Case Report

Urothelial Bladder Carcinoma in Students at a Dental Technical College: A Report of 3 Cases

Nicolaie Suditu\textsuperscript{a} Irina Negru\textsuperscript{a} Bogdan Novac\textsuperscript{b}

\textsuperscript{a}Department of Surgery, Arcadia Hospital, Iasi, Romania; \textsuperscript{b}Department of Urology, “Dr. C.I. Parhon” Hospital, Iasi, Romania

Keywords
Urothelial bladder carcinoma · Risk factors · Dental materials · Students · Dental technical college

Abstract
Bladder cancer is one of the main types of neoplasia affecting men, with the highest incidence reported toward the end of the seventh decade of life. Unlike other malignancies, bladder cancer is attributable to specific widely occurring carcinogenic risk factors in 60–70\% of cases, and numerous professions have been linked to higher rates of the disease. The present study includes the cases of three male graduates (mean age, 23 years) from the same dental technical college, two of whom were students at the Faculty of Dental Medicine of the Iași University of Medicine and Pharmacy (Iași, Romania) at the time of diagnosis. The individuals were occupationally exposed for a mean of 43.66 months. Histopathological examinations following resection indicated the presence of benign lesions (1 case) and malignant lesions of low aggressiveness (2 cases). The patients’ outcomes were favorable, and there was no tumor recurrence over a mean observation period of 56 months. The aim of the present study was to highlight the young age at which these patients developed bladder tumors under similar etiological conditions and over short periods of exposure to known occupational risk factors. This shorter time of exposure to risk factors makes it even harder to establish causality with the occurrence of bladder tumors. However, the present cases could lead to a suspicion of a direct association between the exposure and the tumors or an entirely coincidental occurrence.
Introduction

Bladder cancer is the ninth most common type of cancer worldwide, comprises 3% of cases, and occurs predominantly in men, with an incidence fourfold higher than that in women [1, 2]. The incidence of bladder cancer peaks in the seventh decade of life, with a lower incidence among young populations [3]. Fortunately, the vast majority of bladder tumors in young patients are histologically noninvasive papillary urothelial carcinomas. Advanced age at diagnosis has also been related to behavioral and environmental etiological factors acting on the urothelium over long periods (estimated at 20–30 years) [3–5]. According to certain studies, 60–70% of bladder cancer cases can be attributed to specific etiopathological factors, an uncommon phenomenon within the overall etiopathogenesis of cancer. Although the main risk factor for bladder cancer is cigarette smoking, another identified risk factor is occupational exposure to chemical substances and contaminated water [5]. The chemical substances most prominently associated with the onset of bladder cancer are aromatic amines (mainly linked to incidence) and polycyclic aromatic hydrocarbons (mainly linked to mortality) [4]. These carcinogenic substances are employed in a broad range of professions. Cumberbatch et al. [4] identified 61 occupational groups with an increased risk of developing bladder cancer, including dental medicine practitioners. Awareness of these etiopathological factors has enabled the design and development of national prevention programs but with debatable results in managing bladder cancer incidence and mortality. Overall, there has been an increase in the incidence but a decrease in mortality [6–8]. The aim of the present case study was to highlight cases of healthy individuals with no significant personal or family medical history who developed bladder tumors at an early age but who were exposed to typical occupational risk factors over a short period and in an educational rather than an occupational context during their training at the same university.

Case Presentation

Case 1

A 23-year-old male patient from Roman (Neamț County, Romania) presented with macroscopic hematuria in December 2014. A clinical examination, imaging tests (ultrasound and computed tomography), and cystoscopy revealed a papillary bladder tumor measuring 10 × 6 mm on the left lateral wall. Following transurethral tumor resection, anatomopathological examination revealed a low-grade papillary urothelial carcinoma with no involvement of the lamina propria or muscle layer (pTaN0M0G1) (Fig. 1). The patient underwent local chemotherapy with epirubicin, and subsequent regular cystoscopic examinations showed no evidence of tumor recurrence. The patient had smoked in the past (1.5 pack-year index) but had no significant personal or family medical history. At the time of diagnosis, the patient had graduated from a 3-year program at the Dental Technical College of the Iași University of Medicine and Pharmacy and had subsequently been employed as a nurse for 6 months.

Case 2

An asymptomatic 22-year-old male patient from Bârlad (Vaslui County, Romania) was incidentally diagnosed with a bladder tumor following abdominal ultrasonography in November 2016. Computed tomography confirmed the presence of a bladder tumor measuring 15 × 8 mm on the left hemitrigone. Cystoscopic examination revealed the tumor's papillary nature and located it at the upper extremity of the left urethral orifice. Transurethral resection
(single procedure) was performed. Anatomopathological examination identified the tumor as a low-grade papillary urothelial carcinoma with no involvement of the lamina propria or muscle layer (pTaN0M0G1) (Fig. 2). The patient underwent local epirubicin chemotherapy, and regular cystoscopic examinations showed no tumor recurrence. The patient was not a smoker or passive smoker and had no significant personal or family medical or surgical history. At the time of diagnosis, the patient had graduated from a 3-year course at the Dental Technical College and was a first-year student at the Faculty of Dental Medicine, both at the Iași University of Medicine and Pharmacy.

