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REVIEW

- 243 Endoscopic ultrasound in oncology: An update of clinical applications in the gastrointestinal tract
Valero M, Robles-Medranda C

MINIREVIEWS

- 255 Endoscopic recommendations for colorectal cancer screening and surveillance in patients with inflammatory bowel disease: Review of general recommendations
Huguet JM, Suárez P, Ferrer-Barceló L, Ruiz L, Monzó A, Durá AB, Sempere J

ORIGINAL ARTICLE

Retrospective cohort study

- 263 Endoscopic resolution and recurrence of gastric antral vascular ectasia after serial treatment with argon plasma coagulation
Garg S, Aslam B, Nickl N

Observational Study

- 267 Utility of the balloon-overtube-assisted modified over-the-wire stenting technique to treat post-sleeve gastrectomy complications
Ponte A, Pinho R, Proença L, Silva J, Rodrigues J, Sousa M, Silva JC, Carvalho J

Randomized Controlled Trial

- 273 Multicenter randomised controlled trial comparing the high definition white light endoscopy and the bright narrow band imaging for colon polyps
Singh R, Cheong KL, Zorrón Cheng Tao Pu L, Mangira D, Koay DSC, Kee C, Ng SC, Rerknimitr R, Aniwaniwan S, Ang TL, Goh LK, Ho SH, Lau JYW

CASE REPORT

- 282 Bladder urothelial carcinoma extending to rectal mucosa and presenting with rectal bleeding
Aneese AM, Manuballa V, Amin M, Cappell MS

ABOUT COVER

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Bladder urothelial carcinoma extending to rectal mucosa and presenting with rectal bleeding

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Abstract

An 87-year-old-man with prostate-cancer-stage-T1c-Gleason-6 treated with radiotherapy in 1996, recurrent prostate cancer treated with leuprolide hormonal therapy in 2009, and bladder-urothelial-carcinoma *in situ* treated with Bacillus-Calmette-Guerin and adriamycin in 2010, presented in 2015 with painless, bright red blood per rectum coating stools daily for 5 mo. Rectal examination revealed bright red blood per rectum; and a hard, fixed, 2.5 cm × 2.5 cm mass at the normal prostate location. The hemoglobin was 7.6 g/dL (iron saturation = 8.4%,

indicating iron-deficiency-anemia). Abdominopelvic-CT-angiography revealed focal wall thickening at the bladder neck; a mass containing an air cavity replacing the normal prostate; and adjacent rectal invasion. Colonoscopy demonstrated an ulcerated, oozing, multinodular, friable, 2.5 cm × 2.5 cm mass in anterior rectal wall, at the usual prostate location. Histologic and immunohistochemical analysis of colonoscopic biopsies of the mass revealed poorly-differentiated-carcinoma of urothelial origin. At visceral angiography, the right-superior-rectal-artery was embolized to achieve hemostasis. The patient subsequently developed multiple new metastases and expired 13 mo post-embolization. Comprehensive literature review revealed 16 previously reported cases of rectal involvement from bladder urothelial carcinoma, including 11 cases from direct extension and 5 cases from metastases. Patient age averaged 63.7 ± 9.6 years (all patients male). Rectal involvement was diagnosed on average 13.5 ± 11.8 mo after initial diagnosis of bladder urothelial carcinoma. Symptoms included constipation/gastrointestinal obstruction-6, weight loss-5, diarrhea-3, anorexia-3, pencil thin stools-3, tenesmus-2, anorectal pain-2, and other-5. Rectal examination in 9 patients revealed annular rectal constriction-6, and rectal mass-3. The current patient had the novel presentation of daily bright red blood per rectum coating the stools simulating hemorrhoidal bleeding; the novel mechanism of direct bladder urothelial carcinoma extension into rectal mucosa *via* the prostate; and the novel aforementioned colonoscopic findings underlying the clinical presentation.

Key words: Bladder cancer; Urothelial; Uroepitheal; Transitional cell; Rectum penetration; Cancer spread; Lower gastrointestinal bleeding; Colonoscopy

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Core tip: Comprehensive literature review revealed 16 reported cases of bladder-urothelial-carcinoma involving rectum. None of these cases presented with daily rectal bleeding. Among 11 cases with direct extension, none had pathologically-proven rectal mucosal involvement. A case is reported of recurrent bladder-urothelial-carcinoma presenting with daily bright red blood per rectum coating stools from bladder-urothelial-carcinoma involving rectal mucosa. A hemorrhagic, multinodular, rectal mass, identified by colonoscopy, from direct extension of Bladder-Urothelial-Carcinoma *via* prostate to rectal mucosa underlies the presentation with daily bright red blood per rectum. This report shows that bladder-urothelial-carcinoma can cause rectal bleeding by directly extending to rectal mucosa.

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INTRODUCTION

Bladder urothelial carcinoma rarely spreads to the gastrointestinal (GI) tract, with comprehensive literature review revealing only 33 previously reported cases; even more rarely surrounds or extends into the rectum with only 16 previously reported cases; and has not been previously reported to appear at colonoscopy as a rectal mucosal nodular mass from direct cancer extension from the bladder *via* the prostate (3 prior patients had rectal mucosal metastases without direct extension) (Tables 1-3)^[1-21]. A novel case is reported in which bladder urothelial carcinoma directly extended to rectal mucosa, *via* the prostate; mimicked hemorrhoidal bleeding in presenting with chronic, daily, painless, bright red blood per rectum coating the stools; and demonstrated novel, colonoscopic findings underlying the clinical presentation.

The literature was systematically reviewed using PubMed with the following medical subject heading (MeSH) or keywords: {"rectum" or "rectal" or "sigmoid" or "descending colon" or "transverse colon" or "ascending colon" or "cecum" or "large intestine" or "large bowel" or "colon" or "duodenum" or "jejunum" or "ileum" or "jejunoileum" or "small intestine" or "small bowel" or "stomach" or "gastric" or "esophageal" or "esophagus"} and {"bladder cancer" or "bladder carcinoma" or "urothelial carcinoma" or "transitional cell carcinoma"}. Two authors independently reviewed the literature, and decided by consensus which articles to incorporate in this study. Patients with bladder adenocarcinoma; renal cell carcinoma, even with bladder involvement; or urothelial (transitional cell) carcinoma solely extrinsic to the bladder were excluded. One article written in French was professionally translated^[15]. Data about 2 cases in one article, written in Japanese, were obtained from the abstract written in English^[20]. Data regarding 4 cases were derived from a table present in one reference^[20]. This case report received exemption/approval by the IRB at William Beaumont Hospital, Royal Oak, on August 27, 2015. Informed consent for publication was unobtainable from the patient because he had expired prior to writing this case report.

