

A novel combination of double primary malignancies: penile carcinoma and glioblastoma. A series of two cases

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Abstract

Aim: Penile squamous cell carcinoma (pSCC) and glioblastoma (GB) are rare malignant tumors that develop especially in the elderly. The aim of our paper is to present two patients diagnosed and treated for a cerebral GB developed after a prior pSCC and to discuss the possible mechanism of their association. **Patients, Materials, and Methods:** The medical records of 632 patients admitted for a GB in the Department of Neurosurgery, "Prof. Dr. Nicolae Oblu" Emergency Clinical Hospital, Iași, Romania, between April 2010 and April 2018, were retrospectively searched for those having a prior histological proven cancer. The review found only two patients (0.31% of all cases with GB) and their demographics, clinical presentation, medical history, treatment and pathological diagnosis were reviewed and discussed. **Results:** Both patients were 65-year-old on their admission in the Department of Neurosurgery. Their prior penile tumors were both located at the penis glans. In both cases, the histopathological exam revealed a penile keratinized squamous cell carcinoma stage T1aN0M0 at the moment of their first urological diagnosis. At the time of the neurosurgical evaluation, brain radiological investigations demonstrated right frontal cystic neoformation in the first case, and a right frontal-parietal solid, expansive lesion for the second patient. The patients underwent subtotal surgical excision of their brain masses. The histopathological exam revealed in both cases a *World Health Organization* (WHO) grade IV GB. **Conclusions:** This is the first clinical report of a new association between pSCC and subsequent development of GB in a series of two patients. Both our patients developed a prior pSCC without any lymph node and distant metastasis at their first diagnosis and this situation reinforces the idea that this type of cancer has a good prognosis and that the patient can develop a second cancer during his post-penectomy life, probably due to a genetic predisposition, post-therapeutic effects, life style factors (smoke effects), sporadic association, or due to the common embryological origin of the nervous and skin tissues.

Keywords: penile squamous cell carcinoma, metachronous glioblastoma, double primary malignancies.

Introduction

The concept of "multiple primary malignancies" is known for more than 100 years and is defined as the presence of two or more primary tumors in the same person. Multiple primary tumors should have different proven histology, different locations relative to each other, and none of them should be a metastasis or recurrence of any of the other tumors already existing [1]. Most commonly, multiple primary malignancies develop from the same type of tissue, such as the association of two or more carcinomas developed from the epithelium of the digestive tract [2] or the epithelium of the urogenital apparatus [3, 4]. Zacharia *et al.* have extensively analyzed the incidence of prior cancer in glioblastoma (GB) harboring patients and identified 7.9% of all 2164 GB patients being under study. They found that patients with prior carcinomas were more likely to harbor an epidermal growth factor receptor (*EGFR*) or methylguanine-deoxyribonucleic acid (DNA) methyltransferase (*MGMT*) mutation.

The most common pathologies associated with GB were breast (18.8%) and prostate (18.8%) cancer [5].

Cases of multiple primary malignancies originating in different tissues are rare, but the inclusion of GB among them is an even rarer event. There are few cases of GB associated with other intracranial primary tumors with different histogenesis in the same individual. There are rare reports of metachronous or synchronous development of GBs and meningiomas, even in cases with no evidence of phakomatosis or history of radiation therapy [6]. GB can develop in the same time with a papillary thyroid cancer [7] or can appear later in the evolution of a breast cancer suggesting a hormonal pathway between those two cancers [8]. There are studies that reported the metachronous development of GB a few years later after a colon cancer in Lynch syndrome [9], Turcot syndrome [10], and Muir–Torre syndrome [11].

GB can also develop as a second malignancy in patients harboring a melanoma probably due to a common genetic predisposition [12, 13]. There are also very few articles

about a possible association between hematological malignancies and GBs [14].

Even though more and more reports of very diverse associations of two or more cancers have been published in recent years, either originated in the same organ or in different organs, as far as we know there is no report until now of an association between a penile cancer and a metachronous cerebral GB in the same patient.

In our paper, we present two patients diagnosed and treated for a cerebral GB developed after a prior penile squamous cell carcinoma (pSCC) and discuss the possible mechanism of their association.

