Journal of Health Science Research, *Vol 8(1), 2023, 1-6*
ISSN (Online) : 2456-2688
DOI: https://doi.org/10.7324/jhsr.2023.811

Rectal neuroendocrine tumor, urinary obstruction, and bladder calculi: A case report

Vitorino Modesto dos Santos[1]*, Viviane Vieira Passini Soares[1], Alesso Cervantes Sartorelli[2], Mayza Lemes Duarte[1], Ana Lorena Sousa de Vasconcelos Garate[1]

[1]Department of Medicine, Armed Forces Hospital, Brasília-DF, Brazil; [2]Division of Pathology, Armed Forces Hospital, Brasília-DF, Brazil.
Email: vitorinomodesto@gmail.com

Abstract

Rectal neuroendocrine tumors are rare, represent 12–27% of the neuroendocrine neoplasms, and often occur in relatively young people, and distant metastases are uncommon. Herein is described the case of an 86-year-old Brazilian man with a rectal neuroendocrine tumor metastasized to the peritoneum, liver, adrenal glands, lungs, bones, and lymph nodes. Besides, three intravesical calculi were found measuring up to 5 cm in diameter. The huge neoplasm caused compression on the urinary tract, hydronephrosis, and renal failure. Worthy of note was the exceedingly high level of carcinoembryonic antigen (1879 ng/mL). The histopathology and immunohistochemistry data were the base for diagnosis. Case studies of uncommon conditions might contribute to enhance the awareness and suspicion index of no specialist physicians about this ominous tumor with rising incidence.

Keywords: Bladder calculi, Carcinoembryonic antigen, Rectal neuroendocrine tumor

1. Introduction

Neuroendocrine neoplasms (NENs) have origin in chromaffin cells of small or large types, often found in pulmonary or gastrointestinal sites, and can be malignant[1-12]. Neuroendocrine cells are numerous in gastrointestinal tract; 6 however, only up to 4% of the malignancies detected on these locations are colorectal tumors are of this cell type (10). The incidence of rectal NENs is 0.17%, they are 20% of the digestive type of these tumors and 2% of the rectal tumors; besides, the rectum is the second location after the small intestine[5]. Worth of note is that rectal NENs represent between 12% and 27% of all NENs, more often occurring in relatively young people, and their distant metastases are uncommon[5,10]. However, the incidence of rectal NENs and the frequency of lymph node and distant implants of this malignancy has increased in the last few decades, with individual differences[1,5]. These tumors may have a good prognosis, depending on the stages and the cell subtypes[2,7]. Western people with rectal tumor Stage IV have a 5-year survival rate from 20.6% to 32.3%, whereas the 3-year survival rate among Chinese with the same tumor stage is 0%[1].

Due to the low incidence, the associated risk factors of rectal NENs remain unclear[4]. We report a non-smoker 86-year-old man with a large rectal NEN, scattered metastases, and serum levels of carcinoembryonic antigen (CEA) extremely elevated[13-15].

2. Case Report

In October, an 86-year-old hypertensive male came to the hospital due to urinary incontinence, weight loss (4 kg in 3 months), and a conspicuous mesogastric mass. There was diarrhea alternating with constipation, without abdominal pain, nausea, vomiting, or fever. He denied

*Author for correspondence

How to cite this article: dos Santos VM, Soares VVP, Sartorelli AC, Duarte ML, de Vasconcelos Garate ALS. Rectal neuroendocrine tumor, urinary obstruction, and bladder calculi: A case report. J Health Sci Res 2023;8(1):1-6.

alcohol consumption and smoking. Physical examination showed pallor and dehydration; distended, flaccid, and painless abdomen, and palpable mesogastric tumor. With urine culture positive for *Staphylococcus aureus*, he used ciprofloxacin and oxacillin. With the diagnosis of sepsis, hemodynamic instability, hematemesis, and acute renal failure, the patient was referred to ICU. Oxacillin was changed by meropenem for 14 days with a good response. Computed tomography (CT) of the abdomen without contrast revealed a hypodense nodule (21 × 17 mm) suggestive of the left adrenal adenoma; bilateral reduction of renal parenchyma thickness; bilateral renal cysts and nephrolithiasis; right ureteral and pelvicalyceal dilation; multiple intravesical lithiases with up to 36 × 27 mm (Figure 1a and c); and prostate enlargement.

