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Abstract. It is estimated that >10,000 patients who undergo cystectomy for bladder cancer in the US each year receive a conventional ileal conduit and that >2,000 receive a continent urinary diversion. Case reports of primary intestinal adenocarcinomas in urinary conduits have been published recently, mainly in the urology literature. An epidemic of such cancers in this small, high-risk population seems to be emerging, particularly in conduits that utilize the colon. A case report and literature review was carried out. We describe a patient with a new primary adenocarcinoma arising in a colonic neobladder. We summarize prior literature describing intestinal adenocarcinomas that developed in an intestinal segment used for urinary diversion. Patients with urinary conduits of all types (particularly those utilizing colon rather than ileum) are at high risk of developing a second primary intestinal adenocarcinoma in the conduit. This population is likely to benefit from surveillance measures aimed at detecting such cancers. The primary form of therapy remains adequate surgical resection. General surgeons should be aware of such patients as they may be involved in the diagnosis of, and surgery for, the cancer in the conduit.

Introduction

In 2008, the World Health Organization projected that cancer would become the leading cause of death in the world (1). Carcinoma of the urinary bladder is the ninth most commonly diagnosed type of cancer in the world (2). Over 70,000 people in the US develop this cancer every year (3) and the incidence is projected to increase (4). Comparable data are reported from other wealthy nations (5). In the US and most other countries, tobacco abuse is the main known environmental risk factor for the development of bladder cancer (6-8). The incidence in smokers is estimated to be two to three times as great as the incidence in non-smokers. In countries where *S. haematobium* is endemic, bladder infestation is the leading cause (2). In river basins draining the Himalayas (e.g., India, Pakistan, Myanmar, Vietnam), the groundwater contains high concentrations of arsenic, which is a major cause of bladder carcinoma (9). Additional known etiologic agents include exposure to certain aromatic amines such as those found in dyes and rubber, the chemotherapeutic agent cyclophosphamide, ionizing radiation, and various textiles and metals (7,10,11).

Colorectal carcinoma is the third most commonly diagnosed type of cancer in the world (1). Over 150,000 people in the US develop cancer of the colon or rectum every year (12). Adenomas arising in subjects without known polyposis syndromes are the most common precursor lesion. Hamartomas are also well-described precursor lesions, as in Peutz-Jehgers syndrome. Other known causes of colorectal cancer include hereditary polyposis syndromes, Li-Fraumeni syndrome, inflammatory bowel disease, and ionizing radiation (13,14). Charred food and diets high in red meat and low in fiber, fruits and vegetables have been implicated as causative environmental agents (15-17). There is some evidence that a human colonic bacterium promotes colonic tumorigenesis (18). Tobacco abuse, including secondhand smoke exposure, is also associated with colorectal carcinoma development (19), and the relationship appears to be dose-dependent (20).

Over 6,000 new cases of small intestinal cancer are diagnosed in the US annually (12). These include carcinoid, adenocarcinoma, lymphoma, and sarcoma/gastrointestinal stromal tumor. Cancer of the small intestine accounts for about 1-2% of all gastrointestinal cancers. Predisposing causes include familial polyposis syndromes, Peutz-Jehgers syndrome, Crohn's disease, hereditary non-polyposis colon cancer syndromes, and cystic fibrosis (21). Because of the rarity of these cancers, the role of environmental agents such as tobacco-derived carcinogens has not been fully explored (22).

About 75% of bladder cancers are low-grade and non-muscle-invasive. They are usually managed by cystoscopic resection. Radical cystectomy is the mainstay of treatment for muscle-invasive carcinoma (though partial cystectomy is occasionally utilized). After radical cystectomy, some form of urinary diversion is required. Direct implantation of the ureters into non-isolated intestinal segments, particularly colon, was employed quite frequently after it was first described in 1852 by Simon (23). Feris and Odel reported that patients with a uretero-sigmoidostomy often had intractable hyperchloremic metabolic acidosis and other metabolic complications so this procedure is now used infrequently (23). Uterosigmoidostomy was also found to lead to adenocarcinoma of the colon adjacent