CASE REPORT

An 87-year-old, severely debilitated man with a 20-year-long oncologic history presented in 2015 with daily, painless, bright red blood per rectum coating the stool for five months. He had been treated in 1996 for prostate adenocarcinoma stage-T1c-Gleason-6 with external beam radiotherapy; retreated in 2009 for recurrent prostate adenocarcinoma with leuprolide hormonal therapy every 3 mo; and treated in 2010 for bladder urothelial carcinoma *in situ* stage-TCC-Ta-G1-2

Table 1 Direct extension of bladder urothelial carcinoma to rectum

Patient No., age and sex	Prior oncologic history	Clinical presentation with GI involvement	Radiologic imaging subsequent endoscopy/surgery	Metastatic location: Pathologic diagnosis	Treatment	Outcome	Ref.
1. 87-year-old man	Nineteen years PTA underwent external beam radiotherapy and leuprolide hormonal therapy for prostate cancer stage T1c Gleason 6. Five years PTA underwent Bacillus Calmette-Guérin immunotherapy and adriamycin chemotherapy for bladder urothelial carcinoma <i>in situ</i> stage Ta G1-2	Painless, bright red blood coating stools for 5 mo. Rectal exam: Bright red blood per rectum and large, hard, fixed, multinodular, "prostate" mass. Hemoglobin = 7.6 g/dL	CT angiography: Mass containing air-fluid cavity replacing prostate, with rectal invasion. Colonoscopy: Ulcerated, friable, oozing, multinodular, hemorrhagic, 2.5 cm × 2.5 cm mass on anterior rectal wall, just proximal to dentate line	Rectum: Poorly differentiated carcinoma of urothelial origin	Abdominopelvic angiography: Successful right-superior-rectal-artery embolization using embolospheres	Stopped bleeding for 3 mo. Subsequently rebled. Underwent palliative colostomy for the rebleeding. Died 13 mo after diagnosis of rectal lesion	Current report
2. 64-year-old man	Sixteen month PTA, underwent radical cystectomy, left nephroureterectomy, and right ureterocutaneostomy for Grade 3 urothelial carcinoma Stage pT3aN0. 11 mo PTA, received 3 courses of MVAC chemotherapy for lymph node metastases	Anorexia, tenesmus	Abdominopelvic CT: Focal, annular thickening of rectal wall	Rectum: Urothelial carcinoma	Fecal diversion	Died 2 mo later	Katayama <i>et al</i> ^[1]
3. 60-year-old man	Prior high grade bladder urothelial carcinoma	Anal pain, fatigue, weight loss, and anorexia. Rectal exam: Hard, fixed, annular, constrictive mass, 6 cm from anal verge. Hemoglobin = 11.6 g/dL	Pelvic CT: Mass posterior to bladder. Perirectal wall thickening	Rectum: Grade 4 urothelial carcinoma	Chemotherapy with VP-16 and cisplatin in 3 mo cycles and external beam RT	Died 9 mo after initiating RT	Stillwell <i>et al</i> ^[2]
4. 58-year-old man	Two year PTA underwent partial cystectomy for grade 3 N0 bladder urothelial carcinoma	Anorexia, weight loss, fatigue, straining with bowel movements, narrow-caliber stools, rectal pain, and tenesmus for several months. Rectal exam: hard, annular, constricting lesion with a narrowed lumen, at 8 cm from anal verge	Pelvic CT: Large mass encircling rectum, lytic lesion in third lumbar vertebra, and bilateral hydronephrosis. Proctoscopy: Constricting lesion with normal overlying mucosa, suggestive of extrinsic compression. Exploratory laparotomy: Hard mass extending from posterior bladder wall, obliterating rectovesical pouch, and encompassing rectum	Rectum: Biopsy during proctoscopy showed normal mucosal tissue. Transrectal (deep) and transperineal biopsy: Poorly differentiated grade 3 urothelial cancer	Sigmoid loop colostomy, RT to pelvis and lumbar spine, followed by single dose of cisplatin	Died 3 mo later from liver metastasis	Stillwell <i>et al</i> ^[2]
5. 73-year-old man	Three years PTA underwent radical cystoprostatectomy, with clear margins, and ileal loop urinary diversion for Stage pT3a N0 bladder urothelial carcinoma. At that time, biopsy also demonstrated areas of adenocarcinoma and signet ring cell carcinoma	Diarrhea, rectal pain, fatigue, weight loss, and fecal incontinence for 1 mo. Physical exam: Thin elderly male, bilateral lower extremity edema. Rectal exam: rectal stenosis 1 cm from anal verge. Guaiaac negative stool	Abdominopelvic CT: annular rectal mass. Exploratory laparoscopy: Solid pelvic tumor adherent to sacrum	Rectum: Urothelial cancer invading muscularis propria of rectal wall	Diverting loop colostomy	Chemotherapy planned, but patient developed lower extremity ischemia, requiring leg amputation. Died shortly thereafter	Langenstroer <i>et al</i> ^[3]

6. 76-year-old man	Underwent left nephroureter-ectomy. 1 mo PTA underwent right ureteral diverting cutaneostomy for grade 3 bladder urothelial carcinoma. Bladder mass firmly attached to pelvic wall and to thickened lateral pedicles	Symptoms of rectal obstruction. Rectal exam: Stenosis with intact rectal mucosa	Pelvic CT: Annular thickening of rectal wall and thickened lateral pedicles, bilaterally	Rectum: Urothelial carcinoma	Diverting colostomy and unspecified immunotherapy	Died 5 mo later	Kobayashi <i>et al</i> ^[4]
7. 66-year-old man	No prior oncologic history	Rectal exam: Severe rectal stenosis with intact rectal mucosa	Abdominopelvic CT: Thickened bladder and rectal walls, bilateral hydronephrosis. Colonoscopy: Narrow rectal lumen with edematous mucosa, suggesting extrinsic compression	Rectum: Grade 3 urothelial carcinoma	Ileal-conduit and colostomy	Died 3 mo after surgery	Kobayashi <i>et al</i> ^[4]
8. 51-year-old man	1 mo PTA underwent ureterocutaneostomy for unresectable grade 3 bladder urothelial carcinoma attached to pelvic wall, causing bilateral hydronephrosis	Thin stools. Rectal exam: Narrow rectal lumen	Pelvic CT: Annular constriction of rectum	Rectum: Grade 3 urothelial carcinoma	Diverting colostomy and one course of M-VAC chemotherapy	Died 10 mo after surgery	Kobayashi <i>et al</i> ^[4]
9. 74-year-old man	Eleven months PTA underwent radical cystectomy for grade 3 urothelial carcinoma of bladder	Continuous watery rectal discharge and thin stools	Barium enema: Stenosis of lower rectum Pelvic MRI: Thickened rectal mucosa and muscle layer without evident tumor	Rectum: Grade 3 pT3a urothelial carcinoma	Colostomy, MVAC chemotherapy, and radiation	Died 7 mo after presentation	Ito <i>et al</i> ^[5]
10. 54-year-old man	Underwent radical cystoprostatectomy with neobladder for grade 3 bladder urothelial carcinoma	Presumed refractory ulcerative proctitis	Pelvic MRI: Circumferential thickening of rectum. Endoscopy: Circumferential rectal wall thickening 11 cm from anal verge. EUS: Circumferential hypoechoic infiltrate extending through all rectal wall layers	Rectum: Urothelial carcinoma	Chemotherapy	NR	Gleeson <i>et al</i> ^[6]
11. 55-year-old man	Underwent radical cystoprostatectomy with neobladder for grade 3 bladder urothelial carcinoma	Constipation	Abdominopelvic CT: No evident metastasis Endoscopy: Circumferential rectal wall thickening with stricture 16 cm from anal sphincter EUS: Diffuse circumferential thickening of rectal wall	Rectum: Urothelial carcinoma	Chemotherapy	NR	Gleeson <i>et al</i> ^[6]
12. 60-year-old man	Underwent radical cystoprostatectomy with neobladder, for grade 3 urothelial cancer of bladder	Constipation	Abdominopelvic CT: Abnormal perirectal lymph nodes. Endoscopy: Circumferential rectal wall thickening. EUS: Diffuse circumferential thickening of all layers of rectal wall with several hypoechoic lymph nodes in extraluminal space	Rectum: Urothelial carcinoma	Chemotherapy	NR	Gleeson <i>et al</i> ^[6]