Other changes also observed were colon diverticula; umbilical hernia; bilateral pleural effusion; and pulmonary atelectasis. The ultrasound study of the prostate and urinary tract showed bilateral hydronephrosis and renal cysts; overactive bladder in addition to and an enlarged prostate (91 g), but with a normal post voiding residue. The esophagogastroduodenoscopy (EGD) revealed erosive esophagitis Forrest II c. The patient had an uneventful open cystolithotomy and removal of three intravesical calculi, with the biggest stone measuring approximately 5 cm in diameter (Figure 1b). In good general condition and with urinary catheter, he was discharged for outpatient follow-up. Five months later, he came to hospital with recurrent blood in stools and urinary infection. Physical examination showed abdominal distension and diffuse pain, without peritonitis. The EGD revealed hemorrhagic esophagitis Forrest IIc, esophageal candidiasis, and biliodigestive reflux. Abdominal CT of control showed an expansive solid rectal mass (24 × 16 × 12 cm, and estimated 2396 cm^3), probably of neoplastic nature and extending to the level of the iliac crest and compressing the bladder (Figure 1d). There was no cleavage plane with the bladder and prostate, and obliteration of the rectal lumen and of the retro rectal space. Additionally to the involvement of adjacent structures, there was metastatic involvement of liver (Figure 1e), lymph nodes, adrenal glands, peritoneum, bones, and lungs; left nephrolithiasis and ureterolithiasis; and increased bilateral hydronephrosis due to extrinsic compression by the huge pelvic mass (Figure 1f). Worthy of note was the CEA serum level extremely elevated (1879 [normal: ≤5] ng/mL). Histopathology and immunohistochemistry evaluations of percutaneous biopsy samples of the rectal mass allowed establishing the diagnosis of a neuroendocrine tumor (Figure 2).

With better general condition, he was referred to the Oncology section. Two days later, he had an acute respiratory failure evolving to death despite of medical care. The autopsy study was not authorized by the family of the patient. Laboratory control data are shown in Table 1.

