CASE REPORT

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Unusual triple combination of prostate, lung and skin cancer

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Abstract

Multiple malignancies are an increasing combination in the recent years in cancer patients, due to prolonged survival rate and to the advances in diagnostic techniques and therapeutic management. We present the case of a patient diagnosed with prostate cancer and metachronous in one year with basal cell carcinoma of the skin and small lung cell carcinoma with lymph nodes and pararectal metastasis. To our best knowledge, this is the only case presented in the medical literature with these three different types of primary malignancy. In conclusion, multiple malignancies in the same patients are a real challenge to the physician, because an early diagnosis and specific treatment modalities are essential for successful patient management and increasing life expectancy.

Keywords: prostate cancer, lung cancer, pararectal metastasis, basal cell skin carcinoma.

Introduction

The phenomenon of multiple primary malignant tumors (MPMTs) in the same individual was described for the first time by Billroth and the first described criteria for establishing a definitive diagnosis were published by Warren & Gates [1, 2]. Since then, multiple primary malignant neoplasms have been reported in the medical literature. There are two categories of MPMTs, metachronous, when tumors follow one another and synchronous, when tumors arise simultaneously or within six months from the primary tumor. The terms synchronous and metachronous are a little confusing and they only refer to the time that neoplasms are discovered with no connection with the tumor genesis.

The incidence of prostate cancer is high in the elderly age group [3]. However, the occurrence of prostate, lung and skin cancer in the same patient represents a difficult treatment challenge because different patterns of MPMTs should be considered and the need for a multidisciplinary and patient-oriented approach [4, 5]. Also, the presence of gastrointestinal metastasis from lung cancer is very rare.

Here, we report the case of metachronous tumors, respectively prostate cancer, small cell lung carcinoma with pararectal metastasis and cutaneous basal cell carcinoma discovered within one year. This is, to the best of our knowledge, the first case reported with this association of primary tumors in the literature.

Aim

Our reported case emphases the pitfalls in diagnosis multiple malignancies especially when we are dealing with three pathological different types. In addition, the combination of prostate, skin and lung cancer presenting in the same patient was not reported yet in the medical literature, moreover the pararectal metastasis from small lung cell carcinoma is a very rare spread of a lung cancer.

Case presentation

A 75-year-old patient with viral C cirrhosis (Child–Pugh A class) and chronic obstructive pulmonary disease (COPD) presented in the Department of Gastroenterology for physical weakness, pain in the right hypochondrium and hidroses. The clinical exam revealed facial erythrosis and mild heptosplenomegaly. Blood tests showed increased prostate-specific antigen (PSA) levels, trombocytopenia and slightly increase in alpha-fetoprotein (AFP) levels. The prostate appeared enlarged at the digital rectal exam, with a right mobile tumor. The patient had a prostate biopsy, which revealed a prostate carcinoma. For disease extent assessment, the patient was referred to the Department of Radiology and Imaging, where he performed a lung X-ray and a total body computed tomography (CT). The lung X-ray was normal. The CT revealed multiple small subpleural nodules in both lungs, with maximum diameter of 5 mm and mediastinal adenopathy of maximum 1 cm in size, which were considered in sequelar context. The hormonal treatment was begun.

After six months from the prostate cancer diagnosis, the patient underwent surgical excision for right temporal cutaneous basal cell carcinoma.

After another six moths, the patient was hospitalized again for evaluation and also for wet cough, dysuria and nicturia. The blood tests were normal, with the exception of increase values of PSA and AFP. The urological local exam revealed phimosis and secondary hypogonadism after hormonotherapy. The endo-rectal ultrasonography displayed an inhomogeneous prostate parenchyma, with calcification and multiple hypoechoic nodules and also a retrovesical left hypoechoic mass, in contact with the rectum, without invasion of prostate, seminal vesicle or urinary bladder. The CT exam pointed the same aspect and dimensions of pulmonary lesions (identified one year before) and also to the presence of a 3.5 cm antero-lateral left pararectal mass, extralumenal, with rectal

parietal bulging and infiltration of mesorectal peritoneal fat. Also, multiple large size and with necrosis retroperitoneal lymph nodes was noted. The patient undergone total colonoscopy and endoscopic ultrasound (EUS), which revealed the pararectal mass at 5 cm of external anal aperture, hypoechoic, inhomogeneous, in contact but with no invasion of rectal layers (Figure 1A). Also, multiple pararectal lymph nodes were displayed (Figure 1B). The final clinical diagnosis was prostate tumor with multiple lymph nodes and pararectal metastasis. The patient undergone transrectal needle biopsies of the prostate (both lobes) and of the pararectal mass.

