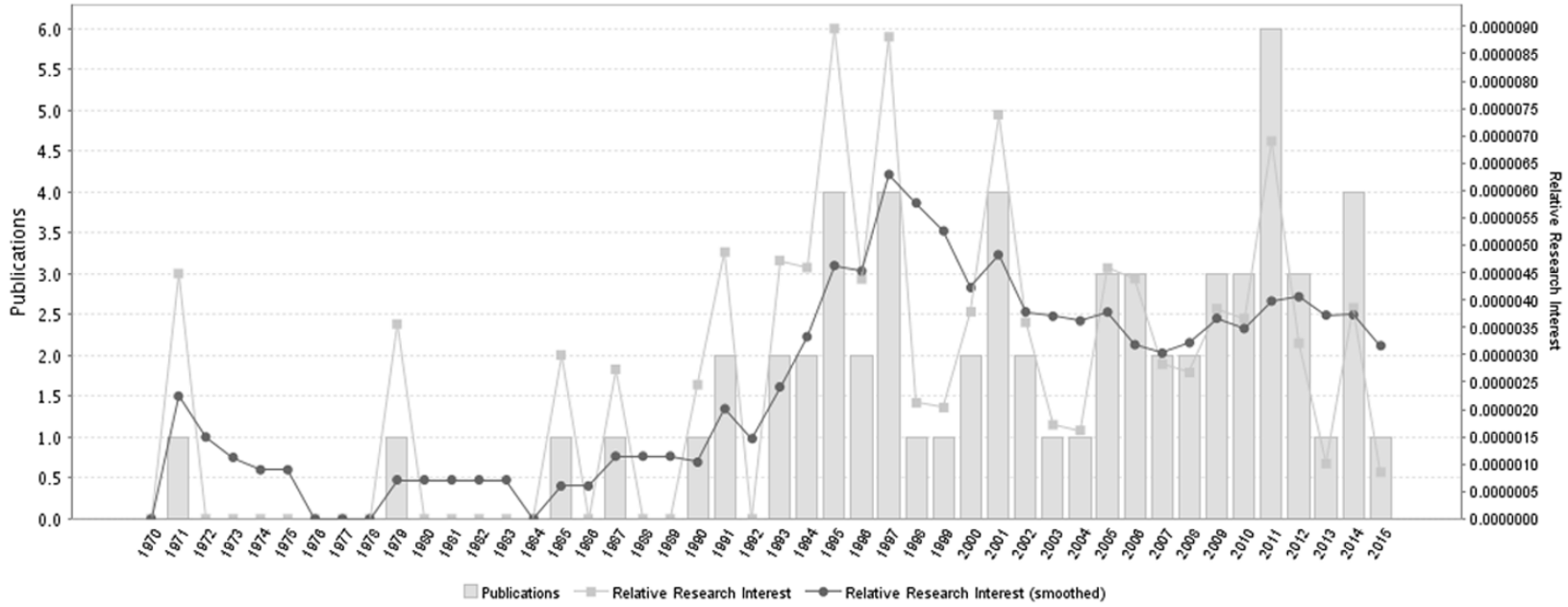


**Figure 9.** A timeline of the publications related to skull PICH. The number of these literatures each year show a general tendency to increase over time.

**Figure 10.** A world map with the global distribution of skull PICH-related publications based on the analysis of their geographical data.

sist of changeable proportions of and glial cells [3, 12] and ganglion cells. Our case is the first reported one with ganglioglioma and breast cancer to our best knowledge.

It is notable that in the majority of breast cancer patients, a treatment of CNS metastases is frequently decided by either MRI of the brain alone or contrast-enhanced CT [13]. Arslan et al have retrospectively gathered 259 CNS metastases breast cancer patients and have discovered that only 32 patients (13%) went through surgery for pathological verification of their CNS metastases [1]. Kim et al also documented a reviewed research containing 400 CNS metastases breast cancer patients and have pointed that only five patients (1.3%) had experienced surgical interference for pathological confirmation [7]. Nevertheless, it is essential in clinic aspect to differentiate between metastatic and primary intracerebral lesions in patients with systemic malignancies, thus providing proper treatment protocols. Different therapeutic modalities and surgical planning among the two disease entities might influence the last consequence of patients largely, as an inappropriate treatment is done exclusively on the basis of the imaging diagnosis [16, 17]. In the research of Maluf et al, it has been detected that as they had brain metastases [10], Four patients were misdiagnosed. These patients had obtained WBRT solely and, hence, the proper chemotherapy and surgical interference tailored for critical CNS malignant gliomas were much delayed [10, 17]. Despite distinctive gliomas from brain metastases merely based on contrast-improved MRI or CT is actually hard owing to alike imaging features among the two diseases, some MRI results may offer clues to differentiate between a brain metastasis [11, 15] and a primary brain malignancy. It has been expounded that lesions involving deep white matter structures, an infiltrative lesion involving the corpus callosum, and extensive infiltration involving both gray and white matter might offer more possibility to advise a glioma instead of a metastatic lesion [2]. In our case, basal ganglion region raised the suspicion of a primary brain tumor and the infiltrative tumor involving the left thalamus, which was consequently identified after histopathologic and stereotactic biopsy testing. As for gangliogliomas, when surgery is finished, the plan of treatment changed according to degree of resection as well as histology. For tumor incomplete resection or regrowth, radiation therapy (50-60 Gray) of external beam was attached. In our case, the tumor was positioned in the basal ganglion region, in which complete or subtotal resection was not possible. Therefore, the patient obtained a radiotherapy.

Although several authors indicated that this association between gliomas and breast cancer could be due to chance or related to the favorable long-term survival of breast cancer patients to allow them to develop glioma at a late age, there are some others who argue against the coincidence, proposing possible common etiopathogenetic mechanisms such

as hereditary cancer syndromes (e.g. Li Fraumeni's, Cowden's, BRCA1&2), hormonal factors and prior irradiation [4, 5, 8, 9, 11, 18, 19]. As tumors are usually considered and treated independently in the setting of two distinct neoplasms, which leads to overtreatment. In conclusion, long-term epidemiological studies of larger cohorts are needed to confirm the association and to establish the common risk factors, pathogenetic mechanisms and better treatment options for both tumors.

## Conclusion

In conclusion, in patients with concurrent brain lesion(s) and systemic malignancies, critical brain malignancy is supposed to be contained in the different treatment, besides secondary metastases. We noted that surgical intervention for histopathologic testing is required for such patients, in particular as there are characterized MRI results reminding of gliomas instead of metastases.

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## Disclosure of conflict of interest

None.

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