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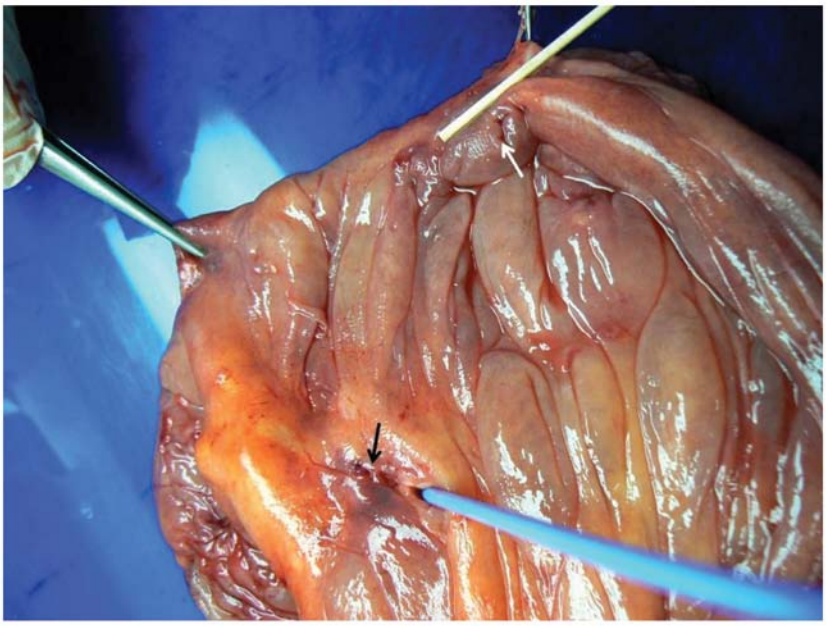

Figure 1. Photograph of the fresh specimen. The wooden pointer indicates the carcinoma (1 cm in diameter). It is adjacent to the lumen of the appendix (white arrow). There is a linear mucosal erosion (black arrow) caused by the blue ureteral stent.

to the location of ureteral implantation in an animal model (24). Austen and Kälble estimated that individuals between the ages of 25 and 30 with this form of diversion have a 477-fold increased lifetime risk of colon carcinoma and that patients between the ages of 55 and 60 years have an 8-fold increased lifetime risk (25).

Currently, urinary diversion into isolated bowel, typically ileum, is the most common method used after cystectomy (23,26). It was introduced by Bricker in the mid-twentieth century (27). Tizzoni and Foggi were the first to attempt creation of a neobladder in 1888 but the results were not satisfactory (23). During the 1970s, continent pouches were introduced again. In this procedure, a segment of bowel is isolated on a vascular pedicle, detubularized and reconfigured to create a spherical, low-pressure conduit. Ureters are implanted and the pouch is either connected to the native urethra (orthotopic neobladder) or a catheterizable stoma is created. Today, in young patients without major comorbid conditions, the orthotopic neobladder is the most commonly utilized form of urinary diversion and allows for a good quality of life (28,29).

The pattern of carcinogenesis in patients with urinary diversions that maintain separation of urine and feces is different than that of patients with ureterosigmoidostomies. Cancers occurring after uterosigmoidostomy are almost all colon adenocarcinomas; those in isolated intestinal segments used for urinary diversion are usually adenocarcinomas but sarcomas and transitional cell, squamous cell, and oat cell carcinomas also occur occasionally. The location of cancer developing in patients with ureterosigmoidostomy in practically always at the ureteroenteric anastomotic sites; those arising in isolated intestinal segments used for urinary diversion are located at the ureteroenteric anastomotic sites in ~58% of instances and elsewhere in the conduit in the remaining 42% (25).

Despite the risk of metabolic and other complications, the use of intestinal segments for urinary diversion is generally preferable to other options (cutaneous ureterostomy, percutaneous nephrostomy, or tissue-engineered bladder) (29). However, it is now also clear that patients with ileal conduits and continent diversions of various types (e.g., continent conduits and orthotopic neobladders) are at risk for second primary cancers. About 13,000 individuals receive a cystectomy for bladder carcinoma in the US each year, and~17% undergo continent diversion (28,29). Based on these statistics, we estimate that about 11,000 patients receive an ileal conduit and >2,000 receive a neobladder each year in the US. In the US, the colon is used for the neobladder in about half of those who receive continent diversion; the small intestine is used for the other half. Considering that the neobladder procedure has been regularly used for the past twenty years, perhaps 10,000 people in the US currently have a neobladder. The typical latency period for developing cancer in an intestinal segment used for urinary diversion is about two decades. Because the mean survival duration for patients who have received curative-intent treatment for bladder carcinoma continues to increase, the risk of developing cancer in a urinary conduit for each patient is also increasing. It seems likely that an epidemic of such cancers, particularly in those who continue to smoke, is emerging at present. We sought to alert general surgeons about this phenomenon as they are likely to be asked to provide surgical care for such patients more frequently in the future.