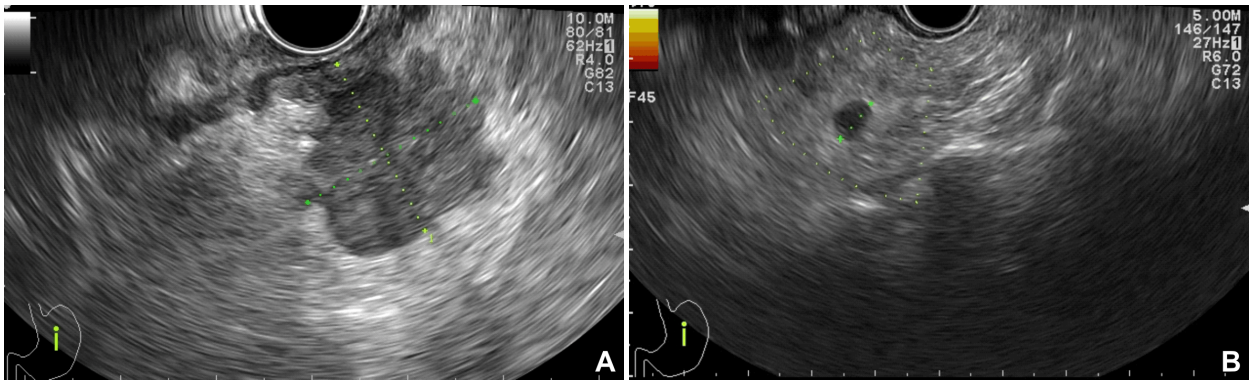

Figure 1 – ***Endoscopic ultrasound. Pararectal mass of 2.4/3/3 cm, hypoechoic, inhomogeneous, in contact but with no invasion of rectal layers (A) and pararectal lymph nodes (B).***

All tissue fragments were immediately immersed in 10% buffered formalin and transported to the Department of Pathology. After proper fixation (20 hours in 10% buffered formalin, at room temperature), they underwent standard processing for paraffin embedding (using a Thermo Scientific STP 420ES tissue processor). Thus, tissue samples were washed with water, dehydrated in ethanol (20 minutes in 70°, one hour in 90°, one hour in 96°, then one hour for three baths of absolute ethanol), clarified with xylene (three baths) and then embedded in paraffin (three baths, at 56°C). Processed samples were embedded in paraffin (using paraffin-embedding station Leica EG1150H) and sectioned in 2.5 µm sections (with Leica RM2235 manual rotary microtome). For each paraffin block (one from the pararectal mass, one from the right lobe and one for the left lobe of prostate) were obtained two slides (at different levels) for Hematoxylin–Eosin (HE) routine staining and 10 additional slides for immunohistochemistry.

After examination of HE slides, several immunohistochemical assays (Table 1) were performed: thyroid transcription factor 1 (TTF1), cytokeratin 20 (CK 20), synaptophysin, chromogranin, PSA, alpha-methylacyl-CoA racemase (AMACR) and Ki67 (MIB-1) for the pararectal mass biopsy, and TTF1, PSA, synaptophysin for the left lobe of the prostate. No immunohistochemical assays were needed for the sample of left lobe of the prostate. Also, a slide from the basal cell carcinoma, previously resected, was solicited and examined (Figure 2). Immunohistochemistry was manually performed.

Table 1 – ***Antibodies used for immunohistochemistry***

Antigen	Clone	Producer	Dilution	Other reagents used
TTF1	SPT24	Leica Novocastra	1:300	Novocastra Epitope Retrieval Solution pH 6 Novolink™ Polymer Detection Systems
CK 20	Ks20.8	Leica Novocastra	1:100	Novocastra Epitope Retrieval Solution pH 6 Novolink™ Polymer Detection Systems
Synaptophysin	27G12	Leica Novocastra	1:300	Novocastra Epitope Retrieval Solution pH 6 Novolink™ Polymer Detection Systems
Chromogranin	5H7	Leica Novocastra	1:200	Novocastra Epitope Retrieval Solution pH 6 Novolink™ Polymer Detection Systems
PSA	PSA 28/A4	Leica Novocastra	Ready to use	Novocastra Epitope Retrieval Solution pH 6 Novolink™ Polymer Detection Systems
AMACR	EPMU1	Leica Novocastra	1:200	Tris-EDTA-based buffer pH 9 Novocastra Epitope Retrieval Solution pH 6 Novolink™ Polymer Detection Systems
Ki67	MM1	Leica Novocastra	1:200	Novocastra Epitope Retrieval Solution pH 6 Novolink™ Polymer Detection Systems

EDTA: Ethylenediaminetetraacetic acid.

Pararectal mass biopsy (Figures 2–7) included four fragments from a malignant proliferation composed out of slightly discohesive sheets, trabeculae and clusters of small sized (~4× neutrophils) oval and fusiform-shaped cells, with minimal, eosinophilic, granular cytoplasm, hyperchromatic and hypertrophic nuclei with indistinct nucleoli. Some nuclear molding was focally identified. Mitotic rate was high. Tumor cells fare forming perivascular rosettes and are palisading in the periphery of a small nervous branch. Although necrosis was not identified, a prominent Azzopardi effect was seen. Tumoral stroma was scanty, delicate, with small capillaries and no inflammatory infiltrate. Tumor cells had a characteristic immunophenotype for a small cell lung carcinoma: TTF1 strongly positive, chromogranin and synaptophysin positive, focally with paranuclear dot pattern, CK 20, PSA and AMACR negative. Ki67 index was very high (approximately 90%).

