A novel combination of multiple primary carcinomas: Urinary bladder transitional cell carcinoma, prostate adenocarcinoma and small cell lung carcinoma - report of a case and review of the literature

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Abstract

**Background:** The incidence of multiple primary malignant neoplasms increases with age and they are encountered more frequently nowadays than before, the phenomenon is still considered to be rare.

**Case presentation:** We report a case of a man in whom urinary bladder transitional cell carcinoma, metachronous prostate adenocarcinoma and small cell lung carcinoma were diagnosed within an eighteen-month period. The only known predisposing factor was that he was heavy smoker (90–100 packets per year). The literature on the phenomenon of multiple primary malignancies in a single patient is reviewed and the data is summarized.

**Conclusion:** It is important for the clinicians to keep in mind the possibility of a metachronous (successive) or a synchronous (simultaneous) malignancy in a cancer patient. It is worthy mentioning this case because clustering of three primary malignancies (synchronous and metachronous) is of rare occurrence in a single patient, and, to our knowledge, this is the first report this combination of three carcinomas appearing in the same patient.

Background

The phenomenon of multiple primary malignant neoplasms in the same individual was described firstly by Billroth at the end of the 19th century [1]. Since then, several cases of double or even triple primary malignant neoplasms have been reported. It is believed that multiple primary malignant neoplasms now occur more frequently than before. Although, not uncommon, they occur more often in elderly patients, as the incidence of malignancies increases with age. The diagnosis of second primary neoplasms is rising as a result of prolonged survival of patients treated for previous malignancy with alkylating agents, topoisomerase II inhibitors, and/or radiotherapy [2]. A review of the recent literature indicates clearly
that they appear more frequently in the upper digestive tract, respiratory system, head and neck region, or urogenital system; the reported incidence ranges from 2% to 10% [3].

In this report we present a patient who developed primary bladder carcinoma and metachronous prostate and small cell lung carcinoma (SCLC) within an eighteen-month period. This combination of multiple primary carcinomas, to our knowledge, has never been reported in the literature.

**Case presentation**

A 75-year old ex-smoker (90–100 packet per year) underwent a transurethral resection of urinary bladder papilloma in February 2002. The histology of resected specimen was papillary transitional cell carcinoma grade II (Figure 1A). The tumor cells were positive for cytokeratin 7 (Figure 1B) and negative for cytokeratin 20. There were no muscle fibers in the examined tissue. The ultrasound examination of the urogenital system revealed nodular hyperplasia of the prostate. The tumor clinical stage according to the American Cancer Committee U.I.C.C. (1992) was Ta. Patient's cancer relapsed at the end of the same year and he underwent a programmed transurethral resection of the tumor, which proved to be papillary transitional cell carcinoma grade I-II. No lamina propria or muscle invasion was detected. The patient was also treated with intracystic infusion of bacille Calmette-Guerin (BCG). Ten days later, because of urine retention, he underwent transurethral resection of the prostate. Multiple tissue fragments of total dimensions 4.5 × 3.5 × 2.2 cm were examined histologically. Seven out of the 10 examined slides revealed foci of partially mucinous (Figure 2A) adenocarcinoma of the prostate, grade II-III (A. hematoxylin and eosin × 40, B: hematoxylin and eosin × 100). The tumor cells were strongly positive for PSA (C: PSA × 40)

Histologically, in most of the prostate tissue fragments were recognized areas of, partially mucinous, adenocarcinoma of the prostate, grade II-III (A, hematoxylin and eosin × 40, B: hematoxylin and eosin × 100). The tumor cells were strongly positive for PSA (C: PSA × 40).

**Figure 1**

Microscopically, the extracted urinary bladder tissue particles proved to be pieces of papillary transitional cell carcinoma grade II [A] hematoxylin and eosin × 40 and immunohistochemically they expressed cytokeratin 7 [B] cytokeratin 7 × 100.

**Figure 2**

Histologically, in most of the prostate tissue fragments were recognized areas of, partially mucinous, adenocarcinoma of the prostate, grade II-III (A. hematoxylin and eosin × 40, B: hematoxylin and eosin × 100). The tumor cells were strongly positive for PSA (C: PSA × 40).