Materials and methods

We recently encountered a patient who developed a new primary adenocarcinoma in an orthotopic neobladder created at the time of radical cystectomy for transitional cell carcinoma of the bladder 22 years earlier. Two separate literature searches were performed using PubMed on January 17, 2010. To evaluate the prior literature on this topic, one search mimicked that used by Austen *et al* (25). The search criteria were 'urinary diversion' and

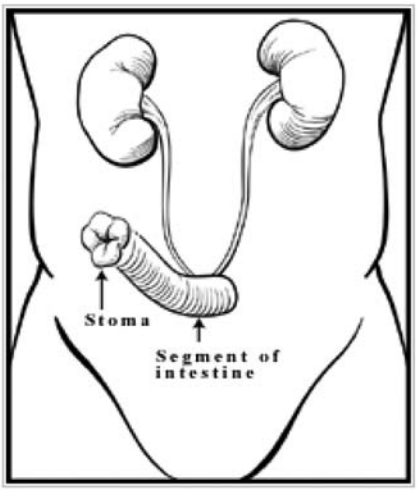

Figure 2. Conventional ileal diversion. A segment of the intestine directs urine through a stoma into an external collecting bag. Cleveland Clinic: Treatment and Procedures. Urinary Reconstruction and Diversion. http://my.clevelandclinic.org/services/urinary_reconstruction_and_diversion/hic_urinary_reconstruction_and_diversion.aspx

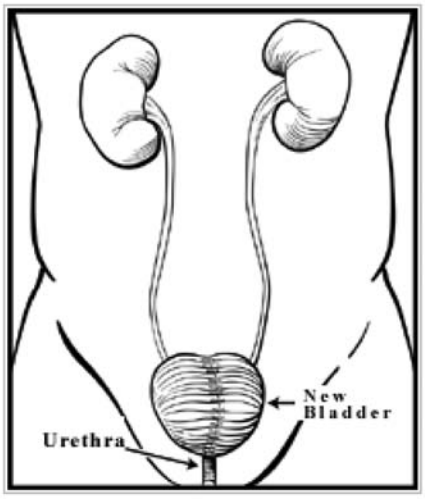

Figure 3. Neobladder. Intestine is made into a reservoir and connected to the urethra. Cleveland Clinic: Treatment and Procedures. Urinary Reconstruction and Diversion. http://my.clevelandclinic.org/services/urinary_reconstruction_and_diversion/hic_urinary_reconstruction_and_diversion.aspx

'carcinoma', using 'case reports' as a limitation. All languages were accepted. The second literature search, also using PubMed, was identical in all respects except that the search criteria were 'neobladder' and 'carcinoma' with 'case reports' as a limitation.

Results

Case report. In 1987, a 48-year-old male was diagnosed with muscle-invasive transitional cell carcinoma of the urinary bladder. He had smoked 1.5 packs of cigarettes per day for many years. He underwent a cystoprostatectomy and had an ileocolonic neobladder constructed to provide continent urinary diversion. He continued to smoke cigarettes and in 2008 he presented with symptomatic gallstone disease. Urology consultation was requested prior to cholecystectomy in order to determine whether further urologic procedures (revision of the neobladder, treatment of new primary urothelial tumors, etc.) might be indicated at the same operation. New-onset microscopic hematuria was detected and cystoscopy revealed two papillary tumors in the neobladder. One was invasive adenocarcinoma. Colonoscopy revealed no lesions in the colon remaining after the neobladder creation. He underwent open cholecystectomy, radical resection of the neobladder with regional lymphadenectomy, and implantation of ureters into a standard ileal conduit (Fig. 1). The operation was carried out by both surgeons and urologists. The prior radical cystectomy posed significant technical difficulties. Stents proved to be useful in avoiding damage to the ureters. Particular care was required to avoid injury to the obturator nerves, pelvic vessels, and the like, as much of the tissue overlying these structures had been resected at the time of the cystectomy. The pathology report indicated T1N0M0 colon adenocarcinoma. The second lesion seen at cystoscopy was an adenoma. The patient had no evidence of recurrence two years later.

There were 550 reports retrieved with our first computer-generated literature search. Sixty-six described cases of tumor development in patients with isolated intestinal urinary diversions created after cystectomy for bladder cancer (Fig. 2). There were 77 reports retrieved with the second search; 15 described cancers that developed in orthotopic neobladders (Fig. 3). Most were adenocarcinomas but transitional cell carcinoma, squamous cell carcinoma, small cell undifferentiated carcinoma, and mesenchymal cancers such as lymphomas and sarcomas were also reported.

Discussion

It has been known for several decades that aromatic amine exposure in an occupational setting and tobacco abuse account for the majority of cases of bladder cancer in most areas of the world (30). As the exposure to carcinogens arising from industrial sources has been decreasing in the US, the proportion of bladder cancers caused by tobacco abuse is increasing (31). Most experts conclude that the risk of cancer in isolated bowel segments used for urinary diversion after cystectomy is directly and causally related to the tobacco-derived urinary carcinogens bathing the epithelium, since most patients who abused tobacco before developing bladder carcinoma continue to smoke after cystectomy.