☞ Patients, Materials and Methods

Six hundred and thirty-two patients with GB were admitted in the Department of Neurosurgery, “Prof. Dr. Nicolae Oblu” Emergency Clinical Hospital, Iași, Romania, and operated on for their tumor during a period of eight years (between 1 April 2010 and 30 April 2018). Among these patients, we searched the medical records for those who developed a cerebral GB after a prior histological proven cancer. The review showed 16/632 (2.53%) cases having a carcinoma and a metachronous GB, but only two patients, representing 0.31% of all investigated cases, were diagnosed and treated for cerebral GB after a prior penile cancer. Their demographics, clinical presentation, medical history, and treatment were reviewed and discussed.

Both cases underwent an initial surgical excision of the penile tumor. Their initial samples, from the urological surgery, were sent to the Department of Pathology, “Dr. C. I. Parhon” Clinical Hospital, Iași, and were subjected to standard histological technique [fixation in 10% formalin, embedding in paraffin, and staining the 4-μm sections with Hematoxylin–Eosin (HE)].

Both cases were admitted after few years in the Department of Neurosurgery, “Prof. Dr. Nicolae Oblu” Emergency Clinical Hospital, Iași, and written informed consents were obtained from both patients prior to the surgical excision of their GB. The excised tumors were sent to the Department of Pathology, from the same Hospital. Samples of both cerebral tumors were routinely processed [fixation in 10% formalin, embedding in paraffin,

and staining the 4-μm sections with HE]. Representative samples were also stained using an immunohistochemical (IHC) two-step staining technique with EnVision™+, Dako Corporation.

Shortly, the IHC technique consisted in the following steps. Four-μm tumor sections were dried overnight in an oven, at 56°C. Then, the sections were deparaffinized in three exchanges of xylene, rehydrated in three graded series of descending ethanol concentrations (100%, 80%, 70%). Sections were treated with Dako target retrieval solution sodium citrate pH 6, 1:10 dilution (Dako, Carpinteria, USA) before antigen retrieval was done by heating at 95°C, in a steamer, for 30 minutes. Then, the sections were cooled to room temperature for 30 minutes. The endogenous peroxidase activity was blocked with 3% hydrogen peroxide for 10 minutes. Subsequently, the primary antibody [polyclonal rabbit anti-glial fibrillary acidic protein (GFAP), clone 6F2, 1:50 dilution, Dako Glostrup, Denmark] was applied on the corresponding section, at room temperature, for 30 minutes.

After washing with Tris Buffered Saline, sections were incubated for 30 minutes at room temperature with Dako EnVision™+ Dual Link System (Dako Carpinteria, USA), followed by a 5-minute incubation with 3,3'-Diaminobenzidine tetrahydrochloride (Dako Liquid DAB + Substrate Chromogen System, 20 μL/1 mL substrate, Dako Carpinteria, USA) for color reaction, and then counterstained with Mayer's Hematoxylin (3 minutes) to visualize nuclei. Slides were then washed in distilled water, dehydrated in graded alcohols (70%, 90%, and 100%), cleared in xylene and mounted in Entellan. Finally, the slides were evaluated on a light microscope. GFAP staining was considered positive when definite expression was observed in the cytoplasm of tumor cells.

☞ Results

Patient characteristics were detailed in Tables 1 and 2.

Both patients were operated ahead in the same Department of Urology for a penile cancer and had a medium average time of 33.5 (range 21–46) months until their metachronous GB was diagnosed.

Table 1 – Main characteristics of the patients at their urological evaluation

Case No.	Age at diagnosis [years]	Symptoms	Pathology	Treatment	Tumor recurrence in evolution	Metastasis on neurosurgical evaluation
1.	63	Penian pain, ulcerating-infiltrative tumor on penis glans	Squamous cell carcinoma (pT1aN0M0), no metastases	Subtotal penectomy Chemotherapy	N0	N0
2.	61	Penian pain, fungating tumor located on penis glans	Squamous cell carcinoma (pT1aN0M0), no metastasis	Tumor excision	After four years, treated with subtotal penectomy (pT1aNxMx) Chemotherapy	Pelvic lymph node metastases

Table 2 – Main characteristics of the patients at neurosurgical evaluation

Case No.	Age at diagnosis [years]	Time between tumors diagnosis [months]	Symptoms	Neuroimaging (CT/MRI)	Pathology	Type of resection
1.	65	21	Headache, nausea, and vomiting	Right paramedian frontal tumor	WHO grade IV GB	Subtotal excision
2.	65	46	Headaches, left upper limb weakness, and Jacksonian seizures	Right fronto-parietal tumor	WHO grade IV GB	Total excision

CT: Computed tomography; MRI: Magnetic resonance imaging; WHO: World Health Organization; GB: Glioblastoma.