**Figure 3**

The bronchial mucosa showed extensive invasion from small blue round cells (A: hematoxylin and eosin × 100) that were positive for the neuroendocrine marker CD56 (B: × 200) and pan-cytokeratin (C: × 200).
Table 1: There are summarized the cases of triple or more malignancies, the first author, journal, year of publication and combination of neoplasms.

| Year | Author                | 1st Malignancy              | 2nd Malignancy              | 3rd Malignancy              | 4th Malignancy              | 5th Malignancy              |
|------|-----------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|
| 1949 | Crail H.W. [6]        | Thyroid Carcinoma          | Rectal Carcinoma           | Medulloblastoma             |                            |                            |
| 1974 | Hamoudi A.B. [7]      | Colon Carcinoma            | Thymus Carcinoma           | Skin Carcinoma             | Astrocytoma G3             |                            |
| 1975 | Ohsato K. [8]         | Colon Carcinoma            | Astrocytoma G3             | Duodenal Carcinoma         |                            |                            |
| 1976 | Kawanami K. [9]       | Ileum Carcinoma            | Glioblastoma               | Colon Carcinoma            |                            |                            |
| 1976 | Rovinescu L. [4]      | Clear Cell Carcinoma Of Kidney | Transitional Cell Carcinoma Of Bladder | Prostate Carcinoma       |                            |                            |
| 1979 | Itoh H. [10]          | Colon Carcinoma            | Stomach Carcinoma          | Astrocytoma G3             |                            |                            |
| 1979 | Mullen J. [11]        | Squamous Cell Carcinoma Of Larynx | Squamous Cell             | Squamous Cell Carcinoma In Esophagus |                            |                            |
| 1980 | Cohen J. [13]         | Multiple Cutaneous Cell Carcinomas | Multiple Cutaneous Basal Cell Carcinomas | Diffuse Poorly Differeniated Lymphocytic Lymphoma |                            |                            |
| 1982 | Friedman C.O. [14]    | Breast Carcinoma           | Colon Carcinoma            | Glioblastoma In Brain      |                            |                            |
| 1983 | Li F.P. [15]          | Colon Carcinoma            | Astrocytoma G3             | Leukemia                   |                            |                            |
| 1984 | Haibach H. [16]       | Thyroid Carcinoma          | Renal Carcinoma            | Duodenal Carcinoma         |                            |                            |
| 1985 | Alessi E. [17]        | Multiple Sebaceous Tumors  | Keratoacanthoma            | 3 Primary Adenocarcinomas Of Colon |                            |                            |
| 1985 | Kobayashi T. [18]     | Uterus Carcinoma           | Stomach Carcinoma          | Breast Carcinoma           | Glioblastoma In Brain      |                            |
| 1985 | Megghian D. [19]      | Squamous Cell Carcinoma Of Parotid | Squamous Cell Carcinoma Of Tongue | Squamous Cell Carcinoma Of Soft Palate | Squamous Cell Carcinoma Of Larynx | Squamous Cell Carcinoma Of Hypopharynx |
| 1985 | Staren E.D. [20]      | Carcinoma Of Larynx        | Carcinoma Of Floor Of Mouth | Dual Primary Bronchogenic Carcinomas |                            |                            |
| 1986 | Craig D.M. [21]       | Squamous Cell Carcinoma Of The Floor Of The Mouth | Adenocarcinoma Of Lung Carcinoma Of Larynx | Squamous Cell Carcinoma Of The Tongue | Squamous Cell Carcinoma Of Larynx | Squamous Cell Carcinoma Of Hypopharynx |
| 1986 | Ogasawara K. [22]     | Breast Carcinoma           | Breast Carcinoma           | Lung Carcinoma             | Glioblastoma In Brain      | Thyroid Carcinoma          |
