Int J Clin Exp Med 2018;11(11):12717-12722
www.ijcem.com /ISSN:1940-5901/IJCEM0072079

Case Report

Metachronous triple primary malignancies of the nose, lung, and urinary bladder in a male patient: a case report and literature review

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Received January 4, 2018; Accepted July 2, 2018; Epub November 15, 2018; Published November 30, 2018

Abstract: Due to recent advances in diagnostic techniques for cancer, cases with two or more neoplasms have gradually increased. This study reports a 74-year-old male with multiple primary carcinomas, suffering from cancers with three different pathologic types. These include basal cell carcinoma of nasus externus, squamous cell carcinoma of the lung, and urothelial carcinoma of the urinary bladder. Combination of carcinomas in the nose, lungs, and urinary bladder with different histological types has not been described to date. The patient's nasal basal cell carcinoma was treated by external radiotherapy. Central bronchogenic carcinoma was well controlled by combined chemoradiotherapy, while the malignant bladder tumor underwent resection by partial cystectomy. Currently, the patient is alive without any signs of progressive or metastatic disease. This case report provides an experience of diagnosis and treatment of multiple primary malignancies. Additionally, contrast-enhanced CT scans may be indispensable for geriatric patients with high cancer risks along with fluorine-18-FDG PET.

Keywords: Triple primary malignancies, metachronous, nose, urinary bladder

Introduction

Multiple primary malignancies (MPMs) are defined as more than two malignant neoplasms detected in an individual patient. MPMs consist of synchronous and metachronous types [1, 2]. According to Moertel's definition, metachronous MPMs occur after 6 months of diagnosis of previous malignant neoplasms [1]. Standardized incidence ratios (SIR) for subsequent bronchogenic and urinary bladder tumors after basal cell carcinoma are 1.12 (95% CI = 1.00-1.25) and 1.15 (95% CI = 1.08-1.21), respectively [3]. This present study reports a rare case of metachronous triple primary malignant neoplasms. The male patient suffered from three different pathologic types of carcinomas in the nose, lung, and urinary bladder. 2-[18F]-fluoro-2-deoxy-D-glucose positron emission tomography (fluorine-18-FDG PET) is often used to detect multiple primary neoplasms [4]. Compared to FDG-PET, contrast-enhanced computed tomography (CT) may be a cheaper diagnostic method of identifying MPMs, especially in patients with high risks from developing countries. Additionally, contrast-enhanced CT is an available examination method for subsequent lung cancers.

Case presentation

On August 2, 2008, a 1 × 0.5 cm mass was found on the right wing of the nasus externus of a 66-year-old man. He was a farmer, habitual drinker (500 g liquor per day for 34 years), and heavy smoker (30 cigarettes per day for 53 years). He was diagnosed with nasal basal cell carcinoma at Shandong Armed Police Hospital with pathological biopsy [immunohistochemical result: CKpan (+), CK5 (+), CK8/18 (+), P63 (+), S-100 (-), CK10/13 (-), HMB-45 (-), Ki-67 (3%+)] (**Figure 1A**). Because of the mass enlargement and subsequent exudation, he was treated by external radiotherapy (total dose, 60 Gray) at Chengwu People's Hospital on December 18, 2012. Due to the lack of effective treatment,

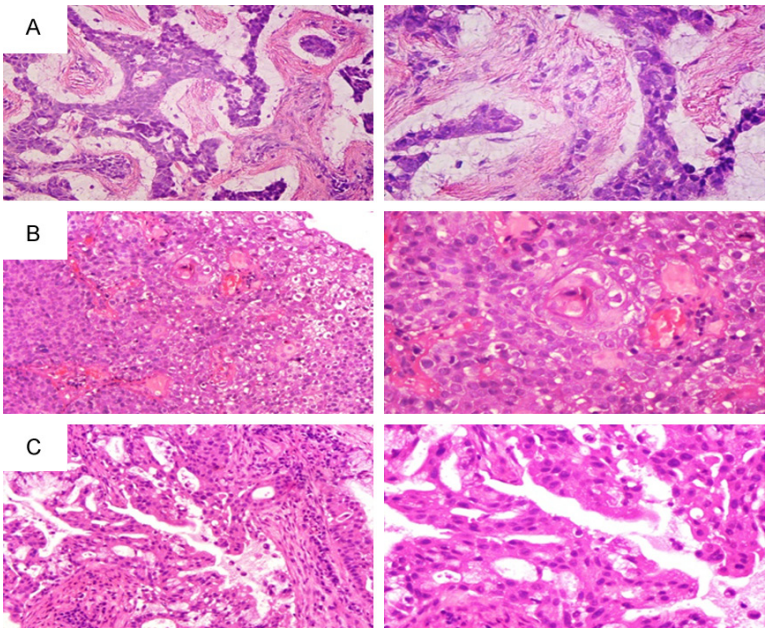

Figure 1. Histopathological examination. Tissue samples were stained by hematoxylin-eosin. Left column photos were under 100 × and the right column photos were under 200 ×. A. Nasal basal cell carcinoma. B. Bronchogenic squamous cell carcinoma. C. Urothelial carcinoma of the urinary bladder.