Both patients were 65-year-old on their admission in the Department of Neurosurgery and had their first primary penile cancer when they were 63-year-old and 61-year-old, respectively (average 62 years). They were cigarette smokers, but had no history of multiple sexual partners. Both patients were uncircumcised. The penile tumors were both located at the penis glans. First patient underwent a subtotal penectomy and bilateral inguinal lymphadenectomy followed by chemotherapy. The second patient underwent an excision of the tumor, but he presented a tumor recurrence four years later, with inguinal and pelvic lymph node metastasis. He underwent a subtotal penectomy and was referred for chemotherapy.

In both cases, the histopathological exam revealed a penile keratinized squamous cell carcinoma (moderately differentiated in the first case and well differentiated in the second), with marked inflammatory infiltration of tumor stroma (Figures 1 and 2), both being in stage T1aN0M0 (tumor invaded only the subepithelial connective tissue), with no lymph node or distant metastasis at the moment of their first diagnosis. Regarding their medical history, the first patient had type II diabetes mellitus and grade II essential hypertension with high additional risk; the second patient was diagnosed earlier with periurethral adenoma and a left kidney cyst.

At the time of their neurosurgical evaluation, the first patient presented severe headache, confusion syndrome, dizziness, and weakness on left side of the body, and the second one showed discomforting headaches associated with progressive left upper limb weakness, and Jacksonian seizures of the left part of his body. Their neurological symptoms installed over a 2-week period of time (range 1–3 weeks).

Brain computed tomography (CT) scan in the first case (Figure 3) demonstrated a right paramedian frontal neoformation, having the dimensions of 48/30/48 mm, central necrosis and peripheral edema, considered to be a metastasis from the penile cancer. For the second case, magnetic resonance image (MRI) (Figure 4) identified a solid, expansive, heterogeneous lesion of 36×39×22 mm, located in the right frontal-parietal area that seemed to develop on the external surface of the brain, with minimal

infiltration in the adjacent nervous tissue. It was diagnosed by the radiologist as an anaplastic meningioma.

Facing the medical history of a penile carcinoma in both cases, neurosurgeons took into consideration the possibility of a brain metastasis and made subtotal surgical excision of those two brain masses. The histopathological exam based on HE staining and GFAP immunostaining revealed in both cases a *WHO* grade IV GB (Figures 5 and 6). Both tumors demonstrated hypercellularity, cellular pleomorphism, with giant bizarre multinucleated tumor cells (mostly in the second case), nuclear atypia, mitotic activity, microvascular proliferation, and coagulative necrosis with pseudopalisading of tumor cells in its periphery. In both cases, there was a strong immunopositivity for GFAP. No genetic data were available for these cases.

Both patients had a good postoperative recovery and were referred to the Department of Oncology for further treatment.

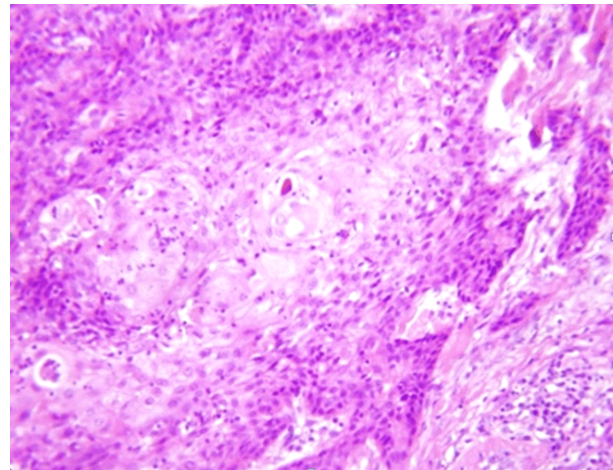


Figure 1 – Penile tumor of Case No. 1. The pathological features of the penile tumor (November 2011) showed a keratinized, moderately differentiated squamous cell carcinoma invading the subepithelial connective tissue and presenting an intense inflammatory reaction into the tumor stroma (HE staining, ×200).