| 1987 | Hayashi K. [23]       | Colon Carcinoma            | Rectal Carcinoma           | Glioblastoma In Brain      |                            |                            |
| 1987 | Kobayashi T. [24]     | Uterus Carcinoma           | Stomach Carcinoma          | Glioblastoma In Brain      |                            |                            |
| 1988 | Ohi H. [25]           | Skin Carcinoma             | Medulloblastoma            | Thyroid Carcinoma          |                            |                            |
| 1991 | Bajgir R.J. [26]      | 7 Primary Carcinomas       |                            |                            |                            |                            |
| 1991 | Solan M. [27]         | Two Breast Carcinomas      | Thyroid Carcinoma          | Multiple Skin Carcinomas   |                            |                            |
| 1992 | Melkert P.W. [28]     | Squamous Cell Carcinoma Of Skin | Squamous Cell Carcinoma Of Tongue | Squamous Cell Carcinoma Of Larynx | Squamous Cell Carcinoma Of Anus | Squamous Cell Carcinoma Of Cervix Uteri |
| 1992 | Marcos Sanchez F. [29] | Colon Carcinoma            | Renal Carcinoma            | Breast Carcinoma           |                            |                            |
| 1993 | Brugieres L. [30]     | Soft Tissue Tumor          | Brain Tumor                | Thyroid Carcinoma          | Breast Carcinoma           |                            |
| 1993 | Kikuchi T. [31]       | Glioblastoma               | Colon Carcinoma            | Colon Carcinoma            |                            |                            |
| 1993 | Shishe [32]           | Skin Carcinoma             | Colon Carcinoma            | Glioblastoma In Brain      |                            |                            |
| 1994 | Bumpers H.U. [33]     | Squamous Cell Carcinoma Of Larynx | Squamous Carcinoma Of Lung | Adenocarcinoma Of Breast   | Adenocarcinoma Of Colon   |                            |
| 1994 | Nishihara K. [34]     | Papillary Adenocarcinoma Of Papilla Of Vater | Papillary Adenocarcinoma Of Common Bile Duct | Papillary Adenocarcinoma Of Pancreas |                            |                            |
| 1995 | Angelis-Besson C. [35]| Chronic Myeloid Leukemia, Multiple Squamous Cell Carcinomas |                            |                            |                            |                            |
| 1996 | Hayashi T. [36]       | Squamous Cell Carcinoma In Soft Palate | Squamous Cell Carcinoma In Larynx | Squamous Cell Carcinoma In Esophagus |                            |                            |
| 1996 | Nagan M. [37]         | Tubular Adenocarcinoma Of Stomach | Transitional Cell Carcinoma Of Bladder | Glioblastoma In Brain |                            |                            |
performed. In September of the same year, due to progressively worsening dyspnea a computed tomography was performed that revealed a mediastinal mass in conjunction to the right lung hilum and to the right main bronchus with maximum diameter of 9 cm. Bronchoscopy showed a large mass which invaded the right main bronchus mucosa and extended to the carina. Histology of the bronchial mucosal sample showed infiltration of lamina propria by malignant cells (Figure 3A). Their immunophenotype was: CD56 (+) (Figure 3B), Pan-Cytokeratin (paranuclear dot stain positivity) (Figure 3C) and Leukocyte Common Antigen negative. Combining the morphological and the immunohistochemical results, we concluded that the patient was suffering from small cell lung carcinoma (SCLC). The patient’s stage was IIIB. Ten days after the diagnosis was confirmed, the patient underwent the first cycle of chemotherapy (Cisplatin and Vepesid), during which he died from cardiac arrest due to chemotherapy toxicity.

