CASE REPORT

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Familial aggregation of bladder cancer

Familijarna agregacija raka mokraćne bešike

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Abstract

Background. Except for smoking and certain occupational exposures, the etiology of bladder cancer is largely unknown. Several case reports have described familial aggregation of transitional cell carcinoma of the bladder. Although the majority of patients with bladder cancer do not have family history of transitional cell carcinoma of the urinary tract, the study of familial transitional cell carcinoma may lead to the knowledge on the pathogenesis of this disease. The purpose of this study was to describe three cases of urinary bladder cancer in a single three-member family, i.e. in two generations (mother and son) and a family member related by marriage (the patient's wife). **Case report**. Three cases of urinary bladder cancer occurred in a three-member family within the interval of 5 years. The following common characteristics were detected in our patients: old age (over 60), working as farmers for more than 50 years, negative personal medical history on relevant health disorders, place of birth – village, place of residence – village, the same water supply, similar nutrition, positive family history on urinary bladder cancer or other malignant tumors, the first sign of illness was macroscopic hematuria in all the patients and the same pathohistological type of cancer – *carcinoma papillare transitiocellulare*. **Conclusion.** The stated common characteristics in our cases indicate, above all, the impact of exposure to external surrounding factors on the occurrence of urinary bladder cancer.

Key words:
urinary bladder neoplasms; carcinoma, transitional cell; family; carcinoma, papillary.

Apstrakt

Uvod. Osim značaja uticaja navike pušenja cigareta i profesionalne izloženosti nekim kancerogenima na nastanak karcinoma mokraćne bešike, etiologija tog malignog tumora nije sasvim razjašnjena. Nekoliko epidemioloških studija opisalo je familijarnu agregaciju raka mokraćne bešike – *carcinoma papillare transitiocellulare*. Mada se kod većine obolelih ne registruje pozitivna porodična istorija za tranziciocelularni rak mokraćne bešike, ispitivanje familijarne agregacije može doprineti sagledavanju patogeneze tog malignog tumora. U ovom radu prikazana su tri slučaja raka mokraćne bešike u jednoj porodici, kod dve generacije srodnika (majka i sin) i kod člana porodice koji nije krvni srodnik (supruga obolelog). **Prikaz slučaja.** Tri slučaja raka mokraćne bešike u troćlanoj porodici zabeleženi su u intervalu od pet godina. Oboleli od raka mokraćne bešike imali su sledeće zajedničke karakteristike: stariji uzrast (preko 60 godina), bavljenje poslom poljoprivrednika duže od 50 godina, negativnu ličnu zdravstvenu istoriju ozbiljnih poremećaja zdravlja, mesto rođenja – selo, mesto stalnog boravka – selo, isti način snabdevanja vodom za piće, sličan način ishrane, pozitivnu porodičnu istoriju raka mokraćne bešike i druge maligne tumore, hematuriju kao prvi znak bolesti, isti patohistološki tip malignog tumora – *carcinoma papillare transitiocellulare*. **Zaključak.** Karakteristike obolelih ukazuju na značaj izloženosti faktorima spoljašnje sredine u nastanku raka mokraćne bešike.

Ključne reči:
mokraćna bešika, neoplazme; karcinom prelaznih ćelija; porodica; karcinom, papilarni.

Introduction

According to a large number of hypotheses on etiology, urinary bladder cancer is considered to be an illness with more possible causes [1–5]. Smoking is a single greatest risk factor for bladder cancer [3, 5–7]. Smokers have more than twice the risk of developing bladder cancer as nonsmokers [1, 2, 5, 7, 8]. Organic chemicals called aromatic amines are particularly linked with bladder cancer [3, 9]. Arsenic is a known bladder carcinogen and populations exposed to high arsenic levels in their water supply have reported elevated bladder cancer mortality and incidence rates [10, 11]. The reason for high incidence of urinary tract cancer in individuals suffering from Balkan nephropathy has yet to be determined [12].