**Case 3**

A 24-year-old male patient from Botosani (Botoșani County, Romania) presented with painless macroscopic hematuria in January 2018. Urine analysis showed hematuria and negative culture; cytology was not performed. Clinical and imaging tests led to a diagnosis of bladder tumor, which was confirmed by cystoscopy, showing an 11-mm tumor with a papillary appearance on the right lateral wall. Following transurethral resection (single procedure), anatomopathological examination revealed papillary urothelial proliferation. The outcome was favorable, with no tumor recurrence identified during cystoscopic examinations. The patient was not a smoker or passive smoker and had no significant personal or family medical or surgical history. At the time of diagnosis, the patient had completed 2 years at the Dental Technical College and was a third-year student at the Faculty of Dental Medicine at the Iași University of Medicine and Pharmacy.
Discussion

Bladder cancer, the sixth most common cancer in men worldwide, has a peak incidence after the age of 65 years [3]. The literature is scarce on the incidence of bladder cancer in young populations, particularly in the 21–30-year age group. The Nordic Occupational Cancer (NOCCA) study reported a bladder cancer incidence of 0.02% in the 30–34-year age group, whereas the Canadian Census Health and Environment Cohort (CanCHEC) study reported an incidence of 4.8% in the 25–34-year age group. Both studies were conducted with large survey groups over long periods, with 73,635 patients in the Nordic study (between 1991 and 2005) and 8,170 patients in the Canadian study (between 1991 and 2010) [9]. The actual incidence is likely between two values (1–2.4%) and is probably more accurate for patients aged <40 years [3]. The study by Stanton et al. [3] included patients with a mean age of 23.5 years. However, patients younger than 20 years were also included, comprising 29% of cases. In the present study, the patients’ ages were 23, 22, and 24 years (mean, 23 years), which was consistent with the aforementioned studies. Although bladder cancer has been reported in young patients, this diagnosis should be highlighted so that bladder cancer will be considered a potential diagnosis for young patients presenting with painless macroscopic hematuria. Otherwise, there is a real risk of such cases being incorrectly diagnosed (most often a diagnosis of an infectious condition) and being prescribed unsuitable treatment, which, due to the natural evolution of tumors with macroscopic hematuria, could falsely appear to be effective, leading to a delay in the correct diagnosis and, more importantly, correct treatment [10]. Even if such diagnostic delays, which have been reported in numerous studies, appear not to negatively affect the prognosis in the vast majority of cases, a small percentage of these patients have invasive bladder cancer, the prognosis of which is poor, even following aggressive therapy [10, 11]. Considering this, the etiology of macroscopic hematuria needs to be reviewed in young patients, especially when they are or have been exposed to risk factors.

The relevant literature includes numerous studies and articles concerning urothelial tumor etiopathogenesis, which consistently confirm the presence of proven risk factors in 60–70% of bladder cancer cases, something rarely observed in the etiopathogenesis of tumors, which could, at least in theory, enable the development of efficient preventive measures [12]. Numerous risk factors have been linked to the development of bladder cancer, the most prominent of which are smoking (identified as a causal factor in 50% of cases) and chemical and infectious factors (schistosomiasis). The most prevalent chemical factors are aromatic amines (benzidine, 4-aminobiphenyl, 2-naphthylamine, and 4-chloro-o-toluidine), polycyclic aromatic hydrocarbons, and chlorinated hydrocarbons, identified as carcinogenic in 20% of cases [5]. All of these chemical substances have wide practical applications. Thus, numerous epidemiological studies have identified several professions linked to a high incidence of bladder cancer, with their number ranging from 42 (in the CanCHEC study) and 53 (in the NOCCA study) to 61 [4, 9]. Several of these studies have identified a higher incidence of bladder cancer among medical professionals, irrespective of the professional level and specialization [13–16]. The study by Malker et al. [17], who investigated the medical specializations that comprise risk factors, was one of the first to identify an etiological link between bladder cancer and dental technicians and dentists. The study reported that the bladder cancer incidence among dental technicians in Sweden more than doubled between 1961 and 1979 and increased by 50% among dentists. The latter discovery was deemed insignificant, however, given that the number of those cases remained low. The increased incidence of bladder cancer within these two professional groups could be due to population growth and thus the evolution of dental medicine procedures, particularly with regard to dental casks, bridgework, dentures, and all oral prosthetic devices that involve exposure to acrylics, dyes, and solvents. Leggat et al. [18] identified all occupational risk factors associated with modern
dentistry. However, the present case study focused on the toxic chemical substances contained in materials consistently used in the dental profession, including mercury, methyl methacrylate, and cyanoacrylate. The carcinogenic risk of each of these substances was determined by referring to the International Agency for Research on Cancer (IARC) [19]. Mercury, found in dental amalgam, is used increasingly less often, and its toxicity and carcinogenic risk are disputed [20]. Mercury has been classified, according to compound, into either IARC group 2B or group 3, as either a possible or an unclassifiable human carcinogen, respectively [20]. Methyl methacrylate, which is regularly employed in dental prosthetics, has been classified into IARC group 3 as an unclassifiable human carcinogen, whereas cyanoacrylate is not included in the IARC database at all. Given these classifications, it is unclear whether these substances are indeed risk factors for bladder cancer or whether other chemical substances that have yet to be identified as human carcinogens are involved. Another risk factor identified in the 3 patients of the present study could be laboratory fumes, mainly products of the combustion and pyrolysis of natural gas released and inhaled during the manipulation of prosthetic devices [21].