CT: Computed tomography; GI: Gastrointestinal; M-VAC: Methotrexate, vinblastine, Adriamycin; NR: Not reported; PTA: Prior to admission; RT: Radiation therapy; MRI: Magnetic resonance imaging.

Table 2 Metastases of urothelial bladder carcinoma to the colorectum

Patient age, sex	Prior oncologic history	Clinical presentation with GI involvement	Radiologic imaging, endoscopy, surgery	Metastasis location: Pathologic diagnosis	Treatment	Outcome	Ref.
1. 63-year-old man	Ten months PTA underwent radical cystectomy and MVAC chemotherapy for bladder urothelial carcinoma	Painless jaundice, 5-kg weight loss, and constipation for 2 wk. Physical exam: mild right upper quadrant tenderness. Laboratory: Elevated liver function tests	Abdominopelvic CT: Concentric thickening of rectal wall; bile duct hilar stricture with diffuse intrahepatic ductal dilation. MRI: Diffusely thickened common hepatic duct with extension into secondary branch ducts suspicious for cholangiocarcinoma. Colonoscopy: Concentric rectal constriction blocking colonoscopic intubation. ERCP: Strictures of common hepatic and right intrahepatic ducts; obstructed left intrahepatic duct	Rectum and hepatic duct: Micropapillary variant of transitional cell (urothelial) carcinoma	Rectal tumor: RT with external beam and brachytherapy. Hepatic tumor: Polyethylene stent placed in intrahepatic bile duct. RT is planned	Alive at 4 mo	Hong <i>et al</i> ^[7]
2. 55-year-old man	Fifteen months PTA underwent TURBT and 6 wk of mitomycin C, followed by 4 rounds of gemcitabine and cisplatin chemotherapy for high grade urothelial carcinoma of bladder with iliac lymph node chain involvement. Six months PTA underwent radical cystoprostatectomy with neobladder creation and pelvic lymphadenectomy	Worsening constipation, abdominal distention, anorexia, and dyschezia. Rectal exam: palpable mass 3 cm from anal verge	Abdominopelvic CT: Pelvic and omental nodules. PET: Increased uptake at these nodules. Flexible sigmoidoscopy: 3 cm wide rectal lesion near anal verge	Rectum, omentum, other pelvic structures: Urothelial carcinoma	Diverting loop colostomy	Brain and lung metastases	Asfour <i>et al</i> ^[8]
3. 77-year-old man	Eleven years PTA underwent resection of papillary bladder urothelial carcinoma. Eight years PTA underwent TURBT and RT for recurrence. Underwent periodic cystoscopies and bladder biopsies thereafter	Progressive constipation, weight loss, and malaise	Barium enema: barium could not pass beyond sigmoid colon. Laparotomy: Sigmoid colon obstructed due to adherent tumor of terminal ileum and cecum	Sigmoid, right-transverse colon, cecum, ileum, appendix, omentum: Urothelial carcinoma	Ileotransverse colostomy and loop colostomy of descending colon	NR	Aigen <i>et al</i> ^[9]
4. 60-year-old man	Five months PTA underwent radical cystectomy with ileal conduit for invasive bladder urothelial carcinoma	Painless hematochezia. Rectal exam: Red blood in rectal vault. No externally visible or palpable hemorrhoids. Hemoglobin declined from 11.6 g/dL to 8.7 g/dL	Necrotic pelvic lesions suspicious for metastases vs abscess. Colonoscopy: Irregular, friable, partially obstructing mass at splenic flexure	Splenic flexure: Urothelial carcinoma	None	Refused treatment. Transferred to hospice	Kumar <i>et al</i> ^[10]

5. 57-year-old man	Five years PTA underwent total cystectomy for bladder urothelial carcinoma. One year PTA underwent lymph node resection, RFA, bone cement injection, and chemotherapy for left obturator lymph node and several pulmonary and left pelvic bone metastasis. Five months PTA underwent RT for regrowth of left obturator lymph node metastasis	Massive melena, HR = 120 beats/min, BP = 76/39 mmHg, Hemoglobin = 9.2 g/dL	Abdominopelvic CT: Malignant lymph node invading sigmoid colon, with pseudoaneurysm of mesenteric artery supplying sigmoid Colonoscopy: Large, oozing, ulcerated colonic tumor	Sigmoid colon: NA	Pelvic angiogram: 10 mm × 8 mm pseudoaneurysm of left inferior gluteal artery successfully embolized using microcoils and vasopressin	Alive at 5 mo	Kakizawa <i>et al</i> ^[11]
6. 83-year-old man	No prior oncologic history	Diarrhea and weight loss during prior 6 mo. Rectal exam: Mass 3 cm from anal verge	Abdominopelvic CT: Thickened right posterior wall of bladder, circumferential rectal wall thickening, and infiltrative lesions in multiple skeletal muscles Proctoscopy: Mass 3 cm from rectal verge	Rectum and skeletal muscles: Poorly differentiated urothelial carcinoma	Chemotherapy (regimen not specified)	NR	Ying-Yue <i>et al</i> ^[12]
7. 54-year-old man	Two years PTA underwent radical cystectomy and ileal neobladder reconstruction for grade 3 bladder urothelial carcinoma	Change in bowel habits	Abdominopelvic MRI: Circumferential thickening and high-grade stenosis of rectal wall. Sigmoidoscopy: Luminal narrowing with erythematous and edematous folds. EUS: Hypoechoic, circumferential, rectal wall thickening, mimicking primary rectal cancer. No evident direct cancer extension from bladder	Rectum: Urothelial carcinoma	Chemotherapy (regimen not specified)	NR	Yusuf <i>et al</i> ^[13]
8. 73-year old man	Two years PTA underwent resection of grade 2 bladder urothelial carcinoma	Severe constipation	Sigmoidoscopy: Friable, erythematous, and thickened distal rectal wall, with nearly obstructed lumen. EUS: Hypoechoic, symmetric, circumferential wall thickening, with loss of deep wall layers, and pseudopodia-like extensions into perirectal tissues. No evident direct tumor extension from bladder	Rectum: Poorly differentiated urothelial carcinoma	Total pelvic exenteration and chemotherapy (regimen not specified)	NR	Yusuf <i>et al</i> ^[13]