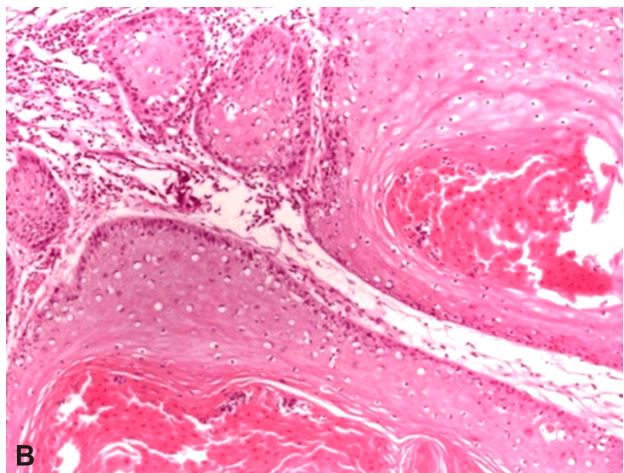
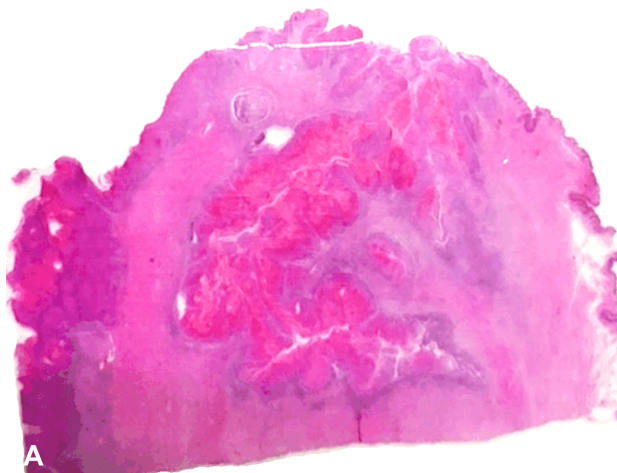


Figure 2 – Penile tumor of Case No. 2 (March 2014): (A) Gross examination of the histological section revealed a penis fragment with an ulcerovogetant tumor expressing a cauliflower aspect – the tumor was infiltrative, but did not infiltrate the urethra; (B) Histopathological exam revealed a keratinized well-differentiated squamous cell carcinoma invading the subepithelial connective tissue and including an abundant neutrophil infiltration into its stroma. HE staining: (A) ×40; (B) ×100.

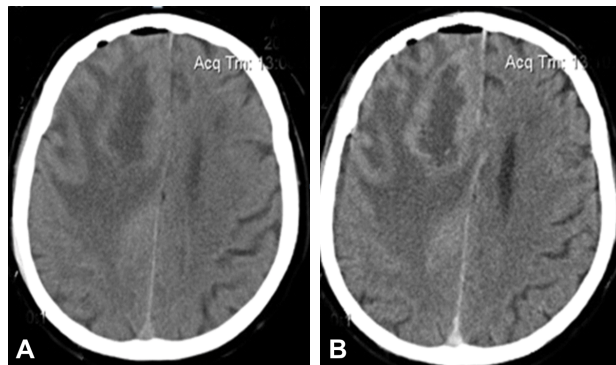


Figure 3 – Radiographic features of GB in Case No. 1. Axial brain CT scan (August 2013) demonstrated a right paramedian frontal neoformation, with thick, irregular, minimal enhancing margins, a central necrotic core, moderate peripheral edema, and midline shift: (A) Pre-contrast imaging; (B) Post-contrast sequence at 5 minutes after injection. GB: Glioblastoma; CT: Computed tomography.

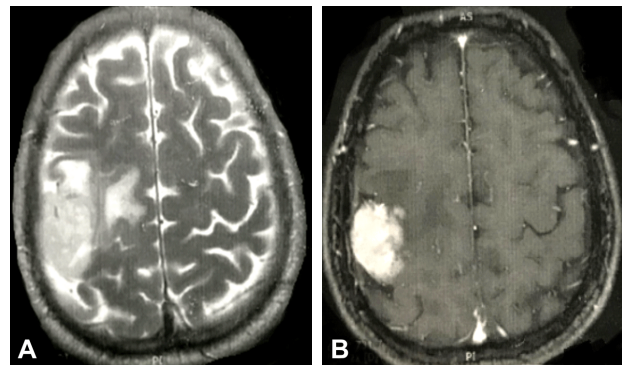


Figure 4 – Radiographic features of GB in Case No. 2. Axial brain MRI (January 2018) identified a solid, expansive, heterogeneous lesion, located in the right fronto-parietal area, that seems to develop on the external surface of the brain, with minimal infiltration in the adjacent nervous tissue: (A) T2 sequence showing apparently an extra-axial solid mass with moderate peripheral edema; (B) T1 post-contrast image showing important gadolinium enhancement of the tumor. GB: Glioblastoma; MRI: Magnetic resonance imaging.

