A novel combination of triple metachronous malignancies of the kidney, oropharynx and prostate: A case report

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Abstract. Synchronous or metachronous malignancies are a rare event, with an incidence rate that increases with age. The present study reports the case of a 70-year-old Caucasian male who was referred to the outpatient office of the Urology Unit, Sapienza University of Rome (Latina, Italy) due to lower urinary tract symptoms. An abdominal ultrasound investigation was performed that demonstrated the presence of a right renal mass. The patient underwent right radical nephrectomy, which resulted in the definitive diagnosis of clear cell type renal cell carcinoma. The patient was eventually diagnosed with triple primary metachronous cancer consisting of renal clear cell carcinoma, prostate adenocarcinoma and squamous cell carcinoma of the oropharynx (palatine tonsil). To the best of our knowledge, this combination of primary neoplasms has not previously been documented.

Introduction

Multiple primary malignant tumors (MPMTs) are rarely observed in clinical practice, however, certain fundamental factors for the potential etiology have been described in the literature, including the environment and behavior (tobacco, occupation, pollution and ultraviolet light), genetic predisposition (Li-Fraumeni or Beckwith-Wiedemann syndromes), previous medical treatment (radiotherapy or chemotherapy) and complex interaction between all these factors (1). The association between varying cancer types can be classified into two categories, which are dependent on the timing of their discovery. An American review stated that the tumors are synchronous when the cancers occur at the same time or within 2 months of each other, whereas metachronous tumors occur when the cancers follow in sequence more than 2 months apart (2). The most widely accepted definition is that described by Moertel, which stated that synchronous neoplasms may be defined as ≥2 primary neoplasms that are diagnosed within 6 months of each other, while metachronous neoplasms may be defined as those detected following an interval of >6 months (3). These definitions are all based on the time that the neoplasms are discovered rather than on the onset of disease. MPMT was documented for the first time in a single patient in a study by Billroth in 1889 (4). The majority of MPMTs that occur in multiple organs are metachronous, while the presence of synchronous lesions is less common, and in accordance with the behavior of malignancy lesions, these tumors are more frequent with aging. Ray *et al* reported that 13.5% of patients with multiple primary malignancies have genitourinary tumors (5). The current study presents the case of a patient who developed primary right renal cell carcinoma (RCC), and metachronous prostate and left palatine tonsil neoplasms. To the best of our knowledge, this combination of primary tumors has not previously been reported.

Case report

A 70-year-old male ex-smoker (20 to 30 cigarettes per day from the age of 20 years old) was referred to the outpatient office of the Urology Unit, Sapienza University of Rome (Latina, Italy) with lower urinary tract symptoms due to benign prostatic enlargement. The laboratory investigations were within normal limits, with a prostate-specific antigen (PSA) level of 3.91 ng/ml (normal range: 0-4 ng/ml). The digital rectal examination (DRE) was negative. The medical history revealed high blood pressure and diabetes. The family history was negative for malignancies. The ultrasound examination of the urogenital system revealed nodular hyperplasia of the prostate and a right renal mass. A full-body computed tomography (CT) scan was performed for staging of the disease and showed a lesion with irregular contours in the superior pole of the right kidney. The largest diameter of the tumor was 11.5 cm. The CT scan also revealed lymphadenopathy in the context of the hepatogastric ligament, coeliac artery and interaortocaval region. The patient underwent right a radical nephrectomy to remove the lesion, with a wedge resection. Pathological examination showed renal parenchyma infiltrate by the proliferation

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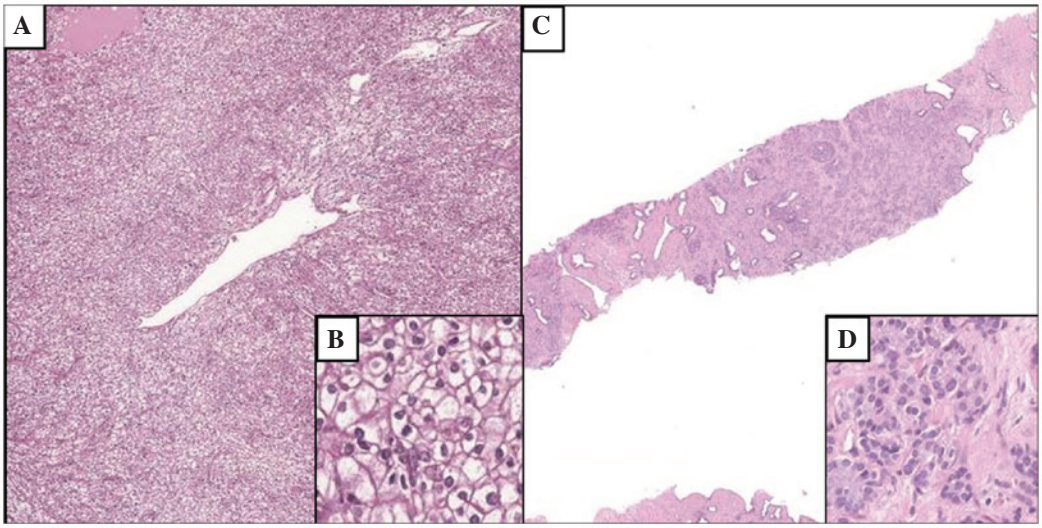