Several epidemiological studies have indicated a possible familial component to bladder cancer [13–16]. Kiemeney and

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Schoenberg [14] mention familial aggregation of this neoplasm and possible genetic predisposition for its occurrence. Genealogical analysis of subjects up to the second degree of kinship indicated a considerably more frequent occurrence of urinary bladder benign tumors in the patients' families than in the families of the test group members (first-degree relatives). In the Spanish bladder cancer study, the odds ratios (OR) of bladder cancer among subjects reporting a family history of bladder cancer was 2.34 [95% confidence interval (95% CI) = 0.95–5.77] [17]. Plna and Hemminki [18] analyzed the risk of bladder cancer in offsprings according to parental and sibling cancer and founded that the highest familial risk of 7.26 (95% CI = 2.61–14.24) in brothers of bladder cancer probands diagnosed before the age of 45 years. Lin et al. [13] reported that a positive family history of bladder cancer may have interacted with smoking habits to increase the risk of bladder cancer. Recent metaanalyses of 31 case-control studies assessing the risk of bladder cancer conferred by N-acetyltransferase 2-slow acetylating genetic variants and of 28 case-control studies assessing the risk of bladder cancer conferred by glutathione S-transferase M1-null variants estimated OR of 1.4 (95% CI = 1.2–1.6) and 1.5 (95% CI = 1.3–1.6), respectively [19].

In epidemiologic studies, family history confers increase in bladder cancer risk, but it is uncertain whether this represents an evidence of genetic and/or shared environmental basis for familial aggregation [13, 15, 16].

The aim of this work was to describe three cases of urinary bladder cancer in a single rural family, i.e. in two generations (mother and son) and a family member related by marriage (the patient's wife).

Cases report

A 68-year-old man was admitted to the hospital at the beginning of 2003 because of the occurrence of blood in his urine and frequent urination. There was no evidence of several diseases in patient's personal medical history (urinary infections, lithiasis, bladder cancer, tumors of the kidney, diabetes mellitus, sexual diseases and any form of cancer). The patient was a farmer for more than 50 years. He smoked 1.5 packs of cigarettes a day for 50 years.

Family case-history showed that the patient's mother died in 2000 of bladder cancer. The patient's household was made of him and his wife diagnosed with bladder cancer in 2001. Our subjects had been married for 46 years. Thay had 4 children, 1 dead son (first-born child, lived for a week) and 3 daughters (the eldest daughter with myoma uteri from the age of 29 years, but now with no disease). The eldest daughter had one grandson, 13 years old. The family trees of our patient and his wife are given in Figure 1. According to family tree, the patient's mother died of bladder cancer at the age of 85. The patient's relative died of breast cancer at the age of 55. No other family members were affected by cancer.

The surgeon-urologist performed a partial cistectomy by the end of February in 2003, when the enlarged and immovable right ileal lymph glands were detected by an intraoperative and palpatory process. A biopsy specimen revealed *carcinoma papillare transitiocellulare*, a histological grade 3, with signs of muscle infiltration (Figure 2). Death occurred in June 2003.