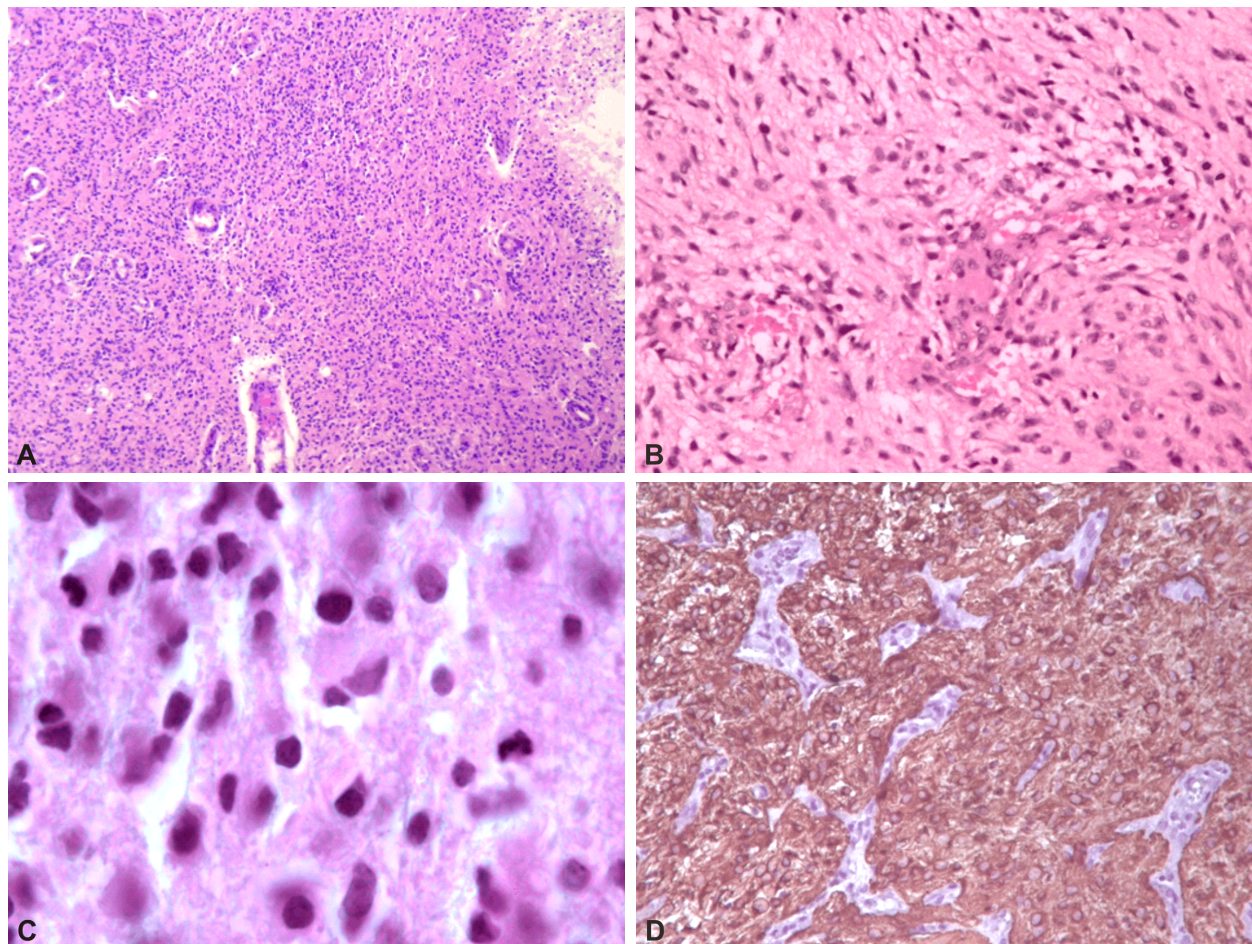


Figure 5 – The pathological features of GB in Case No. 1 (August 2013): (A) At low magnification, a highly malignant glial tumor arranged in a diffuse pattern and containing irregularly shaped glial cells with indistinct cellular borders, pleomorphic and hyperchromatic nuclei, and scant cytoplasm could be identified – an increased number of newly formed vessels and an area of extensive necrosis with pseudo-palisading tumor cells in its periphery were also revealed; (B) Tumor expressed microvascular proliferation with thickened vascular walls due to endothelial cell hyperplasia and hypertrophy; (C) Higher magnification demonstrated pleomorphic glial cells with marked atypia and atypical mitoses; (D) Strong cytoplasmic immunopositivity for GFAP. HE staining: (A and B) $\times 100$; (C) $\times 200$. Anti-GFAP antibody immunomarking: (D) $\times 200$. GB: Glioblastoma; GFAP: Glial fibrillary acidic protein; HE: Hematoxylin–Eosin.