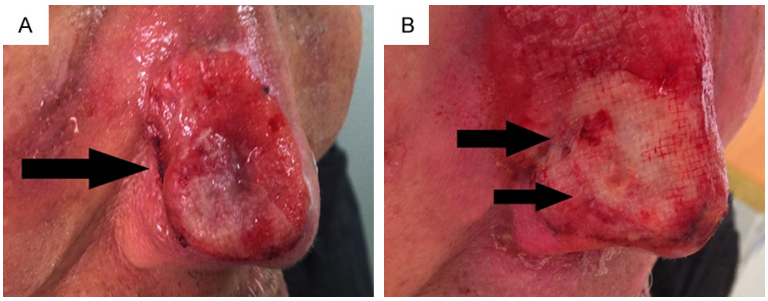

Figure 2. A. Physical examination revealed a 3.8 × 3.2 cm nasal mass (arrowed). The tumor invaded and destructed surrounding normal tissues due to lack of treatment. B. After one-cycle radiotherapy, nasal tumor regressed significantly (arrowed).

the nasal tumor invaded and destructed surrounding tissues significantly over the last three years. He was then admitted to Shandong Cancer Hospital for radiotherapy of the nasal mass (size of 3.2 × 3.8 cm) on December 1, 2016 (**Figure 2A**). After conducting external radiotherapy (200 cGray × 30 times, within 6 weeks), the nasal tumor regressed significantly (**Figure 2B**).

This patient had no positive clinical symptoms of bronchogenic carcinoma. Chest inspection was normal. Reduced language tremors and breathing sound appeared on the affected lung. Percussion revealed dullness in the right upper lung lobe. Contrast-enhanced CT examination of chest, abdomen, and pelvic cavity were performed for disease evaluation on December 2, 2016. A central bronchogenic tumor (size of 3.3 × 2.4 cm) and atelectasis of the right upper lung lobe were found by imaging examination (**Figure 3A-C**). Suspicious lymph nodes appeared in his mediastinum, but could not be identified as metastatic.

Notably, the chest X-ray scan showed a right upper lobe collapse over a reverse S shaped minor fissure (Golden S sign) (**Figure 3A**). For further diagnosis, bronchoscopy was applied, finding that the mass was at the opening of right upper lung lobe. Histopathological examination revealed squamous cell carcinoma with a immunohistochemical result: CK5 (+), P63 (+), GATA-3 (-), CK7 (-), CK20 (-), TTF-1 (-)], cT3N2M0 (stage IIIA) (**Figure 1B**). Neoadjuvant chemotherapy, before radiotherapy, was administered after a departmental discussion. With the reduction in tumor volume and recovery of atelectasis after chemotherapy, three-dimensional conformal radiotherapy (3D-CRT) (200 cGray × 30 times, within 6 weeks) was performed. After one-cycle of combined treatment, reexamination of the disease was performed. Contrast-enhanced CT revealed that the lung tumor was under control and stable (size of 2.6 × 1.9 cm) on January 2, 2016 (**Figure 4A**, **4B**). Moreover, atelectasis of the right upper lung lobe was obviously relieved (**Figure 4B**, **4C**).

On August 24, 2010, due to hematuria and multiple tumors of the urinary bladder found by cystoscopy, the patient was admitted to the Department of Urology in Shandong Cancer Hospital. The doctor in charge performed par-