The present study estimated the period during which the 3 patients were expected to have been exposed to the aforementioned risk factors. The patient in case 1 was likely exposed to potential chemical risk factors for 42 months, 36 of which were spent as a student and 6 as a professional. The patient in case 2 was exposed for 38 months as a student, and the patient in case 3 was exposed for 51 months as a student. The mean time of exposure to dentistry materials and procedures among the 3 patients was 43.66 months, which is an estimated value. The actual time of exposure was shorter, given that during this period, the patients did not work a regular 8-h daily shift but rather undertook only laboratory work and practical assignments. The provided interval also included university term breaks. Bladder cancer frequently occurs in old age and is clearly associated with longer periods of exposure to the aforementioned carcinogenic risk factors [3], which was not the case for the 3 patients of the present study who nevertheless developed bladder tumors. Statistically, an etiopathogenic relationship between these 3 patients and the occupational risk factors is highly unlikely, and we should consider the present cases as belonging to an “at risk” category for developing bladder tumors. Although dental professionals fall into this category, other aspects should also be considered: the individual’s genetics, previous lifelong exposures, and increased frequency of performing imaging scans. Understanding the etiopathogenesis of bladder cancer in young people is therefore more challenging, particularly when no other carcinogenic factors are evident, and unknown factors or genetic mutations could have some role with idiopathic mechanisms.

Although the patients were from different geographical areas, they studied at the same college and university and were therefore subjected to similar levels of exposure. Furthermore, none of the 3 patients presented with any familial pathological malignancies, and only one had been a smoker, albeit a 1.5 pack-year smoker. Anatomopathological examinations revealed one case of benign lesions and 2 cases of low-potential malignant lesions, with the latter undergoing local chemotherapy following surgery. Their outcomes were favorable, and all cystoscopic examinations revealed no sign of tumor recurrence over a mean follow-up of 56 months.

The literature on this topic reveals no similar cases to the ones presented in this report at any other dental technical school in the world. In Romania, the curriculum is the same at all dental technical colleges and is approved by the Ministry of Education, in accordance with European regulations. Accordingly, we could not identify any specific aspect at this college, and these students’ cases were not analyzed by the institution’s administration. The association between bladder cancer and the risk factors of dental professionals is known. However, having the experience of just these 3 cases makes it impossible to determine a direct association between the educational exposure and these tumors. It would probably be more reasonable to consider that this was an entirely coincidental occurrence.
It is obvious that this case study cannot issue fundamental medical theories or principles, its purpose being only to present unconventional aspects of a well-known urological disease. The small number of cases with the same atypical presentation is the main shortcoming of this study. However, the communication of these cases brings up new information, which can alert practitioners and researchers in several fields (education, genetics, dentistry, and urology) and can be a starting point for further studies.

**Conclusion**

The aim of the present case study was to highlight known aspects of bladder cancer incidence and etiopathogenesis in young individuals and to emphasize other uncommon elements. We deemed it important to report the detection of bladder tumors in 3 young patients presenting with identical and rather unconventional etiopathogenetic conditions to demonstrate that the described occupational risk factors could also affect young patients, even over short periods of exposure. This shorter time of exposure to risk factors makes it even harder to establish causality with bladder tumors. However, the present cases could lead to a suspicion for a direct association or an entirely coincidental occurrence.

**Statement of Ethics**

Written informed consent was obtained from the patients for publication of this case report and any accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

**Funding Sources**

There is no funding received for this manuscript.