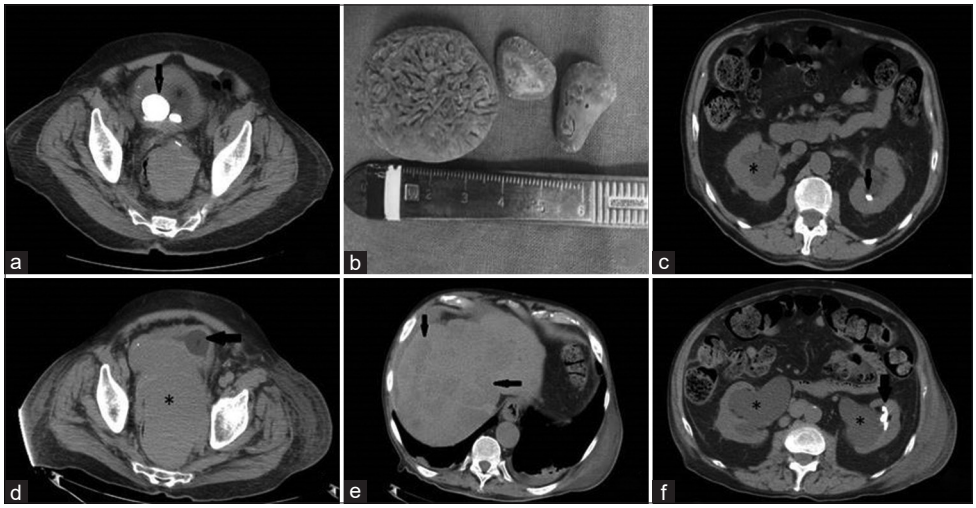

Figure 1. (a) Computed tomography (CT) images of diffuse bladder wall thickening, and diverse stones (arrow); (b) Gross features of three huge bladder calculi removed by cystolithotomy; (c) CT images of calculi in the left kidney (arrow), and right pelvicalyceal and ureteral dilatation (asterisk); (d) CT images of multiple hypoattenuating solid nodules scattered by the liver parenchyma (arrows) corresponding to metastatic involvement; (e) CT images of the very large solid rectal mass (asterisk), which appears oval and lobulated extending anteriorly with compression of the bladder (arrow); and (f) CT images of control 4 months later showing left nephrolithiasis, and bilateral hydronephrosis (asterisk) due to compression by the mass.

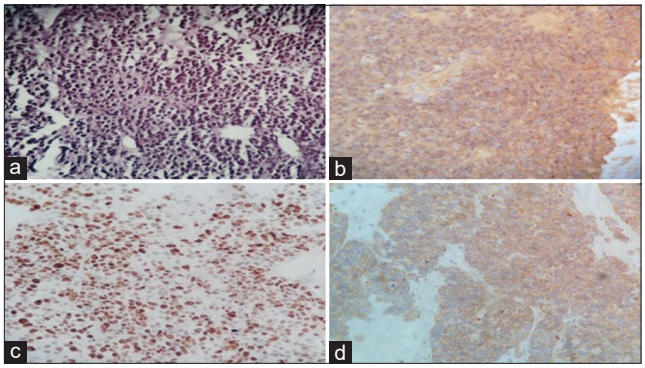

Figure 2. (Photomicrographs of histopathology and immunohistochemistry studies) (a) Solid neoplasm showing of small cells with high nucleocytoplasmic ratio, hyperchromatic nuclei, and absence of nucleoli, which are characteristics of small cell carcinoma (H and E; ×400); (b) An image of the cytokeratin (AE1/AE3) positivity revealing the epithelial origin (×400); (c) Positivity for chromogranin, confirming the neuroendocrine differentiation (×400); and (d) The high Ki-67 (proliferation index), indicating the malignant nature of the mass (×400). Additionally, lymphoma was ruled out by the leukocyte common antigen (CD45) negativity.

3. Discussion

Rectal NENs are rare conditions that had an incidence of approximately 3.0/100,000 person-years and have been growing in frequency[1]. They were considered not ominous entities, but malignant features as metastases in lymph nodes or dissemination may occur; the previous 5-year survival rate of about 88% reduced to 13% in 3-years[1]. Rectal NENs are classified into three heterogeneous groups: well-differentiated (G1), indolent and with good prognosis; moderately-differentiated (G2), with intermediate risk of metastasis; and poorly-differentiated (G3), with an elevated risk of metastasis and very poor outcome[4]. Because G1 tumors represent 80–90% of NENs, the metastatic risks of G2 and G3 can follow underestimated without their respective clinicopathologic, treatment, and prognosis data[4]. Microvascular invasion (MVI) and perineural invasion (PNI) are related to higher risk of lymph node metastasis, and radical excision seems the best choice in this patient group[4]. As even small rectal NENs can yield extensive lymphatic metastases, this phenomenon stress the role of the evaluation for lymph node implants, because radical resection can be curative[8].

Chi *et al.* reviewed 48 patients with rectal NENs in China to study factors for their survival. The main symptoms were hematochezia and diarrhea; 43 cases were typical NENs, whereas the other 5 were atypical carcinoids/poorly differentiated NENs/small cell carcinomas.[1] The patients were 31 males and 17 females, with a median age of 53.5 (range: 27–77) years; the stages of tumors were I (83.3%), II (4.2%), III (8%), and IV (4.2%); except one patient was not surgically treated due to the Stage IV of disease with liver metastases. Concordant with literature, the authors found tumor diameters related to prognosis; and the absence of distant metastases was associated with better outcome and long-term survival; however, elderly patients often die due to comorbidity rather than NEN-specific factors[1].