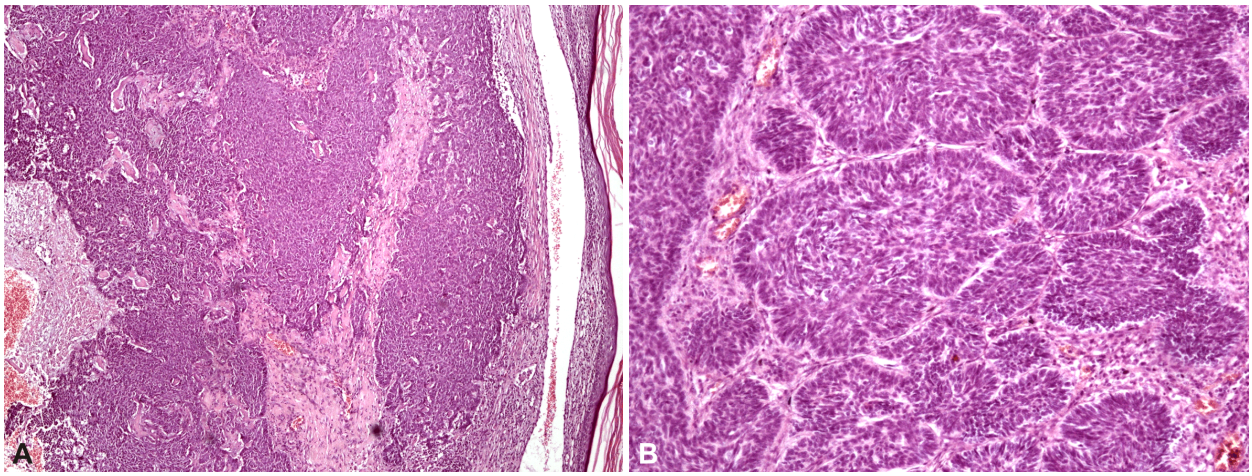

Figure 2 – ***(A and B) Cutaneous basal cell carcinoma. Examination of cutaneous tumor previously resected revealed a nodular proliferation of basaloid atypical cells with scant basophilic cytoplasm and elongated, hyperchromatic, irregular nuclei with low mitotic activity. Characteristic palisading of tumoral nuclei in the periphery of tumor nodules. HE staining: ×100 (A); ×200 (B).***

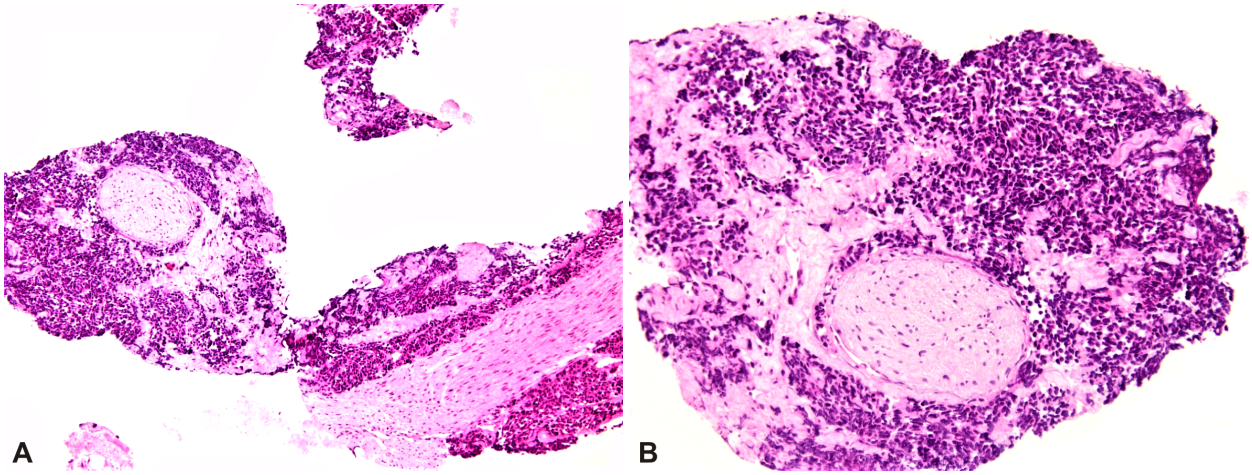

Figure 3 – ***Pararectal tumor. Dense proliferation of small, oval-shaped cells with hyperchromatic nuclei. Perineural invasion. HE staining: ×100 (A); ×200 (B).***