Figure 1. (A) Low-power photomicrograph showing a solid renal neoplasia composed of nests of cellular elements with distinct cell membranes and optically clear cytoplasm (magnification, x4). (B) High-power photomicrograph showing cells of a medium-large size with slightly irregular nuclei and easily visible nucleoli (magnification, x40). (C) Low-power photomicrograph showing a prostatic needle core biopsy with an area of neoplastic proliferation (magnification, x4). (D) High-power photomicrograph showing a proliferation of small/medium size glands, often fused, composed of cellular elements with hyperchromatic nuclei, evident nucleoli and slightly eosinophilic cytoplasm (magnification, x40).

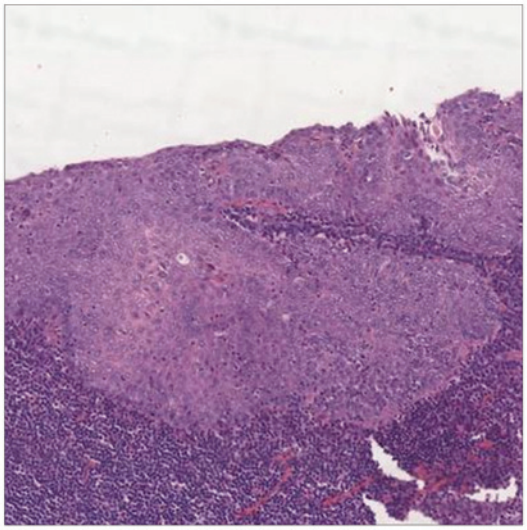

Figure 2. Low-power photomicrograph showing epithelial neoplasia, with ulcerated and infiltrating subepithelial connective and lymphoid tonsillar tissue, consisting of squamous cells arranged in solid nests, composed of cells with polymorphic nuclei, occassionally with evident nucleoli and large eosinophilic cytoplasm, with ill-defined limits (magnification, x4).

of medium-large size cells with slightly irregular nuclei, with the nucleoli easily visible, clear cytoplasm and distinct cell membranes, organized in nest structures; the diagnosis was renal cell carcinoma, clear cell type, nuclear Furhman grade 2, with involvement of the renal vein and perinephric fat (Fig. 1A and B). The tumor pathological stage according to the American Cancer Committee Union for International Cancer Control (2009) was pT2b (6).

At ~7 months after the kidney surgery, positron emission tomography using 2-[^{18}F]fluoro-2-deoxy-D-glucose, in combination with CT, demonstrated a pathological cancer focus in the left palatine tonsil. During a routine follow-up examination, a serum PSA level of 5.93 ng/ml was detected. DRE was negative again and finally, a transperineal ultrasound-guided sextant biopsy of the prostate was performed. Histological examination of the tonsillar tissue revealed a poorly-differentiated (G3) squamous cell carcinoma (Fig. 1C and D).A histological examination of the prostatic needle core biopsies showed a proliferation of small/medium size glands, often fused, composed of cellular elements with hyperchromatic nuclei, with evident nucleolus, and slightly eosinophilic cytoplasm. The diagnosis was adenocarcinoma of the prostate, Gleason score 8 (4+4) (Fig. 1C and D). The patient began a treatment program with external beam radiotherapy (EBR; 70 Gy in 1.8 to 2.0 Gy fractions) and concurrent chemotherapy with carboplatin (target AUC 2 on days 1, 8 and 15 for 6 cycles every 28 days) for the palatine tonsil squamous tumor. Furthermore, at the end of the tonsil cancer treatment, the patient is scheduled to start prostate EBR and hormonal therapy with a luteinizing hormone-releasing hormone agonist. The patient provided written informed consent for publication of this case report.

Discussion

The incidence of MPMT is estimated to be between 0.73 and 11.7% (7). In order to establish a definitive diagnosis of multiple neoplasms, the criteria described by Warren and Gates in 1932 must be adhered to (8). Each of the tumors must present a definite picture of malignancy and each one must be distinct from the other; the probability of one tumor being a metastasis of the other must excluded (8). The present case met the criteria set by Warren and Gates. The study reported a patient who developed three distinct malignancies, all of which originated from epithelial elements; the RCC, and metachronous prostate and left palatine tonsil neoplasms occurred within a period of <1 year. There were no predisposing factors for these tumors, with the exception that the patient was a heavy smoker.