Li *et al.* reviewed 156 patients with rectal NENs in China to study factors of lymph node metastasis and prognosis[3]. The main symptoms were hematochezia and changes in bowel habits; the patients were 104 males and 52 females, with a median age of 50.8 ± 11.56 years; the stages of tumors were I (99%), II (4%), and III (12%); 12 patients had lymph node metastasis (7.7% of cases), mainly in tumors larger than 1 cm; local excision (85.3% of cases) and radical resection were performed; and the overall 5-year survival rate was 95.7%. Therefore, the tumor size and invasion depth as well as the lymph node status play a role in outcome[3].

Shafqat *et al.* reviewed the incidence, management, and outcomes of 1367 cases of colorectal NEN in comparison with 72533 cases of high-grade colorectal adenocarcinoma[7]. There was increased incidence rate for NEN and decreased for high-grade adenocarcinoma. The 5-year survival of NENs was 16.3% (small-cell tumor: 10% and non-small cell: 19%); and distribution according to stage was: I (57.4%), II (56.4%), III (26.3%), and IV (3.0%). Patients with localized non-small cell tumors had better overall survival following surgery, and resected NENs with increasing number of involved lymph nodes had poor prognoses. Due to survival rate in early stage NENs, the authors suggested adjuvant systemic therapy[7].

A Korean study by Pyo *et al.* evaluated risk factors related to rectal NENs[6]. They compared the data of 102 patients with data of 52583 normal controls, and described four major risk factors for this type of neoplasm – high cholesterol serum levels, high ferritin serum levels, metabolic syndrome, and first-degree relatives with history of cancer[6]. Two highlighted issues of rectal NENs were the ethnic influences with prevalence among Asian and African descents, and an incidental

Table 1. Laboratory data of a man with rectal neuroendocrine tumor and urinary stones

Parameters (normal range)	D1	D4	D10	D12	D15	D18	D22	D23	D25
Hemoglobin (13–18 g/dL)	**12.6**	**12.1**	**12.4**	13	**12.1**	**12.2**	**11.6**	**11.5**	**12.2**
Hematocrit (42–52%)	**38**	**36.6**	**36.2**	**36.7**	**35.2**	**36.9**	**36.2**	**35.1**	**39.7**
Leukocytes (4–10 × 10^9/L)	**24.6**	**19.6**	**19.6**	**24.5**	**23.9**	**21.1**	**24.8**	**32.2**	**32.5**
Neutrophils (40–70%)	**87**	**86**	**85**	**88**	**88**	**89**	**95**	**95**	**91**
Platelets (140–450 × 10^9/L)	270	194	315	309	282	265	288	234	175
C-RP (0.5–0.9 mg/dL)	**5.4**	**10.2**	**5.6**	**4.0**	**5.2**	**4.7**	**25.8**	**47.1**	**45.0**
Sodium (135–145 mmol/L)	143	141	139	**132**	**134**	**133**	147	146	142
Potassium (3.5–5.2 mmol/L)	**3.0**	**3.3**	4.0	3.7	3.8	4.1	**5.5**	**5.9**	-
Urea (10–50 mg/dL)	**71**	**51.4**	**62.3**	**73.4**	**74**	**94.7**	**168**	**194**	**232**
Creatinine (0.7–1.3 mg/dL)	**1.4**	1.1	**1.6**	**1.6**	**1.4**	**1.7**	**3.0**	**3.9**	**5.0**

D1: Day of admission, D18: Day of discharge, D25: Day of death, CRP: C-reactive protein. The abnormal data are showed in bold

finding of tumors due to current colorectal screenings. The importance of reported data of polyp removal by routine endoscopy was emphasized[6].