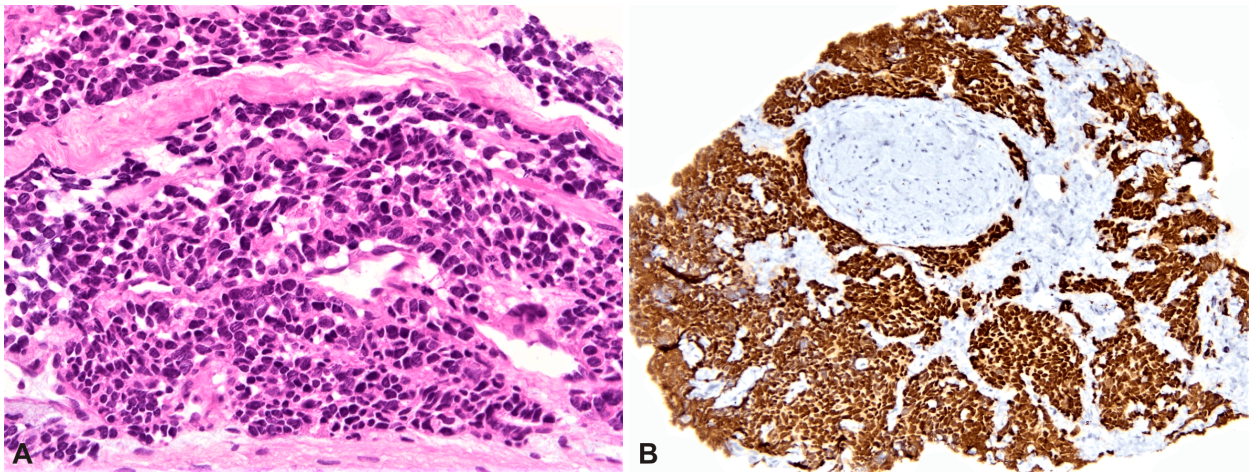

Figure 4 – ***Pararectal tumor. Tumor cells have elongated shape ("oat-cells"), scant cytoplasm and large, atypical nuclei with frequent mitotic figures: (A) Note a perivascular rosette (HE staining, ×400). (B) TTF1 immunostaining (×200) with intense nuclear reaction in all cells (you can see the same nervous branch with perineural invasion as in figures above).***

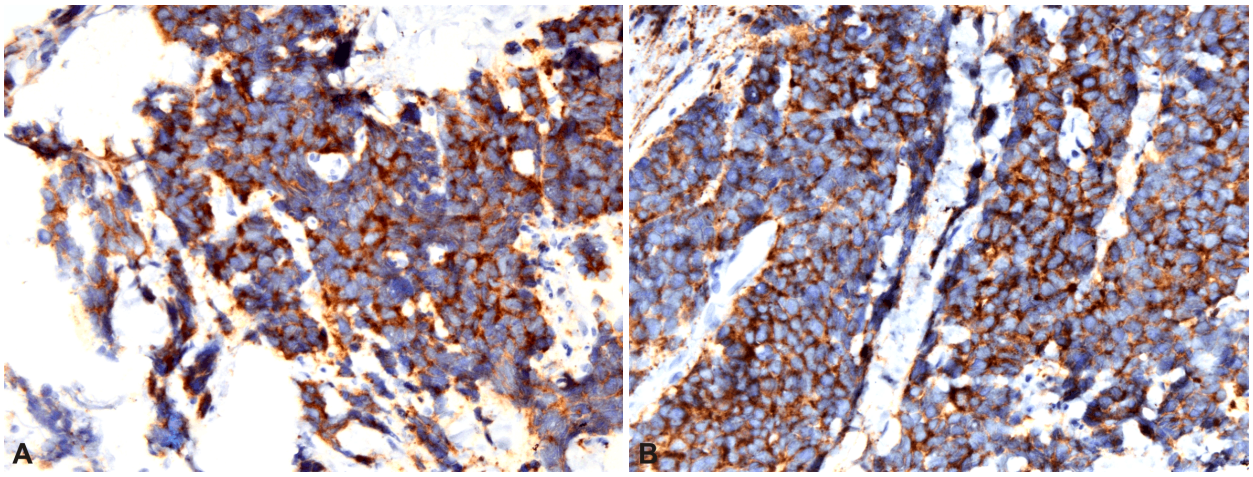

Figure 5 – ***Pararectal tumor. Tumor cells are positive for synaptophysin (A, ×400) and chromogranin (B, ×400). Cytoplasmic positivity reveals, focally, some paranuclear dots (highly suggestive for a neuroendocrine proliferation).***

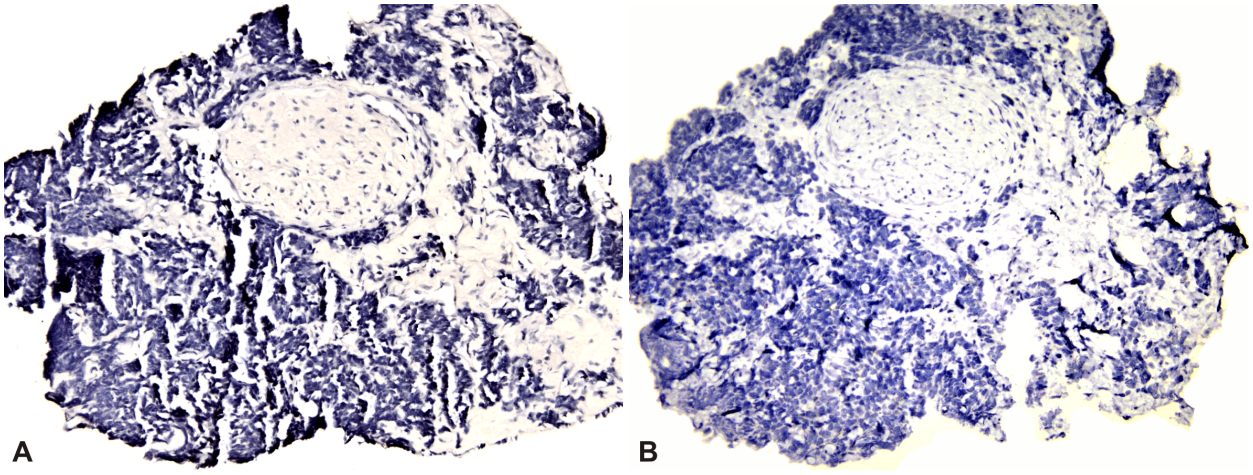

Figure 6 – ***Pararectal tumor. PSA (A, ×400) and AMACR (B, ×400) markers negative in tumor cells. Both stainings were made with external positive control.***