9. 67-year-old man	Eighteen months PTA underwent transurethral excisional biopsy of bladder cancer. Ten months PTA underwent partial cystectomy, chemotherapy with gemcitabine, and RT. 1 mo PTA, nephrostomy tubes inserted for bilateral hydronephrosis	Massive rectal bleeding and altered mental status for one day. HR = 106 beats/min, BP = 65 mmHg/palpable. Rectal exam: Rectal mass and large amount of bright red blood and clots. Hemoglobin = 8.0 g/dL	Selective angiography of celiac trunk, superior mesenteric artery and inferior mesenteric artery: No bleeding source identified. Colonoscopy: Large amount of bright red blood in colon. Emergency laparotomy: Indurated, fixed, mass involving cecum, right lower retroperitoneum, and right pelvic side wall. Dilated colon. Active bleeding from fistula between iliac artery and cecum	Cecum: Urothelial carcinoma	Resection of cecum and terminal ileum, ligation of right external iliac artery, end-ileostomy	Alive at 6 mo	Chin <i>et al</i> ^[14]
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BP: Blood pressure; CT: Computed tomography; ERCP: Endoscopic retrograde cholangiopancreatography; GI: Gastrointestinal; HR: Heart rate; M-VAC: Methotrexate, vinblastine, Adriamycin; NR: Not reported; PET: Positive electron tomography; PTA: Prior to admission; RFA: Radiofrequency ablation; RT: Radiation therapy; TURBT: Transurethral resection of bladder tumor; EUS: Endoscopic ultrasound; NA: Not available.

Table 3 Metastases of urothelial bladder carcinoma to the esophagus, stomach, and small intestine

Patient age and sex	Prior oncologic history	Clinical presentation with GI involvement	Radiologic imaging, endoscopy, surgery	Metastasis location: Pathologic diagnosis	Treatment	Outcome	Ref.
1. 55-year-old man	1 mo PTA underwent total cystoprostatectomy, bilateral ilio-obturator lymphadenectomy, and bladder reconstruction for bladder urothelial carcinoma pT3-GIII, N0	Hematemesis 8 d after surgery	Chest and abdominopelvic CT: Esophageal mass. EGD: 2-cm-wide mass in proximal esophagus. EUS: No lymphadenopathy	Esophagus: Urothelial carcinoma infiltrating submucosa	Chemotherapy with M-VAC, and RT of metastasis	Developed radiation pericarditis but recovered. Alive at 2 yr	Jung <i>et al</i> ^[15]
2. 66-year-old man	No prior oncologic history	Dysphagia, anorexia, weight loss, headaches, and lightheadedness for 6 wk. Palpable, tender, 2 cm mass on left neck	Neck and thoracic CT: 3 cm × 2 cm soft tissue mass with dilation and thickening of proximal esophagus. EGD: Focal stricture at 25 cm from incisors with a 2 cm × 1 cm ulcer with irregular margins	Esophagus: Poorly differentiated urothelial carcinoma	None	Died 10 d after discharge from hospital	Dy <i>et al</i> ^[16]
3. 80-year-old man	Four years PTA underwent RT and chemotherapy (after declining radical cystectomy) for bladder urothelial carcinoma. Three years PTA underwent lung lobe wedge resection for solitary lung metastasis. 1 mo PTA had a normal EGD and colonoscopy in evaluation of anemia	Malaise, dizziness, dyspnea, melena. Rectal exam: Positive occult blood in stool. Hemoglobin = 5.4 g/dL	Small bowel enteroscopy: 3 cm, ulcerated, infiltrating tumor in distal duodenum. Tumor has an adherent, friable, clot	Duodenum: High-grade urothelial carcinoma	Duodenectomy and duodenomy jejunostomy	PET scan 2 mo later: Metastases to liver and lungs. Patient expired soon thereafter from cardiac arrhythmia	Girotra <i>et al</i> ^[17]

4. 62-year-old man	Two years PTA underwent partial cystectomy with lymph node dissection and adjuvant chemotherapy for stage IIIb bladder urothelial carcinoma	Hematemesis, hemoglobin = 7.0 g/dL	EGD: Large bleeding mass in descending duodenum. Treated with proton pump inhibitor therapy. Repeat EGD 4 d later: large partly obstructing, 7-cm-long mass in descending duodenum	Duodenum: Poorly differentiated urothelial carcinoma	Palliative radiation	Died 6 wk later	Chan <i>et al</i> ^[18]
5. 74-year-old man	Four years PTA underwent exploratory laparotomy which demonstrated nodal metastasis. Completed preoperative chemotherapy, but declined surgical resection	Abdominal pain, bloating, distention, nausea, and vomiting	Serial pelvic CT (to monitor cancer progression): Stable bladder wall thickening Small bowel barium contrast radiography: Narrowing of third portion of duodenum Gastroscopy: Fluid-filled, dilated, stomach without obstruction. EGD: Luminal narrowing with overlying normal mucosa in third portion of duodenum. EUS: Circumferential wall thickening	Duodenum: urothelial carcinoma	Enteral stent and palliative chemotherapy	Died 9 mo later	Yusuf <i>et al</i> ^[13]
6. 42-year-old woman	No prior oncologic history	Nausea, vomiting, abdominal discomfort, and 6-kg weight loss for 2 mo	Barium meal: Abrupt stricture at junction between second and third portion of duodenum. Abdominopelvic CT: Infiltrative soft tissue mass around duodenum, calcified bladder wall. No pelvic lymphadenopathy. EGD: Gastric outlet obstruction with distorted and erythematous duodenum without ulceration, or mucosal tumor	Duodenum: Micropapillary variant of poorly differentiated urothelial carcinoma	Duodenal stent and RT to periduodenal lesion. Administered palliative gemcitabine and carboplatin	Died 15 mo after diagnosis	Hawtin <i>et al</i> ^[19]
7. 87-year-old man	Sixteen months PTA underwent TURBT for grade 3, pT2bN0M0, bladder urothelial carcinoma	Ileus	Abdominopelvic CT: Pneumoperitoneum due to GI perforation Laparotomy: Elastic hard tumor at site of ileal perforation	Ileum: Metastatic urothelial carcinoma	Partial resection of ileum	NA	Hoshi <i>et al</i> ^[20] (in Japanese)
8. 53-year-old man	No prior oncologic history	Gross hematuria	Abdominopelvic CT: Bladder tumor invading prostate. Cystoscopy: Non-papillary, broad based, tumor in right wall of bladder	Ileum and prostate: Urothelial carcinoma pT4aN1M0	Total cystectomy and creation of ileal conduit. Neoadjuvant chemotherapy	NA	Hoshi <i>et al</i> ^[20] (article in Japanese)
9. 56-year-old man	Fifty-nine months PTA underwent TURBT for bladder urothelial carcinoma	Abdominal pain and GI perforation	NA	Small intestine, lymph nodes, lung, and liver: Urothelial carcinoma	NA	NA	Hoshi <i>et al</i> ^[20] (Case from table 2)