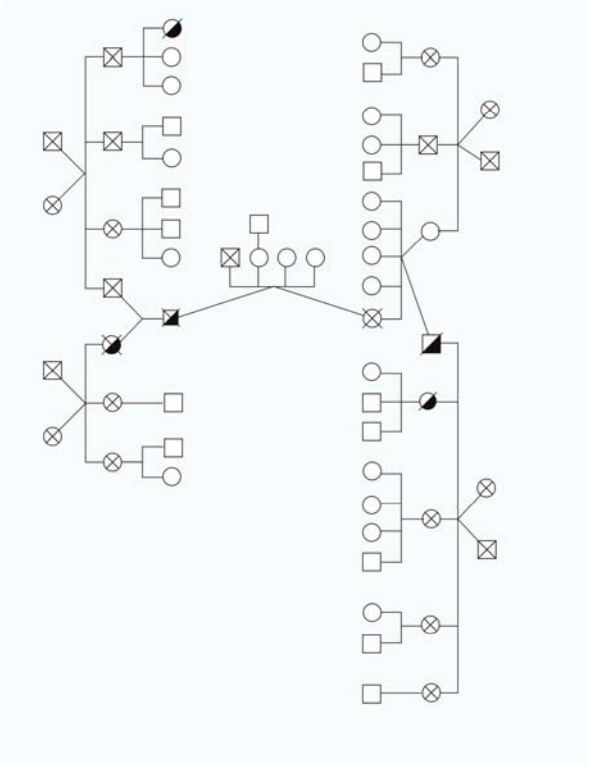

Fig.1 –The affected family tree – alive relatives (male □, females ○); Dead relatives (male ⊠, female ⊗); bladder cancer (case: ⊠, ⊗; dead: ■, ●); other form of cancer (case: ◪, ◯; dead: ◪, ◯)

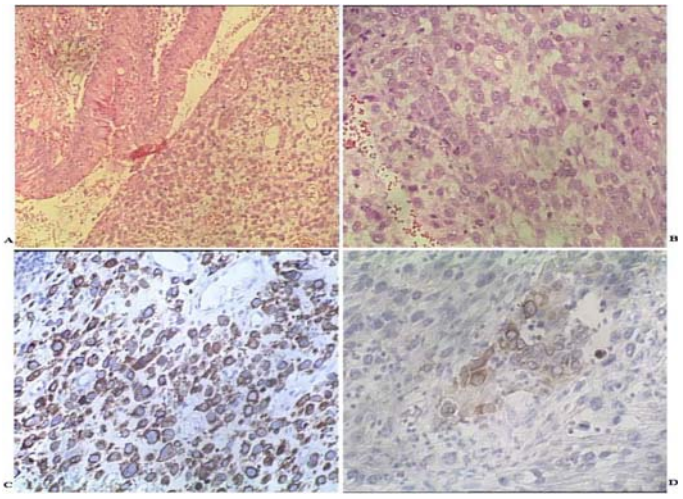

Fig. 2 – Histologic analysis of bladder cancer in the reported patient – A) *carcinoma papillare transitiocellulare* (hematoxylin-eosin, original magnification x 40); B) *carcinoma papillare transitiocellulare* (hematoxylin-eosin, original magnification ×200); C) *carcinoma papillare transitiocellulare* (imunohistochemical analysis, strong expression of CK7, original magnification ×200); D) *carcinoma papillare transitiocellulare* (imunohistochemical analysis, focal expression of CK17, original magnification ×200)

At the beginning of 1997, the patient's mother (born in 1915) was admitted to the hospital for hematuria and frequent urination. Transurethral resection was performed in January 1997, followed by radiation therapy. A biopsy specimen revealed *carcinoma papillare transitiocellulare*, histological grade 2, with signs of submucosa infiltration (Figure 3). In July 1997, recidive was diagnosed and cauterized. In August 1998, the second recidive was diagnosed, followed by another transurethral resection in January 1999. Death occurred in 2000.