Two particularities also merit comments in the present case, the extremely high CEA level[11,12]; and the renal and ureteral multiple lithiasis as well as the huge bladder stone[13-15]. CEA is the tumor marker more often utilized as a prognostic factor both in pre-operative investigation and post-operative follow-up in individuals affected by colorectal cancers[11]. The people with colorectal cancers are categorized according to the CEA levels as normal (0–5 ng/mL), elevated (5-50 ng/mL), and the extremely elevated (> 50 ng/mL) groups[11,12]. The highest serum levels of CEA have been associated with hepatic and distant metastasis, advanced stage of disease, and the poorest prognoses of patients with colorectal cancer. In the present study, the extremely high CEA levels were related to the tumor volume, aggressiveness and distant metastatic dissemination, and age group of the patient[11,12].

Recent reviews about advances in managing and understanding nephrolithiasis have contributed to comprise the relationship between urinary stones and bowel diseases[13-15]. Three varieties of urinary lithiasis – calcium oxalate, uric acid, and ammonium acid urate stones may be associated with digestive disorders including small bowel and colonic diseases, and lack of oxalate degrading bacteria in the intestinal flora[15]. The mechanisms can include low diuresis, hyperoxaluria, hypocitraturia, hypomagnesuria, and the pH alterations[15]. This patient had arterial hypertension in use of losartan, ACE inhibitors, and loop diuretics, other possible etiology for urolithiasis may be collateral effects of drugs[14]. In a Danish cohort study, 2549 (3%) of 75,236 patients with inflammatory bowel disease (IBD) and 11,258 (2%) of 767,403 non-IBD individuals developed urolithiasis, which means a two-fold increased risk of urolithiasis among the group of patients with IBD[13]. Besides the 42% of increased risk before the IBD diagnosis, urolithiasis has been associated with anti-TNF therapy and the surgical procedures which propitiate disorders of the intestinal absorption[13].

Additional comments are on the giant bladder calculi (over than 100 g), more often associated with urinary stasis, and should be removed by invasive surgical procedure[16-18]. The calculi have an association with the low socioeconomic conditions and the cereal-based diets, besides the occurrence of hyperuricemia, hypophosphaturia, and hyperammoniuria[18]. Ahmed *et al.* described a 60-year-old male who had a huge intravesical

caliculus (10 cm and 750 g) with a longstanding course of suprapubic pain, dysuria, and difficult urine voiding. The calculus was removed by cystolithotomy and the chemical composition was not cited[16]. Hela *et al.* described a 30-year-old male patient presenting with lower abdominal pain for the past 1 month, frequency, hesitancy, and dysuria for 4 years, besides episodic hematuria[17]. He underwent an uneventful open cystolithotomy with the removal of two stones measuring 10 cm × 7 cm × 6 cm and 298 g, and 6 cm × 5 cm × 5 cm and 194 g; and stone evaluation showed 70% magnesium ammonium phosphate hexahydrate and 30% carbonate apatite[17]. Interestingly, Pires *et al.* reported a 51-year-old male who had an extracted giant bladder stone (18.5 cm and 1.328 kg), with neither previous urinary tract infections nor surgeries, or any causal factors for neurogenic bladder, benign prostatic hyperplasia, and urethral stricture; laboratory evaluation indicated for stone composition was not obtained in the case study[18].

4. Conclusion

Rectal NENs with distant metastases at diagnosis are rare, with usual poor prognosis. The CEA serum levels are related to the volume of the tumors, distant implants, and aging. The earliest diagnosis confirmation and prompt adequate management are the best tools influencing the outcomes. In spite of the inherent weaknesses of single case studies, the present report might enhance the awareness and the suspicion index about the rectal NENs.

5. Authors' Contributions

All the article has been drafted by the authors.

6. Financial Support and Sponsorship

There is no funding to report.

7. Informed Consent

Informed consent has been obtained from the patient for publishing.

8. Conflicts of Interest

No conflicts of interest are declared.