10. 63-year-old woman	Seven months PTA underwent total cystectomy for pT3b bladder urothelial carcinoma	Abdominal pain	NR	Small intestine: Urothelial carcinoma	NR	NR	Hoshi <i>et al</i> ^[20] (Case from table 2)
11. 46-year-old man	Thirty-eight months PTA underwent RT and chemotherapy for pT3b bladder urothelial carcinoma	Ileus	NR	Small intestine: Urothelial carcinoma	NR	NR	Hoshi <i>et al</i> ^[20] (Case from table 2)
12. 71-year-old man	Thirty-six months PTA underwent total cystectomy for bladder urothelial carcinoma	Melena and anemia	NR	Small intestine: Urothelial carcinoma	NR	NR	Hoshi <i>et al</i> ^[20] (Case from table 2)
13. 55-year-old man	Seven years PTA underwent total cystectomy, pelvic lymphadenectomy, and neobladder reconstruction. Underwent two cycles of adjuvant chemotherapy for pT3apN0 G2 bladder urothelial carcinoma	Massive melena, HR = 120 beats/min, BP = 72/36 mmHg. Hemoglobin = 7.9 g/dL	Abdominopelvic CT: Right hydronephrosis from external iliac lymph node metastasis invading ileum. Angiography: Right external iliac artery successfully embolized using microcoils and n-butyl cyanoacrylate. Then developed ischemic colitis, treated with iliac artery bypass grafting, and right common and internal iliac artery embolization	Ileum: NR	Three cycles of unspecified chemotherapy	Died 4 mo after embolization	Honda <i>et al</i> ^[21]

BC: Bladder cancer; BP: Blood pressure; CT: Computed tomography; EGD: Esophagogastroduodenoscopy; GI: Gastrointestinal, HR: Heart rate; M-VAC: Methotrexate, vinblastine, Adriamycin; NR: Not reported; PTA: Prior to admission; RT: Radiation therapy; TURBT: Transurethral resection of bladder tumor; EUS: Endoscopic ultrasound.

with bacillus-Calmette-Guerin and adriamycin. In 2014 the patient underwent suprapubic catheter placement for severe urinary frequency, urinary incontinence, recurrent urethral stricture, and hematuria. Four months prior to admission the patient underwent cystoscopy for refractory, severe hematuria, which demonstrated a small, contracted bladder, chronic urethral stricture, and friable, hemorrhagic tissue at the bladder neck felt most likely secondary to recurrent (invasive) urothelial carcinoma, but radiation cystitis could not be excluded. The hemorrhagic area was treated with electrocautery during cystoscopy, and by continuous bladder irrigation administered for 24 h. No biopsies were obtained during cystoscopy because the patient refused aggressive therapy of chemotherapy or surgery based on his old age, severe chronic debilitation, and multiple prior cancers.

Physical examination revealed normal vital signs; a soft, nontender, abdomen; and no palpable abdominal mass. Rectal examination revealed a hard, fixed, multinodular, 2.5 cm × 2.5 cm mass, at the normal prostate location; gross bright red blood on the examining finger; and no visible or palpable hemor-

roids. The hemoglobin = 7.6 gm/dL, with iron deficiency anemia (iron = 26 mcg/dL, total iron binding capacity = 301 mcg/dL, iron-saturation = 8.4%). Hemoglobin increased to 9.7 gm/dL after transfusing 2 units of packed erythrocytes. The prostate specific antigen (PSA) = 43.3 ng/mL (normal < 2.5 ng/mL). Urinalysis revealed significant hematuria, trace proteinuria, nitrite positivity, and bacteriuria with 26-50 leukocytes/high power field (hpf). There were 10000-50000 colony forming units/mL of *Enterobacter cloacae* isolated from a urine culture. The patient was administered ceftriaxone 1 g/24 h for the bacteriuria.

Abdominopelvic CT angiography revealed focal thickening of the bladder wall at its neck; a mass containing an air cavity replacing most of the prostate; and adjacent rectal invasion (Figure 1). Colonoscopy, with rectal retroflexion, demonstrated an ulcerated, friable, multinodular, 2.5 cm × 2.5 cm mass in the anterior rectal wall, just proximal to the dentate line, at the usual prostate location (Figure 2), no internal hemorrhoids, and no mucosal telangiectasia or other signs of radiation proctitis despite prior prostate radiotherapy. Histologic examination of rectal mucosal



Figure 1 Abdominopelvic computed tomography angiography demonstrating thickened bladder wall (red arrowhead), with adjacent prostate margin (dashed arrow). Air-filled cavity within the prostate gland (white arrowhead), is consistent with the known bladder urothelial carcinoma penetrating, via the prostate, into the rectum (horizontal solid arrows). The colonoscopic findings (Figure 2) strongly support this mechanism of cancer spread.

biopsies revealed poorly differentiated carcinoma (Figure 3A). Immunohistochemical analysis demonstrated the tumor cells stained positively with cytokeratin 20, indicating either a colonic or bladder (urothelial) primary (Figure 3B). Additional diffuse positivity for cytokeratin 7, 34bE12, and GATA-3 (Figure 3B); and focal positivity for CK5/6 strongly supported urothelial origin. Negative immunohistochemical staining for CDX2 (Caudal Type Homeobox 2) confirmed that this tumor did not arise from colonic adenocarcinoma (Figure 3C). The diffuse positivity for cytokeratin 20 and only focal positivity for CK5/6 (< 20% of cells positive) excluded anorectal squamous carcinoma. Immunohistochemical markers for prostate carcinoma, including PSA, PAP and P501S, were all negative. The history of non-invasive urothelial carcinoma in bladder biopsies in 2010, further supported the link between the cancers located in the bladder and rectum. The pathologic diagnosis was therefore poorly-differentiated carcinoma of urothelial origin.

At visceral angiography, the right-superior-rectal-artery was successfully embolized using 900-1200-micron embolospheres to achieve rectal hemostasis. However, the patient experienced recurrent rectal bleeding three months later requiring periodic packed erythrocyte transfusions and eventually requiring palliative colostomy. CT scans of chest, abdomen, and pelvis ten months post-embolization identified new hepatic and pulmonary metastases. At this time the patient also had progression of the bladder urothelial carcinoma with bilateral ureteral obstruction, prominent rectovesical fistula, and bilateral hydronephrosis that required bilateral nephrostomy tube placement. The patient expired 3 mo thereafter.