Discussion
We report a patient who developed three histologically distinct malignancies, i.e. primary bladder carcinoma and metachronous prostate and SCLC within an eighteen-month period. There are several predisposing or causal factors for each malignancy. For our patient there was only one common causal factor, the fact that he was a heavy smoker (90–100 packets per year). No other predisposing factor or a family history was found that might have contributed to the development of these three malignancies. The presence of bladder and prostate carcinomas in the same patient is not a rare event. Chun [3] reported that the rate of bladder carcinoma in patients with prostate carcinoma is eighteen times higher (p < 0,01) and the rate of prostate carcinoma in those with bladder carcinoma is nineteen times higher (p < 0,01) than expected. Although bladder and prostate carcinoma can coexist in the same individual frequently enough, the rare event is the appearance of a third malignancy. There is a case report by Rovinescu et al [4] referring to a patient with three primary malignancies. The first tumor was a clear cell carcinoma of the kidney, which was followed by a transitional cell carcinoma of the bladder and then by a distinct adenocarcinoma of the prostate. More recently, in 2003, Satoh et al [5] also reported the same combination of multiple primary malignancies in a patient. Our case is the first one of an individual having these two primary malignancies of the urogenital system and another tumor of the lower respiratory tract.

Table 1 summarizes the cases with three or more primary malignancies. As can be easily seen, although the appearance of three primary malignancies in one patient is not very common, should not be considered such a rare event. Additionally, studying the existing bibliography, we noticed that there is a little confusion regarding the terms used, such as synchronous, simultaneous and metachronous or successive neoplasms. All of these words have to do with the time of their genesis. The word synchronous is a Greek one that should refer to neoplasms appearing in the same time. It is synonymous to the word simultaneous and they are interchangeable. Metachronous (meta- means after and -chronous is the time) is also a Greek word referring to a neoplasm that is discovered while there is already a known neoplasm in the same patient. The word successive could be used equally to metachronous.

| No. | Year | Author | First Author | Journal | Year of Publication | Neoplasms | Neoplasms | Neoplasms |
|-----|------|--------|--------------|---------|---------------------|-----------|-----------|----------|
| 34  | 1996 | Nagane M. [37] | [37] | Papillary Adenocarcinoma Of Lung Breast Carcinoma | Adenocarcinoma Of Rectum | Gioblastoma In Brain |
| 35  | 1997 | Potsch C.[38] | [38] | Small Cell Lung Carcinoma | Renal Cell Carcinoma | Acute Myelomonocytic Leukemia |
| 36  | 1997 | Shan L.[39] | [39] | 14 Foci Of Primary SCC, Esophagus, Oral Floor, Soft Palate, Uvula, Lingual Radix, Piniform Recess, Hypopharynx, Trachea, Lingual Body | Small Cell Lung Carcinoma | Adenocarcinoma Of Rectum |
| 37  | 1999 | Cribier B. [40] | [40] | Eccrine Porocarcinoma | Tricholemmal Carcinoma | Multiple Squamous Cell Carcinomas |
| 38  | 1999 | Ramay H.M.[41] | [41] | Acute Myeloid Leukemia | Chronic Lymphocytic Leukemia | Basal Cell Carcinomas |
| 39  | 1999 | Schon M.P.[42] | [42] | Basal Cell Carcinomas | Hairy Cell Leukemia | Basal Cell Carcinomas |
| 40  | 2000 | Beswick S.[43] | [43] | Basal Cell Carcinomas | Malignant Melanoma In Situ | Basal Cell Carcinomas |
| 41  | 2001 | Mukai [44] | [44] | Stomach Carcinoma | Duodenal Carcinoma | Esophageal Cancer |
| 42  | 2003 | Satoh H.[5] | [5] | Carcinoma Of Kidney | Transitional Cell Carcinoma Of Bladder | Renal Cancer | Colon Carcinoma In Situ |

Table 1: There are summarized the cases of triple or more malignancies, the first author, journal, year of publication and combination of neoplasms. (Continued)
Conclusion
Summarizing, it is important for the clinicians to keep in mind that the appearance of another tumor in a patient suffering from cancer could be either a metastasis or another malignancy and should always investigate the possibility of a metachronous (successive) or a synchronous (simultaneous) malignancy. Moreover, the combination of the three different neoplasms (bladder, prostate and SCLC) in one patient, to the best of our knowledge, has never been reported before.

Competing interests
The author(s) declare that they have no competing interests.

Authors' contributions
KAV wrote the original manuscript and performed histopathological evaluation of the lung lesion.

DKI participated in the writing of the original manuscript and prepared photomicrographs.

DG performed histopathological evaluation of the urinary bladder lesion.

GE performed histopathological evaluation of the prostate lesion.

FM performed bronchoscopy and patient's management.

SE prepared requested revisions of the manuscript.

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