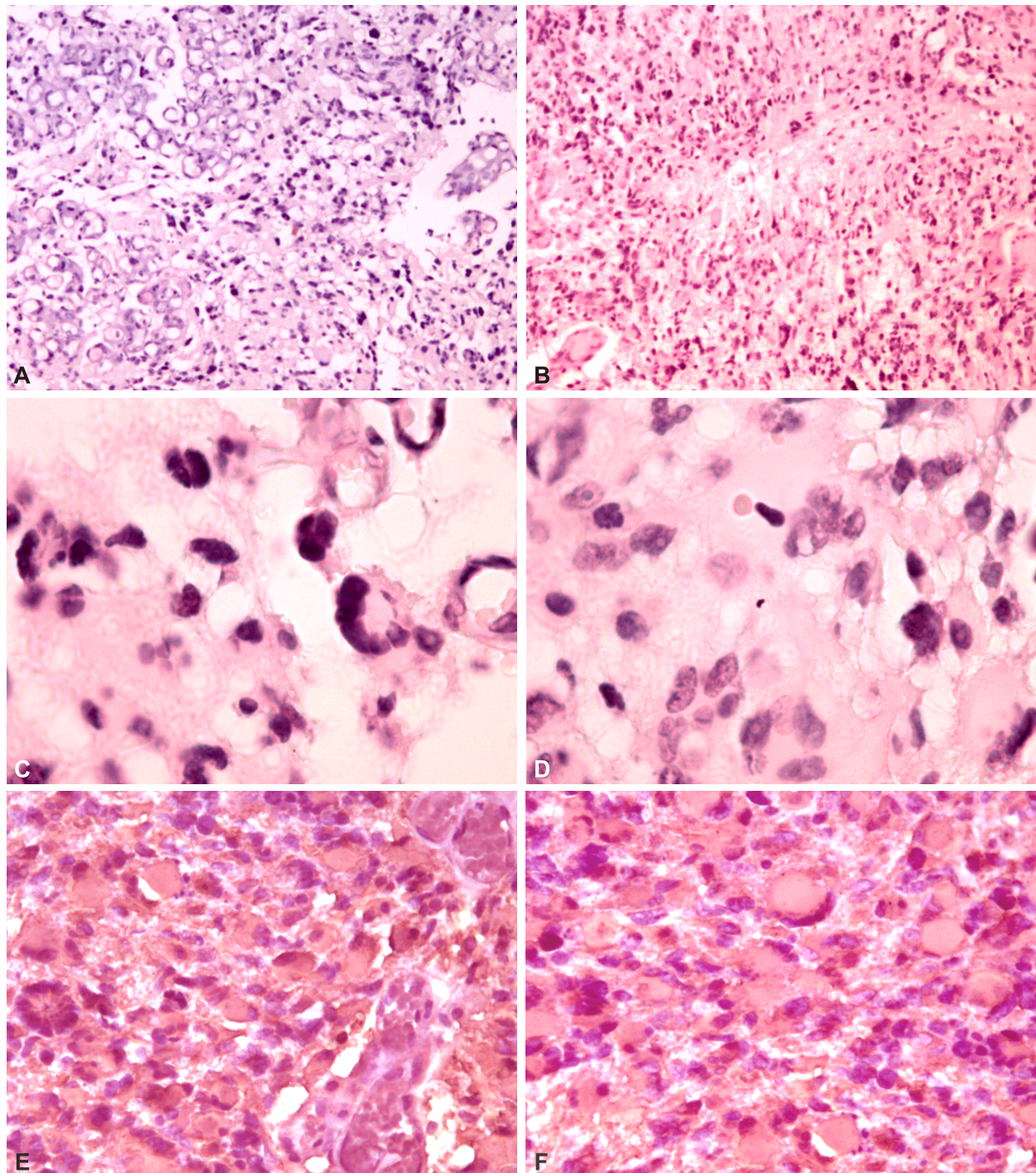


Figure 6 – The pathological features of GB in Case No. 2 (February 2018): (A) Hypercellular tumor made of an admixture of small and giant bizarre appearing tumor glial cells with abundant eosinophilic cytoplasm and two or more pleomorphic nuclei – microvascular proliferation with formation of multiple lumina resembling glomerulus; (B) Small area of coagulative necrosis bordered by tumor cells arranged in a pseudo-palisading manner; (C) Higher magnification revealed giant bizarre appearing tumor glial cells with abundant eosinophilic cytoplasm and two or more pleomorphic nuclei; (D) Higher magnification also identified atypical mitoses; (E and F) Strong immunopositivity for GFAP in the cytoplasm of tumor glial cells. HE staining: (A and B) $\times 100$; (C and D) $\times 200$. Anti-GFAP antibody immunomarking: (E and F) $\times 400$. GB: Glioblastoma; GFAP: Glial fibrillary acidic protein; HE: Hematoxylin–Eosin.

Discussions

Primary malignant brain tumors are rare and account for about 2% of all adult cancers [15]. GB represents 16% of all primary brain tumors and its five-year survival rates are less than 5%. Median age of the patients with GB is 64 years [16].

On the other hand, pSCC is a rare malignancy of the genitourinary tract in the Western world [17], with an annual incidence less than one case per 100 000 men [18], especially in the Israeli-born Jewish population, being correlated with the practice of circumcision procedure [19]. On the contrary, there are countries in Asia, Africa and South America where the incidence

is much higher. For example, in Maranhão, a poorly developed region in Brazil, penile cancer was reported in 53% of men [20].

However, for the period 1983–1987, the highest incidence of penile cancer in the world was reported in Romania (7.26 cases per 100 000 person per year) [19], but no correlation has been identified. However, the major risk factors for the development of a penile cancer are known, namely: phimosis and human papillomavirus (HPV) infection. Other risk factors are: chronic inflammatory conditions such as balanoposthitis and lichen sclerosus, treatment with psoralen and ultraviolet A (PUVA) photochemotherapy, smoking in a dose-dependent manner, sexual promiscuity, poor hygiene and low socio-economic status [20, 21].

Penile cancer occurs predominantly in elderly men (mean age at diagnosis 60 years), almost exclusively in uncircumcised men [22]. The two cases presented in this article had all these characteristics, both of them being diagnosed with penile cancer at the beginning of their seventh decade of life.