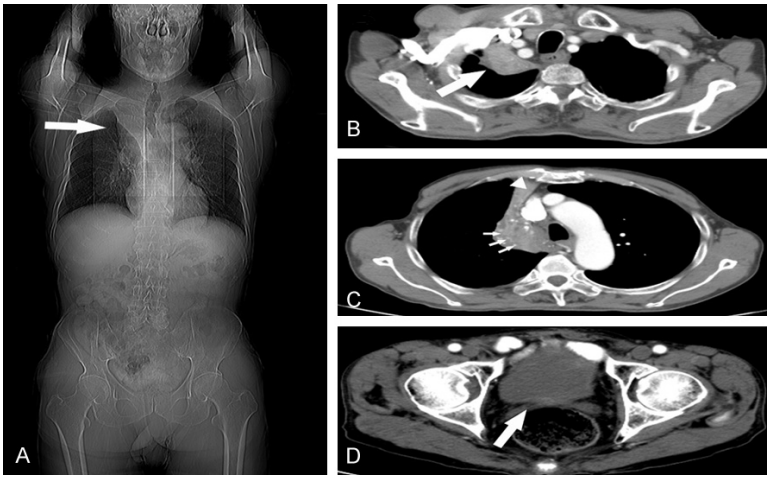

Figure 3. Imaging examination before receiving treatment of lung tumor. A. Whole-body X-ray scan. Obvious lung mass shadow and typical Golden S sign appeared on the right upper lung (arrowed); B. Contrast-enhanced CT image showed upper lobe atelectasis (arrowed); C. Contrast-enhanced CT image showed the lung mass (arrowed) and atelectasis (marked with triangle); D. Contrast-enhanced CT image showed the urinary bladder after partial cystectomy (arrowed).

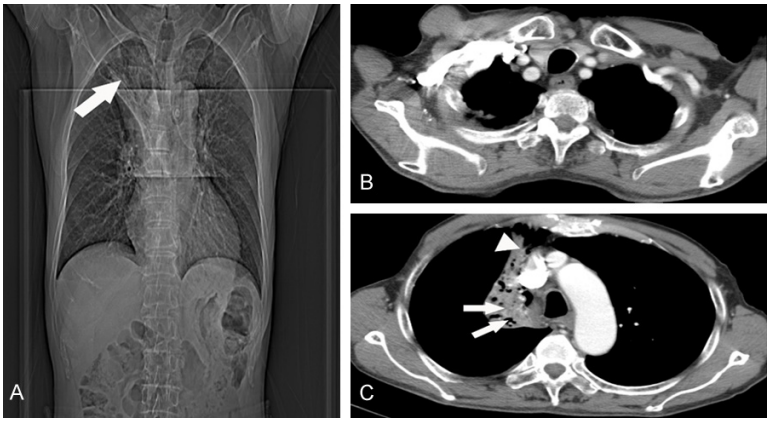

Figure 4. Imaging examination after receiving combined chemoradiotherapy treatment. A. Upper-body X-ray scan. Lung mass shadow on right upper lung faded obviously (arrowed); B. Contrast-enhanced CT image showed that upper lobe atelectasis relieves significantly; C. Contrast-enhanced CT image showed that the lung mass (arrowed) and lobe atelectasis (marked with triangle) relieve significantly.

tial cystectomy of the urinary bladder to retain organ function. Pathological diagnosis (August 28, 2010) indicated urothelial carcinoma from the right ureteral orifice and triangle area of bladder (**Figure 1C**). The tumor was recognized as low-grade and invading lamina propria of mucosa [CK7 (+), CK20 (+), P53 (+), P63 (+), Ki-67 (5%+)]. TNM staging was pathological T2N0M0 (stage II). Adjuvant chemotherapy was administered according to clinical practice guidelines of the National Comprehensive Cancer Network. After the operation, follow up and reexamination were conducted by cystoscopy and urine cytological diagnosis every 3 months. Additionally, every half year, imaging scans of the chest, abdomen, and urinary tract were taken. Currently, there are no signs of tumor recurrence or positive CT scan findings.

Discussion

The actual status of MPMs have remained uncertain due to the absence of a cancer registration system in most countries. Establishment of a cancer registration system is necessary for management and research regarding cancer patients.

The risk of more than two primary malignancies is extremely low. In recent years, some clinicians have reported multiple primary malignancies. A 58-year-old male case with multiple primary malignant neoplasms was reported by Yoshihiro et al. This patient suffered from three histological types of malignant neoplasms in six organs, namely the glottis, renal pelvis, urinary bladder, oral floor, prostate, and esophagus, in chronological order [5]. Synchronous multiple primary cancers have been the focus of clinicians. Tessho et al. described a 69-year-old woman diagnosed with synchronous quadruple multiple primary cancers, namely squamous cell carcinoma of the tongue, invasive ductal carcinoma of the breast, and chromophobe renal cell carcinoma of the right kidney [6]. Furthermore, other cases of synchronous and metachronous multiple primary malignancies at different sites, including thyroid, breast, lung, pancreas, stomach, kidney, and endometrium, have been

recently reported by clinicians [2, 7]. Rabbani et al. found that, in 551 patients with renal cell carcinoma, incidence of double, triple, quadruple, and quintuple primary malignancies were 26.9%, 6.2%, 1.1%, and 0.2%, respectively [8].

According to Warren and Gates criteria, the definition of MPMs is that each cancer must be distinctively diagnosed and exclude the probability of metastasis. Tumors described in this report were all primary carcinomas with different pathological types [9]. Both lung and urinary bladder cancers were diagnosed in 2010 and 2016, respectively, and after more than 6 months of nasal carcinoma in 2008. Therefore, all three neoplasms were determined as metachronous MPMs using the classification method reported by Moertel [1].