**Author Contributions**

Nicolaie Suditu directed patient “case 2” care and collected and analyzed the data. Irina Negru directed patient “case 1” care and collected and analyzed the data. Bogdan Novac made substantial contributions to conception and design. Nicolaie Suditu, Irina Negru, and Bogdan Novac edited the manuscript and approved the final version.

**Data Availability Statement**

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.
References

1. Cumberbatch MGK, Ibrahim Jubber I, Black PC, Esperto F, Figueroa JD, Kamat AM, et al. Epidemiology of bladder cancer: a systematic review and contemporary update of risk factors in 2018. *Eur Urol*. 2018;74(6):784–95.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394–424.
3. Stanton ML, Xiao L, Czerniak BA, Guo CC. Urothelial tumors of the urinary bladder in young patients: a Clinicopathological Study of 59 cases. *Arch Pathol Lab Med*. 2013;137(10):1337–41.
4. Cumberbatch MG, Cox A, Teare D, Catto JW. Contemporary occupational carcinogen exposure and bladder cancer: a systematic review and meta-analysis. *JAMA Oncol*. 2015;1(9):1282–90.
5. Burger M, Catto JW, Dalbagni G, Grossman HB, Herr K, Karakiewicz P, et al. Epidemiology and risk factors of urothelial bladder cancer. *Eur Urol*. 2013;63(2):234–41.
6. Rizzo A, Mollica V, Santoni M, Palmiotti G, Massari F. Pathologic complete response in urothelial carcinoma patients receiving neoadjuvant immune checkpoint inhibitors: a meta-analysis. *J Clin Med*. 2022;11(4):1038.
7. Mollica V, Rizzo A, Montironi R, Cheng L, Giunchi F, Schiavina R, et al. Current strategies and novel therapeutic approaches for metastatic urothelial carcinoma. *Cancer*. 2020;12(6):1449.
8. Rizzo A, Mollica V, Massari F. Expression of programmed cell death ligand 1 as a predictive biomarker in metastatic urothelial carcinoma patients treated with first-line immune checkpoint inhibitors versus chemotherapy: a systematic review and meta-analysis. *Eur Urol Focus*. 2022;8(1):152–9.
9. Hadkhale K, MacLeod J, Demers PA, Martinsen JI, Weiderpass E, Kjaerheim K, et al. Occupational variation in incidence of bladder cancer: a comparison of population-representative cohorts from Nordic countries and Canada. *BMJ Open*. 2017;7:e016538.
10. Paner GP, Zehnder P, Amin AM, Husain AN, Desai MM. Urothelial neoplasms of the urinary bladder occurring in young adult and pediatric patients: a comprehensive review of literature with implications for patient management. *Adv Anat Pathol*. 2011;18(1):79–89.
11. Compérat E, Larré S, Roupret M, Neuzillet Y, Pignot G, Quintens H, et al. Clinicopathological characteristics of urothelial bladder cancer in patients less than 40 years old. *Virchows Arch*. 2015;466(5):589–94.
12. Richters A, Aben KKH, Kimeney LALM. The global burden of urinary bladder cancer: an update. *World J Urol*. 2020;38(8):1895–904.
13. Pukkala E, Martinsen JI, Lyne E, Gunnarsdottir HK, Sparen P, Tryggvadottir L, et al. Occupation and cancer: follow-up of 15 million people in five Nordic countries. *Acta Oncol*. 2009;48(5):646–790.
14. Shaham J, Melzer A, Kaufman Z, Ribak J. [Occupation and bladder cancer]. *Harefuah*. 1996;131(10):382–456.
15. Ji J, Granström C, Hemminki K. Occupation and bladder cancer: a cohort study in Sweden. *Br J Cancer*. 2005;92(7):1276–8.
16. Cassidy A, Wang W, Wu X, Lin J. Risk of urinary bladder cancer: a case-control analysis of industry and occupation. *BMC Cancer*. 2009;9:443.
17. Malker HS, McLaughlin JK, Silverman DT, Ericsson JLE, Stone BJ, Weiner JA, et al. Occupational risks for bladder cancer among men in Sweden. *Cancer Res*. 1987;47:6763–6.
18. Leggat PA, Kedjarune U, Smith DR. Occupational health problems in modern dentistry: a review. *Ind Health*. 2007;45(5):611–21.
19. International Agency for Research on Cancer. *Agents classified by the IARC monographs, Volumes 1–125*. IARC monographs on the identification of carcinogenic hazards to humans. World Health Organization; 2021. [cited 2021 Jun 11]. Available from: https://monographs.iarc.who.int/agents-classified-by-the-iarc.
20. Rathore M, Singh A, Pant VA. The dental amalgam toxicity fear: a myth or actuality. *Toxicol Int*. 2012;19(2):81–8.
21. Chugh A. Occupational hazards in prosthetic dentistry. *Dentistry*. 2017;7(2):1–5.