RCCs account for 90-95% of malignant neoplasms arising from the kidney (9). The Fuhrman histological classification system is the most widely accepted for grading tumors. Identified etiological factors are mainly associated with lifestyle, such as smoking status, obesity and hypertension, however, the majority of patients do not present with any specific symptoms (9). A variety of factors, including tumor size and location, local or distant spread, renal function, comorbidities and performance status, must be considered when assessing the treatment for RCC (9).

Prostate cancer is the most common neoplasm in European men, particularly elderly men (10). In fact, 15% of male cancers are prostate cancers in developed countries. Three well-established risk factors are associated with prostate cancer, namely, increasing age, ethnic origin and heredity. The Gleason score is the recommended methodology for grading prostate cancer (10). Diagnostic techniques for prostate cancer include DRE, analysis of serum PSA concentration and transrectal ultrasound-guided biopsy. The diagnosis of prostate cancer is based on the histological examination. The choice of treatment depends primarily on the characteristics of the patient and the stage of disease, and will vary for patients with low-, intermediate- and high-risk prostate cancer (10).

Squamous cell carcinoma of the head and neck is classified based on the following affected regions: Oral cavity, oropharynx, nasopharynx, hypopharynx and larynx, with the tonsils considered to be a subsite of the oropharynx (11). There is a strict association between this tumor and tobacco use and alcohol consumption. Squamous cell carcinoma of the oropharynx exhibits non-specific symptoms and the rich lymphatic drainage of the tonsils is believed to promote early spread (11). The diagnosis of tonsil palatine cancer is based on histological examination. Treatment of the head and neck cancer can consist mainly of radiation therapy, surgery or surgery with radiation therapy as an adjunctive treatment (11).

The incidence of MPMT is currently rising due to improved diagnostic modalities and therapeutic protocols, which result in a greater number of patients with cancer surviving long enough to develop a second cancer. The incidence of cancer, including MPMT, increases with age (12). With improvements in the survival rates and the aging of the population, the frequency of individuals with multiple cancers will increase in the future. Warren and Gates (8) stated that the occurrence of a first malignancy is a risk for a second malignancy in that individual; in fact, the first neoplasm was likely initiated by factors and agents that may initiate a second neoplasm as well. Luciani and Balducci (12) recognized two etiological hypotheses for MPMT: The inheritance of predisposing genomic defects and field carcinogenesis. The first theory concerns certain germ-line mutations that may result in malignancies in multiple organ systems (such as xeroderma pigmentosum) or in malignancies confined to one organ system (such as familial polyposis coli). The second theory supports the hypothesis that those organ systems with neoplasms are likely to develop multiple and independent neoplasms, as all cells have been exposed to the same dose of carcinogens for the same time. The concept of field carcinogenesis can justify the association of aging and multiple malignancies: The longer a person lives, the greater the risk of developing tumors (12). Luciani and Balducci concluded that the incidence of MPMT increases with the age; this increment does not appear be caused by an aging phenotype, but rather it represents a random event (12).

In a study on 1,425 patients with RCC, Beisland *et al* (13) found that 16% presented with only 1 tumor, 1.6% presented with 2 tumors and 0.2% presented with 3 other primary malignancies. On average, 46.7% of tumors occurred as metachronous tumors. The most common second malignancy was prostatic cancer. This is in agreement with the order of occurrence in the present patient. In the study by Beisland *et al* (13), the cumulative risk of developing second primary malignancy was found to be as high as 26.6% in males with RCC. Therefore, it was concluded that patients with RCC have a significantly higher risk of developing further primary malignancies. Genetic, environmental and dietary factors, as well as obesity, were indicated to be etiological factors for the development of cancer of the prostate, breast, kidney and colon (13). In our previous studies, two cases of urinary tract synchronous involvement from other malignancies were described. The first study reported a case of synchronous primary tumors (bladder, breast and skin) in a male patient (14), and the second reported a case of synchronous ureteral and bladder metastases from invasive ductal breast carcinoma in an elderly female (15).

The present case highlights the fact that synchronous or metachronous malignancies should be considered in cases where a new tumor appears in a previous cancerous patient. Since an association between RCC and other malignancies has been shown in the literature, the present study poses the question as to whether patients with renal cell carcinoma can have an increased risk of subsequent second primary malignancy. To the best of our knowledge, this is the first reported case in the literature of this combination of primary neoplasms.

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