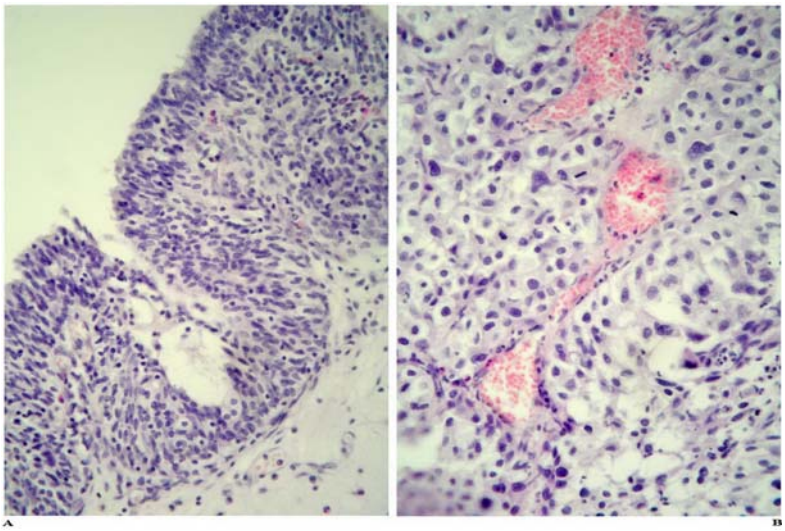

Fig. 3 – Histologic analysis of bladder cancer in the patient's mother – A) *carcinoma papillare transitiocellulare* (hematoxilyn-eosin, original magnification ×100); *carcinoma papillare transitiocellulare* (hematoxilyn-eosin, original magnification ×400)

The patient's wife (born in 1938) and got urinary bladder cancer at the age of 63. She was admitted to the hospital for hematuria and frequent urination in August 2001. A biopsy specimen revealed *carcinoma papillare transitiocellulare*, histological grade of 2 and nuclear grade 3 (Figure 4). The tumor was infiltrating submucosa and the fragments of the smooth muscle. Infiltration of lymph vessels and moderate necrosis points were detected. Transurethral resection was performed in August 2001, followed by radiation therapy. Twenty five months later the patient had no recidives. According to family tree (Figure 1), her father died at the age of 70 of lung cancer, and his relative died of stomach cancer at the age of 66. No other family members were affected by cancer.

The patient's mother and wife in their personal medical histories had no evidence of several diseases (urinary infections, lithiasis, bladder cancer, tumors of the kidney, diabetes mellitus, sexual diseases and of any form of cancer). They were both non-smokers.

Our subjects lived in a village about 10 kilometers away from Kragujevac. Kragujevac is a town with almost 200,000 people in the center of Šumadija Region in Central Serbia. In

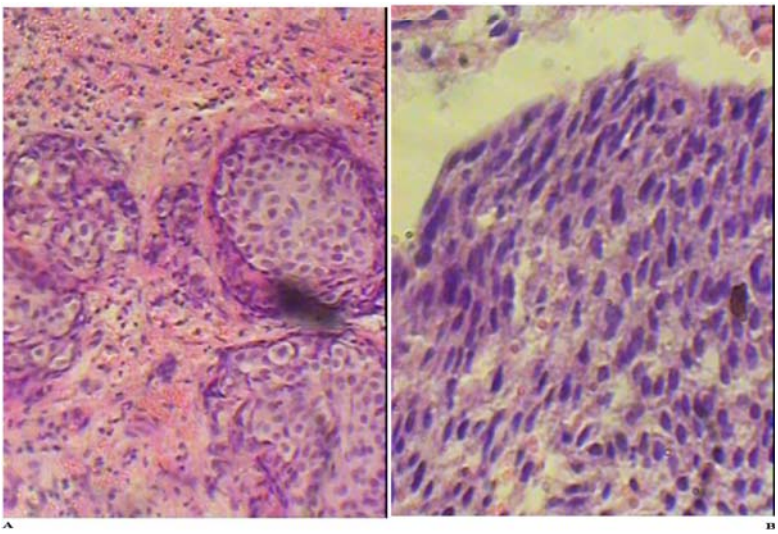

Fig. 4 – Histologic analysis of bladder cancer in the patient's wife – A) *carcinoma papillare transitiocellulare* (hematoxilyn-eosin, original magnification ×100); B) *carcinoma papillare transitiocellulare* (hematoxilyn-eosin, original magnification ×400)

the last few decades on the teritory of Šumadija Region it has been registered sporadic appearance of Balkan endemic nephropathy. The known seats of Balkan endemic nephropathy in Serbia are in other regions. In the neighbourhood of the reported cases there were no cases of Balkan endemic nephropathy.