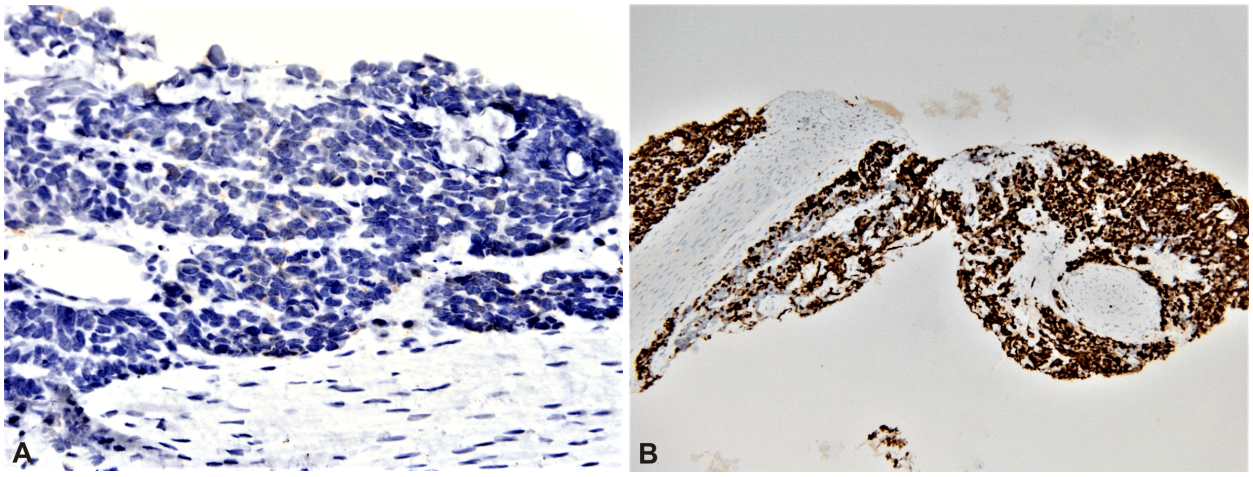

Figure 7 – ***Pararectal tumor. No reaction for CK 20 (A, ×400), excluding a primary rectal small cell carcinoma and a Merkel cell carcinoma). Ki67 (B, ×100) is positive in almost all tumor nuclei, indicating a huge (over 90% proliferation rate).***

On the other hand, the biopsy from the right lobe of the prostate (Figures 8–10) showed a malignant proliferation with disposition in cords, small crowded glands with inconspicuous lumens and isolate cells. Morphology of tumor cells was significantly different from the pararectal lesion: small, round cells with clear or pale eosinophilic cytoplasm, round small hyperchromatic nuclei with minimal polymorphism and low mitotic index. No basal cell layer was identified. Tumoral stroma was more abundant with scattered lymphocytes and plasma cells. Immunohistochemistry test revealed that malignant cells were positive for PSA and negative for synaptophysin.

TTF1 had a peculiar reaction: it was weakly positive in some tumoral cells, aspect that is rarely encountered in high-grade prostate adenocarcinomas (1.2%).

The biopsy from the left lobe of the prostate (Figure 11) showed no histological lesions. Examination of skin tumor revealed a classical nodular basal cell carcinoma without any problems of differential diagnosis.

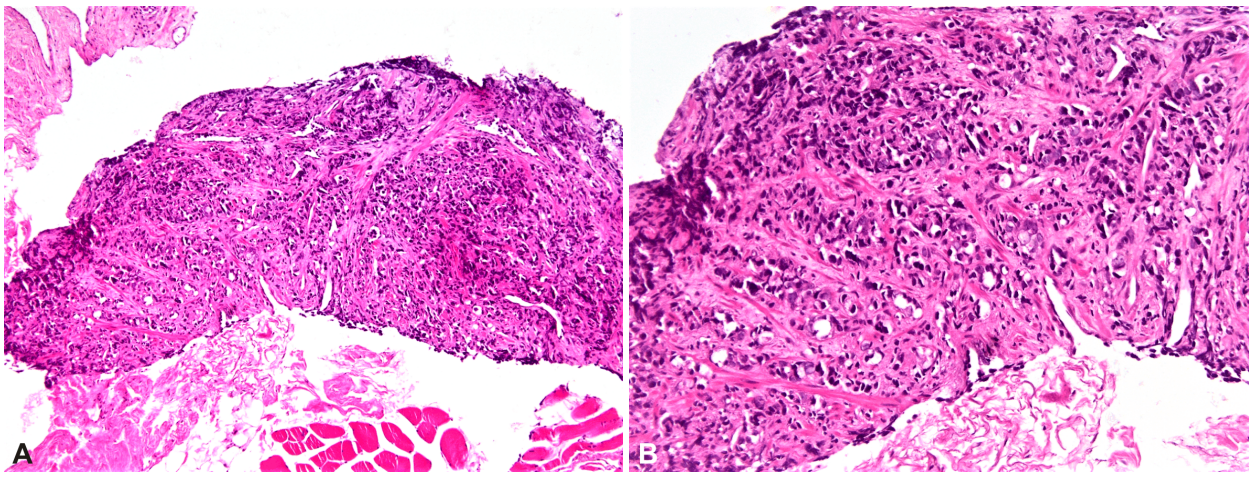

Figure 8 – *(A and B) Prostate – right lobe. Extensive lesions of high-grade prostate adenocarcinoma [Gleason 10 (5+5)]. The malignant proliferation is less dense, with disposition in trabeculae, small tubules and isolate cells. Morphology of tumoral cells is also different: they have more abundant cytoplasm, pale eosinophilic and smaller nuclei. HE staining: ×100 (A); ×200 (B).*