Since ureterosigmoidostomy is such a reliable model of colonic carcinogenesis, potential mechanisms have been investigated. One mechanism which could simultaneously explain tumor occurrence in both isolated and non-isolated gut segment urinary diversions involves inflammatory mediators (32). There are numerous reports implicating epidermal growth factor, various transforming growth factors and cytokines, and cyclo-oxygenase-2 in the process of carcinogenesis, particularly in chronically inflamed tissues such as these urinary conduits (25).

The causative role of tobacco abuse in carcinogenesis has been reviewed by Hecht (33). There are dozens of known carcinogens in cigarette smoke (34). They comprise various classes of agents and many are excreted in urine (35). Those agents believed to be most responsible for bladder carcinoma are 4-aminobiphenyl and other aromatic amines, although their relative potencies on a molar basis are not known. Whether tobacco-derived carcinogens are responsible for carcinoma of the small intestine is unknown at present since research on this topic is minimal (22). Hannan *et al* have provided a quantitative estimate of the risk of colorectal cancer in smokers (36). The relative importance of the various tobacco-derived carcinogens in carcinogenesis of the colon and rectum is uncertain. Many other ingested carcinogens derived from dietary sources are present in the colon. Resident bacterial, fungal, viral, and eukaryotic intestinal organisms, including protozoans (such as amoebas) and metazoans (such as tapeworms) produce an enormous number of metabolic products, most of which are not characterized. The causal relation between cigarette smoking and colorectal carcinogenesis has been well established recently (19,20). Tobacco-derived nitrosamines and heterocyclic amines are likely causative agents (33-39). The carcinogens responsible for carcinomas arising in intestinal segments used for urinary conduits are unknown but renal metabolism and urinary excretion of tobacco-derived chemicals is an important route of elimination of these substances. Because 4-aminobiphenyl and other small aromatic amines are present in urine and appear to be the dominant known chemicals responsible for bladder cancer in tobacco abusers, they may be presumed to cause cancer in intestinal urinary conduits as well.

According to the Centers for Disease Control and Prevention, approximately 45 million Americans smoke cigarettes and are unable to quit (40). A person who continues to smoke after resection of his/her bladder cancer is at risk of developing a primary adenocarcinoma in the diverted bowel segment. The long-term exposure of bowel mucosa to tobacco-derived and non-tobacco-derived fecal carcinogens prior to the cystectomy, followed by exposure to urine containing different carcinogens derived from cigarette smoke, in addition to the proinflammatory environment of the conduit, appears sufficient to explain the development of adenocarcinoma in patients with an orthotopic neobladder such as the patient described herein.

The risk of intestinal adenocarcinoma in a urinary conduit in patients with spina bifida or bladder exstrophy who receive a urinary diversion is appreciable (41). These patients presumably warrant periodic surveillance for this event, like patients after cystectomy for bladder carcinoma. The absolute risk of intestinal adenocarcinoma in a urinary conduit following cystectomy for bladder carcinoma is not known at present although there are many more such patients than spina bifida or bladder exstrophy patients. Sakano *et al* were apparently the first to report a patient who developed adenocarcinoma in an ileal conduit after cystectomy for bladder carcinoma (42). Albertini *et al* were apparently the first to describe an adenocarcinoma arising in the colonic mucosa of a continent urinary reservoir following cystectomy for bladder cancer (43). Reports have usually been in the urology literature and occasionally in gynecology (44) and general surgery (45) studies. The literature prior to 2004 has been summarized by Austen and Kälbe (25). Our literature search yielded four case reports of intestinal adenocarcinoma arising in a urinary conduit created from an isolated segment of intestine since 2004 (46-49). It seems likely that the overall incidence of such second cancers is increasing.

In conclusion, as the results of treatment for bladder cancer are steadily improving, long-term survivors may develop other disorders requiring abdominal surgery, as in the case reported here. A general surgeon contemplating an elective abdominal operation for any reason in a patient who has had a prior cystectomy for bladder carcinoma should be alert to the potential need for an additional procedure involving the urinary system. We believe that urological consultation and appropriate diagnostic tests should be obtained. Purely urological disorders (ureteroenteric stricture, stones, etc.) may be discovered and warrant treatment at the same time. If an intestinal adenocarcinoma is found in the urinary conduit, resection may be curative. Collaboration between the general surgeon and the urologist can yield good results, as we have demonstrated.

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