Each family in the village is supplied with drinking water from its own well. Since there is no local water supply network in the village, our subject's father built one independent, about ten years ago. Drinking water from the water supply network has never been disinfected (that is, chlorinated) nor bacteriologically or chemically tested. To determine sanitery aspect of water for drink which was used by family members, we did the basic bacteriological and chemical analysis of water specimens from the water supply network and well water, and also did testing for heavy metals (arsenic, cadmium, lead, mercury). According to our results, water did not meet legally set criterions in drinking water, because of the presence of *Escherichia coli* in both the water supply network and well water. *Streptoccocus faecalis* was found in well water in the yard. In the water supply network specimen was found troubled water with sediments, excessive dose of ammonia (NH_3) and excessive use of $KMn0_4$, which can indicate for presence of organic substance in water. There were no heavy metals (arsenic, cadmium, lead, mercury) over the allowed concetrations maximum in the tested specimens.

Discussion

Numerous studies have associated bladder cancer with exposure to carcinogens present in tobacco smoke and other environmental or occupational exposures. Nevertheless, familial aggregation of bladder cancer was described in several studies.

Few of anamnestic studies indicate family predisposition for urinary bladder cancer [1, 2, 13, 14]. Kantor et al. [20] detected exceptionally high risk of illness in case of joint hereditary and external factors. The risk of urinary bladder cancer was connected with the existing family history of urinary tract cancer (RR = 1.45), especially among patients under the age of 45, and confirmed smokers (RR = 10.7 those smoking 4 or more packets of cigarettes a day). In a study by Bermejo et al. [21] in Sweden that explored the sex-specific incidences and types of tumors in relatives of bladder cancer patients, among men older than 54 years were at an increased risk of bladder cancer only if their fathers or siblings were diagnosed after the age 65 years. A study by Kiemeney et al. [14] in Iceland, indicated an increase in the risk of urinary tract cancer in first-, second- and third-degree relatives suffering from urinary bladder cancer (RR = 1.24; 95% CI = 0.90–1.67). The finding that the prevalence of urinary tract cancer was 3% in first-degree relatives, and 10% in second- and third-degree relatives, suggests that there may not be a hereditary type of urinary bladder cancer. According to the findings of Petrovic [22], second- and third-degree relatives of the patients more frequently suffered from malignant tumors in comparison to relatives of the test group members of the same degree of kinship. According to the findings of Radosavljevic [23], the number of patients suffering from malignant tumors (except for urinary bladder tumor) in the second degree of kinship within the study group stood in positive correlation with the occurrence of the illness.

The stated common characteristics in our cases indicate above all the impact of exposure to external surrounding factors on the occurrence of urinary bladder cancer. Three cases of urinary bladder cancer occurred in this three-member family within a 5-year interval. The following common characteristics were detected in our subjects: old age (over 60), working as farmers for more than 50 years, negative personal medical history on relevant health disorders, place of birth – village, place of residence – village, the same manner of water supply, similar manner of nutrition, positive family history on urinary bladder cancer or other malignant tumors, the first sign of illness was macroscopic hematuria in all the patients and the same pathohistological type of cancer – *carcinoma papillare transitiocellulare*.

Namely, members of the same family are exposed to the same or at least similar environmental factors, with regard to nutrition, habits, degree of education, financial situation and the like. Numerous factors indicate that environmental factors interact with hereditary ones, thus determining the occurrence and form of illness. However, this interaction is difficult to examine and thus it is impossible to define accurately the degree of participation of hereditary and environmental factors in the etiopathogenesis of the illness, and hereditary factors perhaps only determine the general inclination to neoplasms.

Conclusion

This report on unusual cases have contributed to our understading of the disease, especially with regard to cancer and familial aggregation of bladder cancer and exposure to suspected enviromental factors.

We propose that the etiology of familial bladder cancer may be complex, involving other possible associated malignant neoplasms in addition to specific carcinogenic exposures. There is a serious need for detailed reporting on families prone to bladder cancer wherein all of these potentially important associated factors are considered.

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