DISCUSSION

Bladder urothelial carcinoma, the most common urinary tract cancer, constitutes the fourth leading cause of cancer mortality in males, and the ninth leading cause

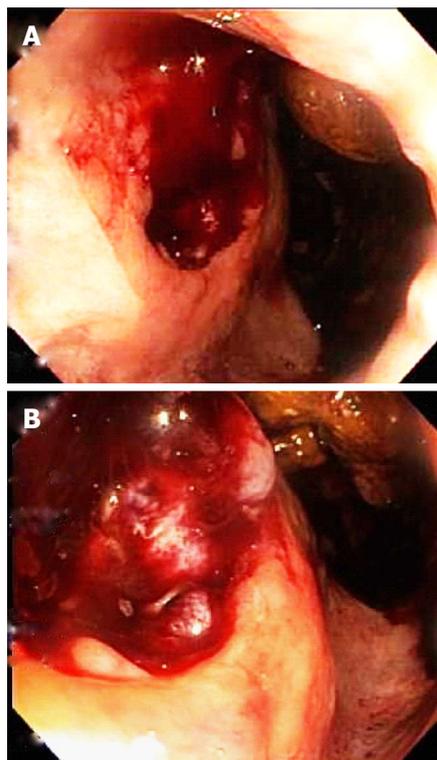


Figure 2 Colonoscopy reveals, just above the anorectal margin (line between pale skin and red mucosa), a multinodular, friable, 2.5-cm-wide, hemorrhagic, mass that replaces the normal prostate and overlying rectum (A, B). Tissue surrounding the lesion appears to be normal. Biopsy of this mass revealed bladder urothelial carcinoma. The finding of bladder urothelial carcinoma in the normal location of the prostate and overlying rectum, just inferior to the bladder cancer, is consistent with direct extension of bladder urothelial carcinoma into the immediately adjacent prostate and its overlying rectal mucosa. This cancer location is highly consistent with the abdominopelvic computed tomography findings (Figure 1).

of cancer mortality in females^[10]. Urothelial carcinoma is the predominant histologic type in the United States and Europe, accounting for 90% of bladder cancers, but non-urothelial carcinomas are relatively more common in other countries^[17].

GI involvement

This cancer most commonly metastasizes to lungs, liver, and bone, via lymphogenous or hematogenous routes. It rarely extends or metastasizes to the GI tract^[10]. Comprehensive literature review revealed only 33 previously reported cases (or 34 cases including the present case) of GI involvement including: Direct extension to rectum-12 (Table 1); metastases to rectum-5, cecum-1, splenic flexure-1, sigmoid colon-1, and multiple colonic segments-1 (Table 2); and metastases to duodenum-4, ileum-3, esophagus-2, appendix-1, and unspecified-3 (Table 3). No metastases occurred in the stomach. The mean patient age was 64.0 ± 11.3 years (SD). Thirty-two patients were male, and only 2 patients were female. Patients developed GI extension/metastases on average, 28.5 ± 30.3 mo after the initial diagnosis of bladder urothelial carcinoma.

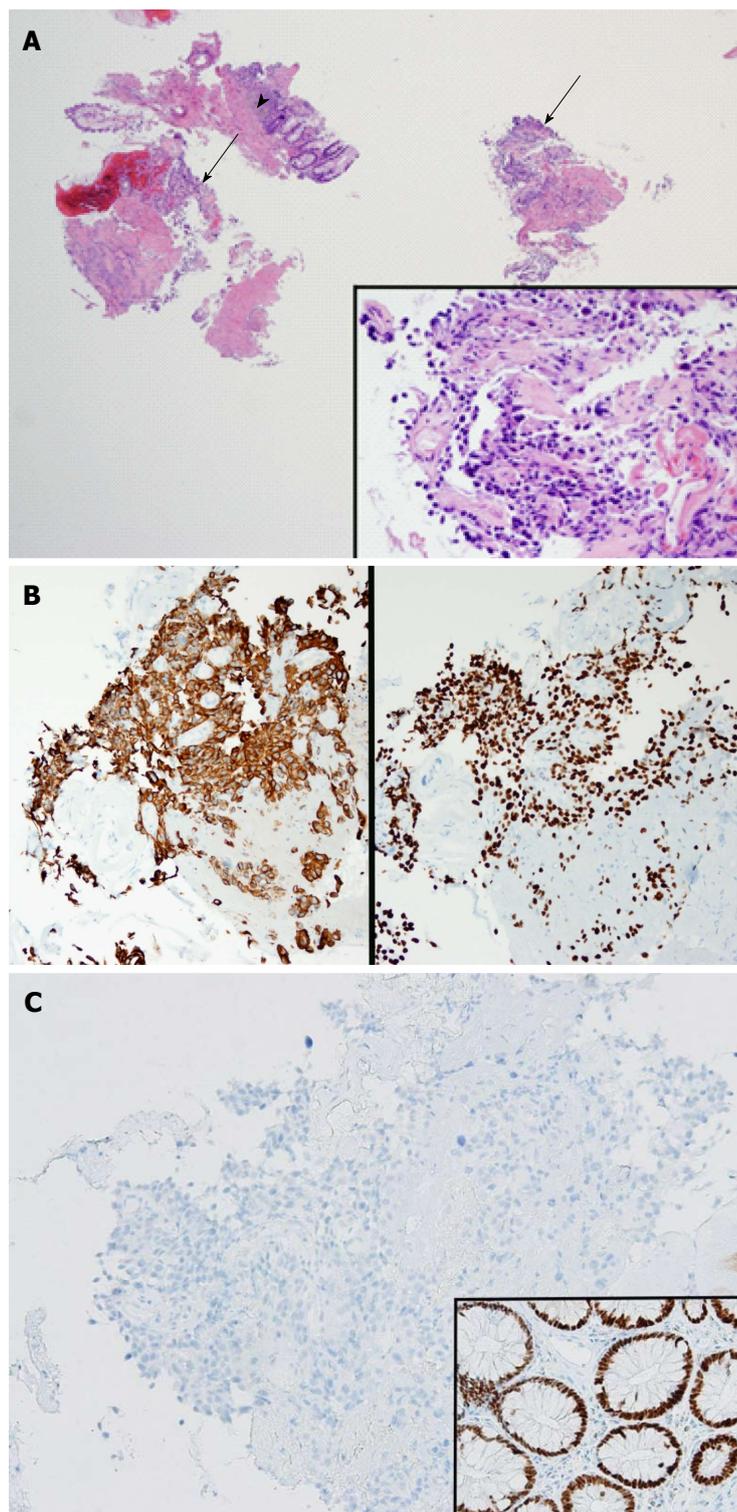


Figure 3 Histologic examination and immunohistochemical analysis. A: Low power photomicrograph shows segments of detached poorly differentiated cancer (arrows), amidst segments of normal rectal mucosa (arrowhead). Right inset shows high power photomicrograph of polygonal tumor cells (HE stain) that have a histologic appearance characteristic for urothelial carcinoma. Immunohistochemistry confirmed the urothelial histology of the cancer (Figure 3B and C); B: Left: Immunohistochemistry for cytokeratin-20 demonstrates positive staining of tumor cytoplasm. Right: Immunohistochemistry for GATA-3 demonstrates positive staining of tumor cell nuclei. This immunohistochemical profile indicates that the rectal mass is of urothelial origin; C: Immunohistochemistry for CDX-2 shows negative staining of tumor cell nuclei, indicating that this tumor is not colonic adenocarcinoma. Right inset is a control of normal colonic glands set on the same slide which demonstrates positive nuclear staining for CDX-2.