Inguinal lymph node metastases are the most important prognostic factors for survival in patients with pSCCs [22]. In our cases, inguinal and pelvic adenopathies have been identified later in the evolution of the pSCC, but there were no metastases in any other organ, even though the patients have been extensively searched by thoracic and abdominal and pelvic MRI. The disease with the most important prognosis has become their GB, which is the most aggressive human cancer.

pSCC is a rare disease and a second development of another primary cancer in the same patient is even rarer, but such cases were published within multiple primary urogenital malignancies. There are few reports of synchronous double genitourinary malignancies including a penile melanoma associated with a renal oncocytoma [23], penile and signet ring cell bladder carcinoma [24], primary pSCC and transitional cell carcinoma of the urinary bladder [25], and well-differentiated SCC of the penis and poorly differentiated adenocarcinoma of the prostate [26]. There is one single report of pSCC associated with other two different located primary malignancies (bladder cancer and SCC of larynx) in one patient [27]. There are also rare reports of multiple primary malignancies including penile carcinoma along with cancers developed in organs other than the urogenital system. Joseph *et al.* have presented the case of a 49-year-old man, a tobacco chewer for 25 years, who developed synchronous SCC of the oral cavity and pSCC with bilateral inguinal metastases [28].

Also, there are only two reports about metachronous development of a pulmonary cancer after a pSCC. It is interesting that these tumors were diagnosed in younger patients than those who present only a penile cancer in their life [29, 30].

pSCC, with all its variants (verrucous, papillary, warty, pseudohyperplastic and carcinoma cuniculatum) represents more than 95% of cases with a penile cancer and has a good prognosis. Even though these histological variants are locally destructive, they rarely metastasize. There are also some other histological variants (basaloid, sarcomatoid, adenosquamous and poorly differentiated

types) with a poor prognosis as they metastasize early and have a high mortality [31]. The remaining 5% represents basocellular tumors, melanoma, Kaposi sarcoma or penile metastasis originating in the kidney and prostate [32].