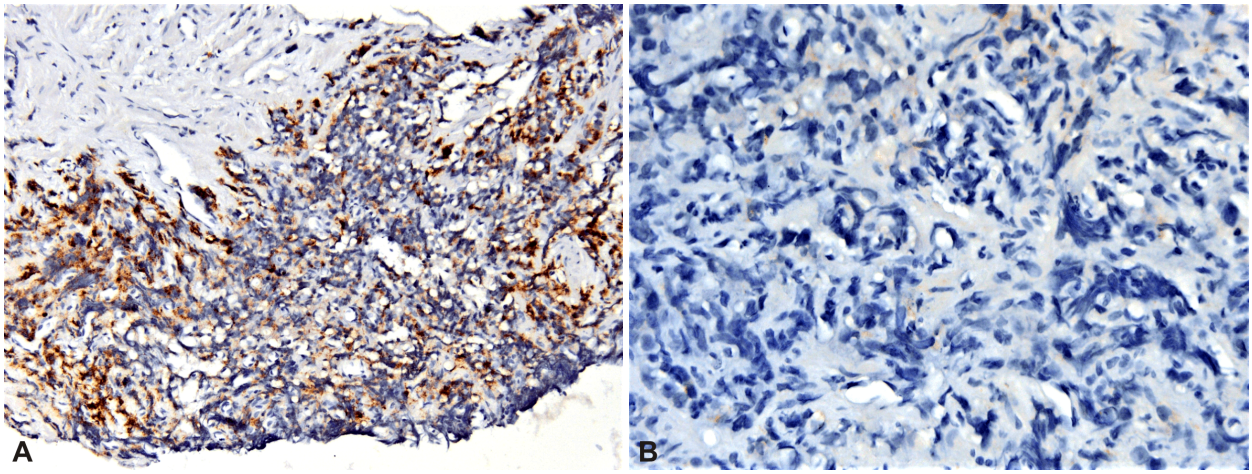

Figure 9 – *Prostate – right lobe. Tumor cells are positive for PSA (A, ×200) and negative for synatophysin (B, ×400). PSA is only focally positive, which is not surprising for a high-grade prostate carcinoma. Synaptophysin stain was made with external positive control.*

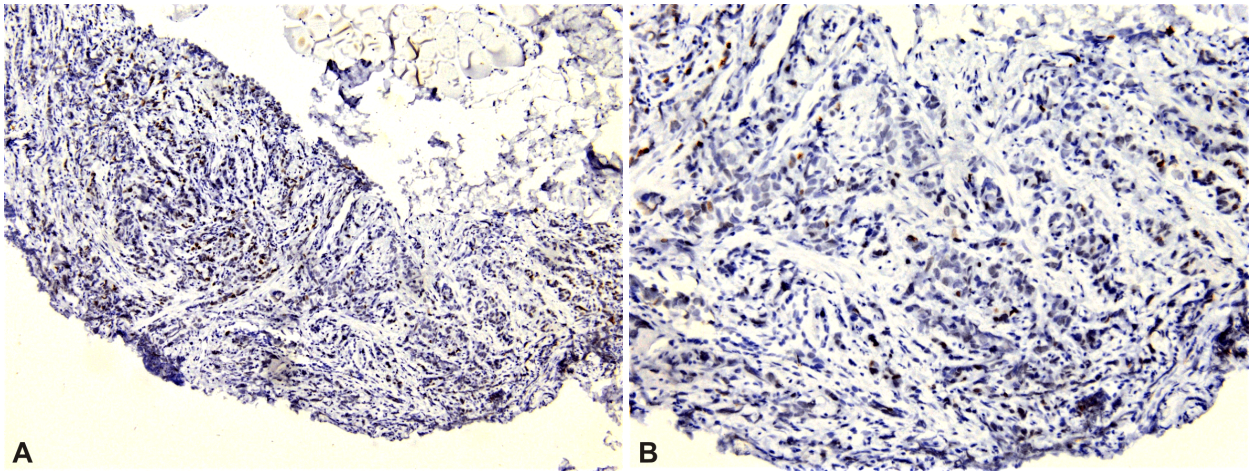

Figure 10 – *(A and B) Prostate – right lobe. TTF1 is weakly positive in some of the tumor cells. Comparing this aspect with the one shown in Figure 4B, it is obvious the difference between the pararectal and the prostate tumor. Poorly differentiated prostatic adenocarcinomas can exhibit some positivity (weak and focal) for TTF1: ×100 (A); ×200 (B).*