Therapies for the primary bladder urothelial carcinoma prior to GI extension/metastases included radical or

partial cystectomy-19, adjuvant chemotherapy-11, and radiotherapy-6 (including patients receiving multiple

therapies). Presenting symptoms with GI involvement included: (1) systemic/extraintestinal symptoms of weight-loss-8, malaise/fatigue-5, anorexia-5, dizziness-2, dyspnea-2, and encephalopathy-1; (2) generalized abdominal symptoms of abdominal pain-4, abdominal distention-2, ileus-2, and GI obstruction-1; (3) GI bleeding including hematemesis-4, melena-4, and hematochezia-3; (4) upper GI symptoms of nausea/vomiting-2, and dysphagia-1; and (5) lower GI symptoms of constipation-7, diarrhea-4, anal pain-3, tenesmus-2, and fecal incontinence-1. Rectal examination, performed in 12 patients, revealed rectal stenosis-6, rectal mass-4, bright red blood per rectum-2, and fecal occult blood-1. The average hemoglobin on presentation was 8.8 ± 2.2 g/dL. Three patients presented with profound hypovolemia, manifesting as severe tachycardia or hypotension.

Colonoscopy, performed in 9 patients, revealed extrinsic colorectal constriction-5, ulcerated/friable mass-3, and profuse bright red blood per rectum-1 (Tables 1 and 2). Flexible sigmoidoscopy, performed in 5 patients, revealed extrinsic constriction-4, and rectal mass-1 (Table 2). Esophagogastroduodenoscopy, performed in 6 patients, revealed stricture of esophagus or duodenum-2; a moderately large, non-obstructive, mass in esophagus or duodenum-2; gastric outlet obstruction-1, and normal findings-1 (Table 3). Enteroscopy revealed a large, ulcerated, duodenal mass in one patient (Table 3). Endoscopic ultrasound performed in 7 patients, revealed hypoechoic, circumferential, rectal wall thickening in 6 patients (Tables 1 and 2).

On presentation with GI metastases, three patients had pathologically-proven extra-intestinal metastases, including one patient with common hepatic duct and intrahepatic duct strictures, identified by endoscopic retrograde cholangiopancreatography. Three other patients had suspected extraintestinal metastases identified by radiologic imaging.

Thirteen patients underwent surgery, including, diverting surgery (such as colostomy and ileostomy)-8, and local bowel resection-5. Seven patients underwent radiotherapy with external beam or brachytherapy. Sixteen patients underwent chemotherapy with carboplatin, cisplatin, etoposide, and gemcitabine; or with methotrexate, vinblastine, adriamycin and cisplatin. The prognosis remains poor for metastatic bladder urothelial carcinoma. Six patients expired from the cancer at a mean of 6.0 ± 4.5 mo. Four patients were reported alive at a mean of 9.8 ± 9.5 mo of follow-up. Most patients, however, had limited follow-up.

Rectal involvement

Bladder urothelial carcinoma has been previously reported to involve the rectum in 16 cases, including 11 cases by direct extension, as demonstrated by abdominopelvic CT-8, rectal endoscopic ultrasound (EUS)-3, and abdominopelvic magnetic resonance

imaging (MRI)-2; and including 5 cases by metastases as demonstrated by abdominopelvic CT-2, EUS-2, MRI-1, and positron emission tomography (PET) scan-1 (1 patient had 2 diagnostic tests) (Tables 1 and 2). Rectal involvement was pathologically proven at surgery-6, by fine needle aspiration during EUS-5, colonoscopic biopsies-3, and transrectal needle biopsy-2. None of the 11 patients with direct bladder extension to rectum had pathologically-proven involvement of rectal mucosa; three of the 5 patients with rectal metastases had pathologically-proven mucosal involvement. Three patients had proven extraintestinal metastases at the time of diagnosis of rectal involvement, including hepatic duct-1, omentum and pelvic organs-1, and skeletal muscles-1. The average patient age at diagnosis of rectal involvement was 63.7 ± 9.6 years. All 16 patients were male. Rectal involvement was diagnosed on average 13.5 ± 11.8 mo after the bladder urothelial carcinoma was first diagnosed (includes 2 patients with simultaneous diagnosis of primary bladder urothelial carcinoma and rectal involvement, excludes 4 cases in which time interval between the two diagnoses was not reported). Patient symptoms included constipation or GI obstruction-6, weight loss-5, diarrhea-3, anorexia-3, pencil thin stools-3, tenesmus-2, anorectal pain-2, fatigue-1, straining with bowel movements-1, fecal incontinence-1, abdominal distention-1, and change in bowel habits-1. Rectal examination, performed in 9 patients, revealed annular rectal stenosis in 6, and rectal mass in 3. One patient presented with mild anemia.

This case report describes the novel colonoscopic appearance of bladder urothelial carcinoma extension, *via* the prostate, into the rectum, forming a multinodular, oval, ulcerated, friable mass. Bladder carcinoma extension *via* the prostate underlies the colonoscopic detection of rectal invasion only over the prostate location, just as the colonoscopic finding of a friable, multinodular, hemorrhagic rectal mass underlies the clinical presentation with daily bright red blood covering the stools. Invasion *via* the prostate may have been facilitated by prior radiotherapy and hormonal therapy for prostate cancer, or perhaps by prostate tissue being receptive to urothelial metastases. Bladder (and prostate) cancer have been reported to cause annular rectal constriction, presenting as constipation or GI obstruction, *via* contiguous spread to the rectal submucosal or muscular layers, but the current report of extension to rectal mucosa is novel. Bladder urothelial carcinoma is believed to break through the bladder wall, and follow along, the fascia of Denonvillier^[2], or spread locally along the lateral pedicles of the bladder to reach the posterior rectal wall, to cause rectal constriction^[4]. The current case, like all the prior 16 cases of rectal involvement, occurred in men. Female internal reproductive organs and their corresponding ligaments and fascia might serve as barriers that protect the rectum from local invasion by bladder urothelial carcinoma, whereas the prostate might be a weak

barrier to protect the rectum from local invasion because of susceptibility to urothelial invasion. Metastasis, to other GI regions, have, likewise, been reported much more frequently in men than women, partly explained by bladder urothelial carcinoma being four times as common in men than women^[22], but other potential contributing factors require further investigation.

The currently reported patient had two reported risk factors for bladder urothelial carcinoma: Prior prostate cancer^[23], and prior radiotherapy for prostate cancer^[24]. The current case demonstrates that the clinical symptoms of rectal mucosal invasion can mimic that of hemorrhoids: chronic, daily, bright red blood per rectum coating the stools. However, the currently reported patient also had an enlarged, hard, fixed, "prostate" on rectal examination, and had prior prostate and bladder cancers, findings suggesting recurrent bladder or prostate cancer.

This study is limited by reporting a single case and by reporting it retrospectively. This study is also somewhat limited by not entirely excluding prostate cancer as contributing to the pelvic mass. However, the cystoscopic findings of friable, hemorrhagic tissue at the bladder neck identified 4 mo prior to admission; the colonoscopic findings of a friable, multinodular rectal mass; the histologic and immunohistochemical findings of multiple rectal biopsies revealing bladder urothelial carcinoma; the CT demonstration of a mass extending from the bladder neck through the prostate into the rectum; and the absence of immunohistochemical markers for prostate cancer in the rectal biopsies all favor the diagnosis of bladder urothelial carcinoma over prostate cancer. In conclusion, a case of bladder urothelial carcinoma penetrating into the rectum *via* the prostate is reported, with apparently previously unreported, but likely characteristic colonoscopic findings. In the previously reported cases, rectal lesions were metastatic, presumably *via* lymphogenous or hematogenous routes, or caused rectal constriction from direct rectal wall extension without rectal mucosal involvement.