In our cases, differential diagnoses of a secondary (cerebral metastasis originated in the pSCC) *versus* a malignant primary tumor (malignant glioma in the first case and anaplastic meningioma in the second case) were taken into consideration in both patients.

Distant metastasis of penile cancer is a rare event, this neoplasia being a loco-regional disease. Systemic metastases may also occur in advanced cases, most often in the lungs, liver and bones. Brain metastases of an early-stage pSCC are extremely rare, until to date only seven cases have been published [32–37] because penile cancer is a loco-regional disease. Our first patient was suspected to have a brain metastasis originating in his prior pSCC. Usually, an intracranial lesion that develops after another primary tumor is suspected to be a cerebral metastasis. However, in cases where cancer rarely metastasizes in the brain, such as penile cancer, the doctor should be cautious when facing an intracerebral tumor, especially if this is a solitary one. In such cases, surgery and pathological diagnosis are essential.

On the other hand, GB can mimic a wide variety of pathologies, including metastatic disease, lymphoma, anaplastic meningioma, arteriovenous malformation, and hemorrhagic stroke. On CT and MRI, cerebral metastases are well-defined tumors with central necrosis and peripheral edema, features which could be also found in GB, especially in giant cells subtype. In addition, brain metastases can originate in any tumor developed in any organ, from lung cancer to conjunctival melanoma [38–41].

Our second patient exhibited MRI features, which were consistent with anaplastic meningioma as it had dural tail and dural contact, but pathological exam could make the difference [42] and in our cases, the microscopic exam revealed GBs. However, radiological investigation could not always lead to the right diagnosis. Neurosurgery is the only one who could bring a large amount of information [43].

In both our cases, the definitive diagnosis of the intracranial tumor was established by the pathological examination. The morphological features identified in the standard HE staining (*i.e.*, atypical squamous cells with limited nuclear atypia and pleomorphism, prominent intercellular bridges, and keratin pearls *versus* polymorphism of tumoral glial cells arranged in a fibrillary background, microvascular proliferation, and necrosis with tumor cells pseudopalisading around) differentiates a SCC from a GB. The use of IHC stainings only confirm the pathological diagnosis because pSCC shows positive staining for cytokeratin 5/6 and p63 [3], but GBs express strong immunopositivity for GFAP, which is a major intermediate filament protein expressed in tumors with astrocytic origin [44].

Both our patients developed a prior pSCC without any lymph node and distant metastasis at their first diagnosis and this situation reinforces the idea that this type of cancer has a good prognosis and that the patient can develop a second cancer during his post-penectomy life probably due to a genetic predisposition. However,

causal mechanisms of multiple primary cancers include genes, but also environmental factors, treatment effects, the increase of the life expectation in cancer patients, but mostly due to combinations of all these mechanisms [45].

In our research, although we have identified only two cases, several more etiopathogenic hypotheses of metachronous development of a GB after a prior pSCC could be advanced, namely: genetic predisposition, post-therapeutic effects, life style factors (smoke effects), sporadic association, or the common embryonal origin of the nervous and skin tissues.

We made an extensive search of English medical literature, but we did not identified any association of penile carcinoma and intracerebral GB in the same patient, be it synchronous or metachronous. Searching for a possible common genetic pathway between these two malignant entities, we found that there are reports that demonstrated the presence of frequent mutations in the cadherin-related tumor suppressor homolog (*FAT1*) gene, both in pSCC and in GB samples. Accordingly, loss of *FAT1* function could be the event that triggers the oncogenesis of both cancers in the same patient [46, 47].

In GB tumorigenesis, multiple side effects of chemotherapy administrated for penile cancer may also be considered [48], because both our patients received chemotherapy after urological intervention. Chemotherapy treatment destroyed the tumor cells for which they are used, but it also produced some changes in the normal cells structure. Consequently, new cell types could appear, some of which having an oncogenic potential that lead to secondary cancers. However, GB associated with pSCC may also be a sporadic event.

✉ Conclusions

This is the first clinical report of a new association between pSCC and subsequent development of GB in a series of two patients. Because the etiopathogenic basis of this phenomenon remains unclear, further studies are needed to determine specific molecular pathways that may be associated with this clinical association.

Conflict of interests

The authors declare that they have no conflict of interests.

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