9. References

1. Chi Y, Du F, Zhao H, Wang JW, Cai JQ. Characteristics and long-term prognosis of patients with rectal neuroendocrine tumors. World J Gastroenterol 2014;20:16252-7.
2. Ilett EE, Langer SW, Olsen IH, Federspiel B, Kjær A, Knigge U. Neuroendocrine carcinomas of the gastroenteropancreatic system: A comprehensive review. Diagnostics (Basel) 2015;5:119-76.
3. Li P, Wu F, Zhao H, Dou L, Wang Y, Guo C, *et al.* Analysis of the factors affecting lymph node metastasis and the prognosis of rectal neuroendocrine tumors. Int J Clin Exp Pathol 2015;8:13331-8.
4. Li YW, He YP, Liu FQ, Peng JJ, Cai SJ, Xu Y, *et al.* Grade G2 rectal neuroendocrine tumor is much more invasive compared with G1 tumor. Front Oncol 2021;11:646536.
5. Maione F, Chini A, Milone M, Gennarelli N, Manigrasso M, Maione R, *et al.* Diagnosis and management of rectal neuroendocrine tumors (NETs). Diagnostics (Basel) 2021;11:771.
6. Pyo JH, Hong SN, Min BH, Lee JH, Chang DK, Rhee PL, *et al.* Evaluation of the risk factors associated with rectal neuroendocrine tumors: A big data analytic study from a health screening center. J Gastroenterol 2016;51:1112-21.
7. Shafqat H, Ali S, Salhab M, Olszewski AJ. Survival of patients with neuroendocrine carcinoma of the colon and rectum: A population-based analysis. Dis Colon Rectum 2015;58:294-303.
8. Shin S, Maeng YI, Jung S, Yang CS. A small, low-grade rectal neuroendocrine tumor with lateral pelvic lymph node metastasis: A case report. Ann Coloproctol 2022;38(4):327-31.
9. Viana C, Marques I, Staubus A, Martins SF. Rectal carcinoid tumor: Diagnosis and management. J Coloproctol 2019;39:184-9.
10. Tsoukalas N, Galanopoulos M, Tolia M, Kiakou M, Nakos G, Papakostidi A, *et al.* Rectal neuroendocrine tumor with uncommon metastatic spread: a case report and review of literature. World J Gastrointest Oncol 2016;8:231-4.
11. Lee SY, Jo JS, Kim HJ, Kim CH, Ju JK, Kim YJ, *et al.* Clinicopathologic features and oncologic outcomes of colorectal cancer patients with extremely high carcinoembryonic antigen. Int J Colorectal Dis 2015;30:63-9.
12. Vukobrat-Bijedic Z, Husic-Selimovic A, Sofic A, Bijedic N, Bjelogrlic I, Gogov B, *et al.* Cancer antigens (CEA and CA 19-9) as markers of advanced stage of colorectal carcinoma. Med Arch 2013;67:397-401.
13. Dimke H, Winther-Jensen M, Allin KH, Lund L, Jes T. Risk of urolithiasis in patients with inflammatory bowel disease: A Nationwide Danish cohort study 1977-2018. Clin Gastroenterol Hepatol 2021;19:2532-40.e2.

14. Gambaro G, Trinchieri A. Recent advances in managing and understanding nephrolithiasis/nephrocalcinosis. F1000Res 2016;5:F1000 Faculty Rev-695.
15. Pradere B, Peyronnet B, Brochard C, Le Balc'h É, Vigneau C, Siproudhis L, *et al*. Urinary stones and bowel diseases: Systematic review. Prog Urol 2015;25:557-64.
16. Ahmed F, Alyhari Q, Al-Wageeh S, Mohammed F. Giant urinary bladder calculi in a 60-year-old man: A case report. Pan Afr Med J 2022;41:78.
17. Hela AH, Wani M, Khandwaw HM, Jyoti D. Giant multiple vesical calculi: A case report. Urol Case Rep 2020;33:101264.
18. Pires JC, de Brito BB, de Melo FF, Souza CL, Oliveira MV. Giant urinary bladder stone in a middle-aged male. EMJ Urol 2022. https://doi.org/10.33590/emjurol/21-00239