Analyzing 506 MPMs patients from Minneapolis Veterans Affairs Tumor Registry, Powell et al. revealed that the cumulative survival ratio of synchronous MPMs patients was higher than metachronous ones (adjusted hazard ratio = 0.5, P<0.001). Lung cancer was the most common second primary malignancy, with an occurrence rate of 23.9%, while second primary bladder or ureter cancer was 9.3%. Additionally, the ratio of primary lung cancer occurring after the bladder or ureter was 2.0% [10]. Total ratio of observed to expected (O/E) subsequent primary lung cancer after diagnosis of urinary bladder cancer was 1.62 and the ratio of first four years after diagnosis was 1.64. O/E of particular cancers after basal cell carcinoma was not mentioned [11].

Basal cell carcinoma is the most common type of skin cancers. Risk factors of basal cell carcinoma are extremely complex but exposure to ultraviolet radiation has been defined as a major cause. The timing, pattern, and amount of exposure are important in tumorigenesis [12]. Additionally, descriptive analysis of a population-based study in 2006 indicated that nonmelanoma skin cancer was the most common malignancy in the USA [13]. Basal cell carcinoma invades locally and destructs surrounding tissues without any effective therapeutic interventions, while metastasis is extremely rare. Due to low metastatic potential, local control of basal cell carcinoma remains the principle of treatment [14]. Surgical treatment includes curettage, cryosurgery, surgical excision, and Mohs micrographic surgery. Radiotherapy and photodynamic therapy are available as nonsurgical methods for basal cell carcinoma [15].

Bladder urothelial carcinoma is the fourth estimated new cancer (76,960 new cases in the USA in 2016) and the eighth reason contributing to death in male cancer patients [16]. The most important risk factor for bladder cancer in developed countries is smoking [17]. Occupational exposure to polyaromatic hydrocarbons, diesel engine exhaust, and hair dyes have been related to increased risk of bladder cancer [18]. Bladder cancer without muscle invasion represents the majority of bladder malignancies. However, from 1975 to 2008, the 5-year relative survival has only improved marginally from 71.5% to 77.5% [19]. Surgical treatment combined with adjuvant chemotherapy is still the major strategy for bladder urothelial carcinoma [20]. Neoadjuvant chemotherapy regimens consisting of cisplatin can improve overall survival of patients with stage II and III disease [21].

In the USA, 224,390 lung and bronchus cancer patients were newly diagnosed in 2016. Lung and bronchus cancers were the leading causes of cancer-related mortality in both sexes [16]. Every year, 90% of lung cancer deaths in male patients and 75% in female patients in the USA are caused by smoking [22]. Second-hand smoke exposure, environmental, and occupational factors are also causes of lung cancer [23]. Detection of early-stage central carcinoma *in situ* (CIS) and micro-invasive carcinoma (MIS) is vital due to a generally better prognosis [24]. With the development of autofluorescence bronchoscopy and narrowband imaging, bronchoscopic examinations are enhanced in the identification of CIS/MIC from proximal central airways. At present, surgical resection, external beam radiation, and bronchoscopic ablative techniques are the main treatment methods for early lung cancer [25].

SEER Cancer Registries (1973-2000) revealed that total O/E of subsequent primary renal pelvic, ureter, and lung cancers after diagnosis of bladder cancer are 13.58, 11.39, and 1.62, respectively [11]. Contrast-enhanced CT scans should cover the chest, abdomen, and pelvic cavity in bladder cancer patients, especially those with high cancer risks. As a routine procedure for inpatients, contrast-enhanced CT

scans are performed covering current cancer and high-risk regions. In this case, the MPMs patient was evaluated with nothing but contrast-enhanced CT in the chest and pelvic cavity. Due to economic factors, the patient refused further examination by FDG-PET. Additionally, patients with several major high risks for particular cancers should be given periodic physical and imaging examinations.

Conclusion

A rare case of metachronous MPMs with different pathologic types in three organs was described in this report. Contrast-enhanced CT scans are crucial for geriatric patients with high cancer risks. Contrast-enhanced CT should be extended to high risk regions to avoid overlooking new MPMs. New established imaging guidelines are needed in patients with basal cell carcinoma and bladder cancer to detect hidden metachronous MPMs. With environmental deterioration in developing countries, MPMs patients have emerged more and more. Early detection and proper intervention of potential cancer patients rely on epidemiological and clinicopathological studies. Periodic imaging and physical examinations should be conducted as protocol after treatment.

Acknowledgements

The patient was admitted to the Shandong Cancer Hospital and Institute Affiliated to Shandong University. This study was supported by a grant from the National Health and Family Planning Commission of China (201402011) and Innovation Project of Shandong Academy of Medical Science.

Disclosure of conflict of interest

None.

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