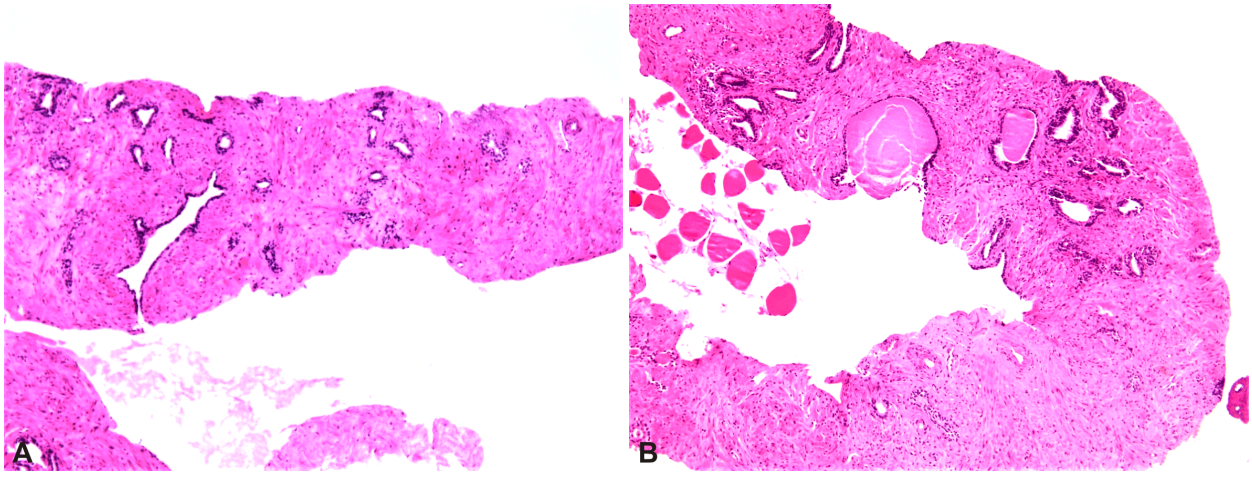

Figure 11 – ***Prostate – left lobe: (A) Normal appearance of prostatic tissue with no tumoral lesions; (B) Note the corpora amylacea. HE staining, ×100.***

Correlation of imagistic and clinical data with histological and immunohistochemical aspects leads to the final diagnosis of synchronous skin (basal cell carcinoma), lung (small cell carcinoma with pararectal metastasis) and prostate (high grade, Gleason 10 adenocarcinoma) cancers.

Since basal cell carcinoma is frequent in elder patients and usually does not raise any problems of differential diagnosis, the most difficult aspect of the case was the differential diagnosis of the two neighbor tumors: the metastasis from pararectal tissues and the prostate adenocarcinoma. Morphological features of these tumors proved significant differences and were suggestive for their histogenesis. We already know that small cell lung carcinoma is the "great pretender" of oncopathology since it can have large size metastasis with uncommon localization (mesentery, adrenal glands, soft tissues, kidney, and retroperitoneal lymph nodes) in the presence of small primitive tumors with bland imagistic features and with very slow local evolution. Diagnosis of a metastatic lesion with morphological and immunohistochemical features of lung small cell carcinoma can lead to a certain diagnosis of undetermined lung nodules. Presence of concomitant prostate lesions is complicated diagnosis, since they can be also metastasis or, as in our case, a primitive prostate malignancy.

In our case, differential diagnosis was enhanced by the fact that from histological and cytological point of view, the morphology of prostate lesion had significant differences that cannot be explained by the polymorphism of malignant proliferations. Immunohistochemical tests were a very important aid that confirmed the morphological hypothesis and made a certain diagnosis for both tumors.

On the other hand, other organs in the area (prostate, bladder, and rectum) can be the origin of small cell carcinomas with neuroendocrine features. These tumors are, usually, difficult to differentiate and their diagnosis needs thorough histological and immunohistochemical evaluation as well as a good collaboration between clinician, imagist and pathologist. Although TTF1 is not specific for lung small carcinomas and can be expressed in all extrapulmonary neuroendocrine small cell carcinomas, an intense, diffuse reaction, involving practically all tumoral cells is a good indicator of lung origin.

In our case, the pararectal tumor expressed intensely TTF1 in all cells, while the prostate lesion had a weak and focal expression for TTF1. Negativity of pararectal lesion for CK 20, as well as clinical and imagistic indication of the fact the tumor was not of rectal origin, excluded the possibility of a neuroendocrine small cell rectal carcinoma. Prostatic origin was ruled out since the patient had another prostate tumor without any neuroendocrine features and imagistic evaluation did not revealed a continuity between prostate and pararectal lesions. Also, CT revealed lung tumors and mediastinal adenopathy that were compatible with a lung small cell carcinoma (without being pathognomonic). All these multidisciplinary data were used for the final diagnosis.

Discussion

Prostate cancer is a malignancy characterized by a long natural history comparing with other solid tumors, with a wide spectrum of biological behavior, varying from indolent to aggressive [6]. Within 10 years after primary treatment, 15–40% of patients can detect a rise in the serum PSA level [7]. A pretreatment imaging staging workup, including both radionuclide bone scans and CT scans of the thorax, abdomen and pelvis plays an important role in evaluating local recurrence and distant spread of disease. The sensitivity of both investigations is low for detection metastasis in lymph nodes or bones, but whole-body CT studies can incidentally reveal clinically silent findings such as tumors thus changing patient management [8, 9]. Screening with serum PSA has an important role in diagnosing localized disease. The improvements in clinical therapies for patients with prostate cancer had increased the current 10-year and 15-year survival rate at 98% and 91%, respectively [10]. This long life expectancy of these patients exposes them to the possibility of developing second primary malignancies. In recent studies, the incidence of developing second malignancies among the cancer survivors is around 16%. The risk factors for second malignancies include previous treatment, aging, lifestyle and environmental factors, common carcinogenic exposure, such as tobacco and alcohol, as long as genetic susceptibility. It is of great importance to identify patients who are at increased risk of developing subsequent malignancies for an optimal treatment and an enhanced screening. The patients with prostate cancer have a higher

risk of developing bladder, kidney, soft tissue, and endocrine cancers, but lower risk of developing leukemia and oropharynx cancers, digestive and lung cancers [11–13].