COMMENTS

Case characteristics

An 87-year-old man was treated in 1996 for prostate adenocarcinoma stage-T1c-Gleason-6 with external beam radiotherapy recurrent prostate cancer treated with leuprolide hormonal therapy in 2009, and bladder-urothelial-carcinoma *in-situ* treated with Bacillus-Calmette-Guerin and adriamycin in 2010, presented in 2015 with painless, bright red blood per rectum coating stools daily for 5 mo. Rectal examination revealed bright red blood per rectum; and a hard, fixed, 2.5 cm × 2.5 cm mass at the normal prostate location.

Clinical diagnosis

The symptom of daily, painless, bright red blood per rectum for 5 mo without other symptoms suggests hemorrhoidal bleeding. First, hemorrhoidal bleeding is very common and is typically unassociated with other symptoms. Second, hemorrhoids generally cause bright red blood because hemorrhoidal blood, despite being venous, is relatively well oxygenated. Third, hemorrhoidal bleeding is generally painless in the absence of hemorrhoidal thrombosis. Rectal examination did not, however, support this diagnosis. No external hemorrhoids were identified by anal inspection, and no internal hemorrhoids were palpated on

digital rectal examination. Moreover, rectal examination revealed a hard, fixed, multinodular, mass at the normal location of the prostate, and gross red blood on the examining finger, findings suspicious for rectal bleeding from prostate cancer. This diagnosis is further suggested by the prior history of prostate cancer in 1996, prostate cancer recurrence in 2009 six years before the current clinical presentation, and palliative hormonal therapy for the cancer recurrence in 2009. The diagnosis of recurrent bladder urothelial cancer is also possible given the prior diagnosis of bladder urothelial carcinoma *in situ* in 2010; recurrent bladder urothelial carcinoma could cause rectal bleeding from metastases or direct extension to the rectum. Radiation proctitis must be included in the differential diagnosis because the patient had undergone external beam radiotherapy for prostate cancer in 1966, 19 years before the clinical presentation. Chronic radiation proctitis can cause rectal bleeding from telangiectasias caused by radiation-induced endothelial injury. Anal fissure must also be included in the differential diagnosis of bright red blood per rectum, but is unlikely in this case because anal fissure is typically very painful and this patient had no anorectal pain. Also the patient did not have the classic symptoms of anorectal bleeding commencing after passing a large, hard stool, the patient had daily rectal bleeding for 5 mo which is atypical for rectal fissure, and anal fissure is relatively uncommon.

Laboratory diagnosis

The key finding in the blood tests is a hemoglobin level of 7.6 gm/dL, with iron saturation of 9%, indicating iron deficiency anemia. Hemorrhoidal bleeding tends to produce minimal-to-mild anemia because of minimal daily bleeding, whereas prostate or bladder cancer invading rectal mucosa can cause much more significant blood loss and more severe anemia.

Imaging diagnosis

Abdominopelvic computed tomography (CT) angiography revealed focal thickening of the bladder wall at its neck; a mass containing an air cavity replacing most of the prostate; and adjacent rectal invasion. These imaging findings strongly support the diagnosis of recurrent bladder urothelial carcinoma penetrating rectal mucosa *via* the prostate, or less likely support the diagnosis of recurrent prostate cancer penetrating rectal mucosa. These CT findings do not support the diagnosis of hemorrhoids. Either of these malignancies would be more likely to produce iron deficiency anemia from chronic blood loss than hemorrhoidal bleeding. Colonoscopy demonstrated an ulcerated, friable, multinodular, oval, hemorrhagic, 2.5 cm × 2.5 cm mass in the anterior rectal wall, just proximal to the dentate line, at the usual anatomic location of the prostate, no hemorrhoids, and no signs of radiation proctitis, such as mucosal telangiectasia despite the prior prostate radiotherapy. These colonoscopic findings are highly consistent with cancer invading rectal mucosa. These CT findings are most compatible with bladder urothelial carcinoma invading rectal mucosa by direct extension.

Pathological diagnosis

Histologic examination of colonoscopic biopsies of rectal tissue biopsies revealed poorly differentiated carcinoma. Immunohistochemical analysis demonstrated the tumor cells stained positively with cytokeratin 20, indicating either a colonic or bladder (urothelial) primary. Additional diffuse positivity for cytokeratin 7, 34bE12, and GATA-3; and focal positivity for CK5/6 strongly support urothelial origin. Negative immunohistochemical staining for CDX2 (Caudal Type Homeobox 2) confirms that this tumor does not arise from colonic adenocarcinoma. The diffuse positivity for cytokeratin 20 and only focal positivity for CK5/6 (< 20% of cells positive) excludes anorectal squamous carcinoma. Immunohistochemical markers for prostate carcinoma, including PSA, PAP and P501S, were all negative. The pathologic diagnosis was therefore poorly-differentiated carcinoma of urothelial origin. This pathology explains all the findings: Clinical presentation of painless, daily bright red blood per rectum from friable rectal mucosa from malignant invasion; iron deficiency anemia from chronic GI bleeding from rectal metastases; CT findings of direct cancer extension to rectal mucosa; and colonoscopic findings of an ulcerated, friable, multinodular, mass in the anterior rectal wall.

Treatment

The patient received palliative therapy for the daily rectal bleeding. The right-superior-rectal-artery was successfully embolized during visceral angiography

using embolospheres to achieve hemostasis. The patient did not undergo curative therapy in accordance with the patient's wishes, because of the minimal likelihood of cure given that the patient presented with recurrent urothelial carcinoma spreading beyond the bladder, previously had recurrent prostate cancer, and was very elderly. The patient experienced recurrent rectal bleeding requiring periodic packed erythrocyte transfusions three months after embolization that required palliative colostomy. The patient expired 13 mo after embolization from widespread metastases from the advanced cancer with rectal penetration treated with palliative therapy.

Related reports

Comprehensive literature review revealed 16 previously reported cases of rectal involvement of bladder urothelial carcinoma, including 11 cases of direct cancer extension and 5 cases of metastases. The current case is novel in that the bladder urothelial carcinoma directly penetrated into rectal mucosa; in that rectal involvement caused daily bright red blood per rectum and iron-deficiency anemia; and in the colonoscopic findings that were in accord with the clinical presentation of daily bright red blood per rectum and the CT findings.

Experiences and lessons

This work demonstrates the novel findings that bladder urothelial carcinoma can directly extend to rectal mucosa *via* the prostate, can cause daily, painless, bright red blood per rectum mimicking hemorrhoidal bleeding; and produce colonoscopic findings of a multinodular rectal mucosal mass from cancer extension.

Peer-review

The authors reported on a single case of urothelial bladder cancer extending to rectal mucosa *via* the prostate and mimicking hemorrhoidal bleeding, and reviewed the literature on this subject. The case is well described and of clinical interest. The background literature review is comprehensive and well done.

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