Small cell lung cancer (SCLC) is a subtype of lung cancer with unique presentation, imaging appearances, treatment and prognosis. This type of lung cancer is rapidly growing, being highly malignant, and with widely metastasis [14]. The most frequent sites of lung cancer distant metastasis are the liver, adrenal glands, bones and brain. Gastrointestinal metastases are uncommon and rectal metastases are extremely rare [15]. All cellular types of lung tumor may develop gastrointestinal metastases, but with rare frequency and in advanced stages [16]. Adenocarcinoma of the lung is the most common type, followed by other types such as adenosquamous, neuroendocrine carcinoma and small cell carcinoma [17]. In a recent study, the incidence of gastrointestinal metastasis from primary lung cancer was 1.77% [18]. CT plays also an important role in identifying the exact cause of abdominal symptoms in patients with lung cancer, the metastatic lesions being seen as wall thickening, an intraluminal polypoid mass or an exophytic mass [19].

Basal cell carcinoma (BCC) is a malignant neoplasm derived from non-keratinizing cells of the epidermis, being the most frequent type of skin cancer in humans. It is a locally invasive skin cancer, with slow spread and rare metastasis [20]. This type of skin cancer represents approximately 75% of non-melanoma skin cancers and is frequent observed in older patients, especially in those intensively exposed to the sun [21]. Thus, the typical site is uncovered skin directly exposed to radiations with high frequency localization in head and neck areas. There is also high prevalence in the elderly and is more common in males [22].

MPMTs in the same patients were first described by Billroth [1]. In the recent years, several studies reported cases of double and even triple synchronous primary malignant neoplasms. MPMTs are classified in two categories, metachronous when tumors follow one another and synchronous, when tumors arise simultaneously or within six months from the primary tumor, with higher incidence of metachronous cancers [23, 24].

Due to the advances in diagnostic techniques and therapeutic options and also prolonged survival of cancer patients, we are dealing with an increase incidence in patients with multiple malignancies with a rate between 0.73–11.7% [25]. The first described criteria for establishing a definitive diagnosis of multiple neoplasms were published by Warren & Gates, in 1932. These criteria include a definite and different picture of each malignancy and the exclusion of one tumor being a metastasis of the other [2]. The above-mentioned criteria are fulfilled by the present case. Our study reported a patient who developed three distinct malignancies, respectively prostate cancer, small lung cancer and basocellular cancer, which occurred within a period of one year without any predisposing factor. In our case, the patient was hormonal treated for prostate cancer and the whole-body evaluation revealed small lung nodules in both lungs, multiple lymph nodes and a pararectal mass suspected for prostate metastasis. The patient was also treated in the course of hormonotherapy for temporal basal cell skin carcinoma. The pathology diagnosis for prostate cancer was low-grade prostate adenocarcinoma, Gleason score 10. The pararectal mass was also surgical removed and histopathology diagnosis was metastasis from small lung cell carcinoma.

The medical literature reveals the connection between the first neoplasm, which is initiated by factors and agents that may initiate a second neoplasm as well. In this study from 2004, two etiological hypotheses are assessed for MPMT [26]. The first theory concerns the inheritance of predisposing genomic defects and the second theory the field of carcinogenesis, as all cells have been exposed to the same dose of carcinogens for the same time. This second concept can justify the association between aging and multiple tumors, thus the longer a person survives, the greater is the risk of developing tumors, as in our case [23].

Thus, the bias of some patients to develop multiple tumors can be explained either by an individual predisposition or by the action of carcinogenic factors [27]. The carcinogenic factors can act on different organs at different times and this can be an explanation for our case regarding the association between low growing prostate cancer and basal cell skin carcinoma and aggressive tumors, such as small cell lung carcinoma [28, 29]. Therefore, multiple and predisposing factor are responsible for the development of metachronous tumors [30–32].

The recent studies refer as case-base studies a high-incidence of multiple tumors, even if there are several reporting limitations in the current literature. Our case particularities consist in the triple association of prostate, skin and lung cancer in a period of one year, and the presence of pararectal lung metastasis, which is also a rare metastasis from lung cancer. To our knowledge there are not other cases with these primary tumors reported in the medical literature, highlighting the fact that multiple malignancies should be considered when a new tumor appears in a previous cancerous patient. In addition, even with the new imaging techniques, the final diagnosis is possible by pathology and immunohistochemistry [33–35].

Conclusions

For successful patient management and increasing life expectancy, the physicians should be aware about different presentation of multiple malignant tumors and also keep in mind that the appearance of another tumor or metastasis in a patient suffering from cancer could be the expression of a novel malignancy. In these cases, a multidisciplinary approach with integration of clinical, paraclinical, imagistic and histological data can be the key for the correct diagnosis. Pathologists and imagists should receive complete clinical and anamnestic data in order to identify possible correlations between examined lesions and other previous or undiagnosed pathologies. On the other hand, pathologists should include in their report comments and suspicions of diagnosis when they have suggestive microscopic data, information that can be cardinal for the final diagnosis.

Conflict of interests

The authors declare that they have no conflict of interests.

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