CASE REPORT

Case Report: Management of rectal squamous cell carcinoma - a treatment dilemma [version 1; peer review: 1 approved, 2 approved with reservations]

Nathaniel A. Parker[1], Yasmine Hussein Agha[1], Charles Scott Buess[1], Daniel Lalich[2], Jeremy M. Deutsch[3]

[1]University of Kansas School of Medicine, 1010 N Kansas St, Wichita, KS, 67214, USA
[2]Wesley Medical Center, 550 N. Hillside St, Wichita, KS, 67214, USA
[3]Cancer Center of Kansas, 818 N. Emporia #403, Wichita, KS, 67230, USA

v1 **First published:** 03 Jun 2020, **9**:503
https://doi.org/10.12688/f1000research.24033.1
Latest published: 03 Jun 2020, **9**:503
https://doi.org/10.12688/f1000research.24033.1

Abstract

Primary rectal squamous cell carcinoma is rare compared to adenocarcinoma, which is the predominant histologic type most commonly discovered at the time of colorectal carcinoma diagnosis. Due to the infrequent nature of this malignancy, data on tumor pathogenesis and risk factors remains sparse. Moreover, no standardized therapeutic regimen exists. This report describes a case of advanced rectal squamous cell carcinoma diagnosed in a 46-year-old female who initially presented with abdominal pain. Her clinical course was uncomplicated and she responded well to the selected therapy. Much work remains to be accomplished for patients with rectal squamous cell carcinoma.

Keywords

Squamous cell carcinoma, Rectum, Chemoradiotherapy, Radiotherapy

Open Peer Review

Reviewer Status ? ? ✓

	Invited Reviewers		
	1	**2**	**3**
version 1 03 Jun 2020	? report	? report	✓ report

1. **Pratiksha Singh**, Mercer County Community College, Trenton, USA
2. **George S. Stoyanov**, Medical University of Varna, Varna, Bulgaria
3. **Mukesh S. Paudel**, Lumbini Medical College, Palpa, Nepal

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: Nathaniel A. Parker (naparker1031@gmail.com)

Author roles: Parker NA: Conceptualization, Investigation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Hussein Agha Y**: Conceptualization, Investigation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Buess CS**: Methodology, Writing – Original Draft Preparation; **Lalich D**: Investigation; **Deutsch JM**: Supervision

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

How to cite this article: Parker NA, Hussein Agha Y, Buess CS *et al.* **Case Report: Management of rectal squamous cell carcinoma - a treatment dilemma [version 1; peer review: 1 approved, 2 approved with reservations]** F1000Research 2020, **9**:503 https://doi.org/10.12688/f1000research.24033.1

First published: 03 Jun 2020, **9**:503 https://doi.org/10.12688/f1000research.24033.1

Introduction

Adenocarcinoma comprises the vast majority of rectal cancers[1]. As a result, primary rectal squamous cell carcinoma (RSCC) is exceedingly rare, occurring in approximately 0.10–0.25 per 1000 colorectal cancers[2,3]. The etiology, pathogenesis, and risk factors are poorly defined, and no general consensus exists regarding the optimal treatment regimen due to the rarity of this cancer. Review of the literature encompasses mostly case series and retrospective studies. Nevertheless, evidence-based management is essential for those who are diagnosed. This report describes a rare case of primary RSCC.

Case report

A 46-year-old Caucasian female administrative assistant, for whom the only pertinent past medical history was chronic tobacco smoking, presented at the emergency department with the chief complaint of generalized abdominal pain. Symptom onset began two months prior to her initial presentation and had been progressively worsening.

Vital signs and measurements were unremarkable. Physical examination was unremarkable. Serum laboratory evaluation was nonrevealing. Computerized tomography (CT) imaging of the abdomen and pelvis showed a sigmoid mass indicating a differential diagnosis of a transmural abscess versus a malignant inflammatory process in the sigmoid colon (Figure 1). There was no evidence of distant metastatic disease. The patient underwent a diagnostic colonoscopy, which showed a rectosigmoid mass that was biopsied between 10 cm and 15 cm from the anal verge. Grossly, the mass was observed to have a flattened and friable mucosa. Histopathology favored a rare, poorly differentiated squamous cell carcinoma of the rectum. To confirm the impression of squamous differentiation, immunohistochemical (IHC) stains were performed on the biopsied specimens. The malignant cells showed strong cytokeratin 5/6 (CD5/6) immunoreactivity (Figure 2). Thus, squamous cell carcinoma of the rectum was diagnosed. Due to the squamous cell origin of her rectal mass, she underwent subsequent gynecologic evaluation. Cervical and endometrial biopsies were negative for malignancy. For tumor staging and evaluate for distant metastatic disease, the patient had a positron emission tomography (PET) scan, which showed a rectosigmoid mass in the colon with a standardized uptake value (SUV) of 16 and multiple PET-avid pelvic lymph nodes with SUVs of 2–3 (Figure 3).

Subsequently, she was diagnosed with stage III RSCC. Given the appearance of the tumor on CT scans, as well as the presence of PET-avid external iliac nodes in the perirectal region,

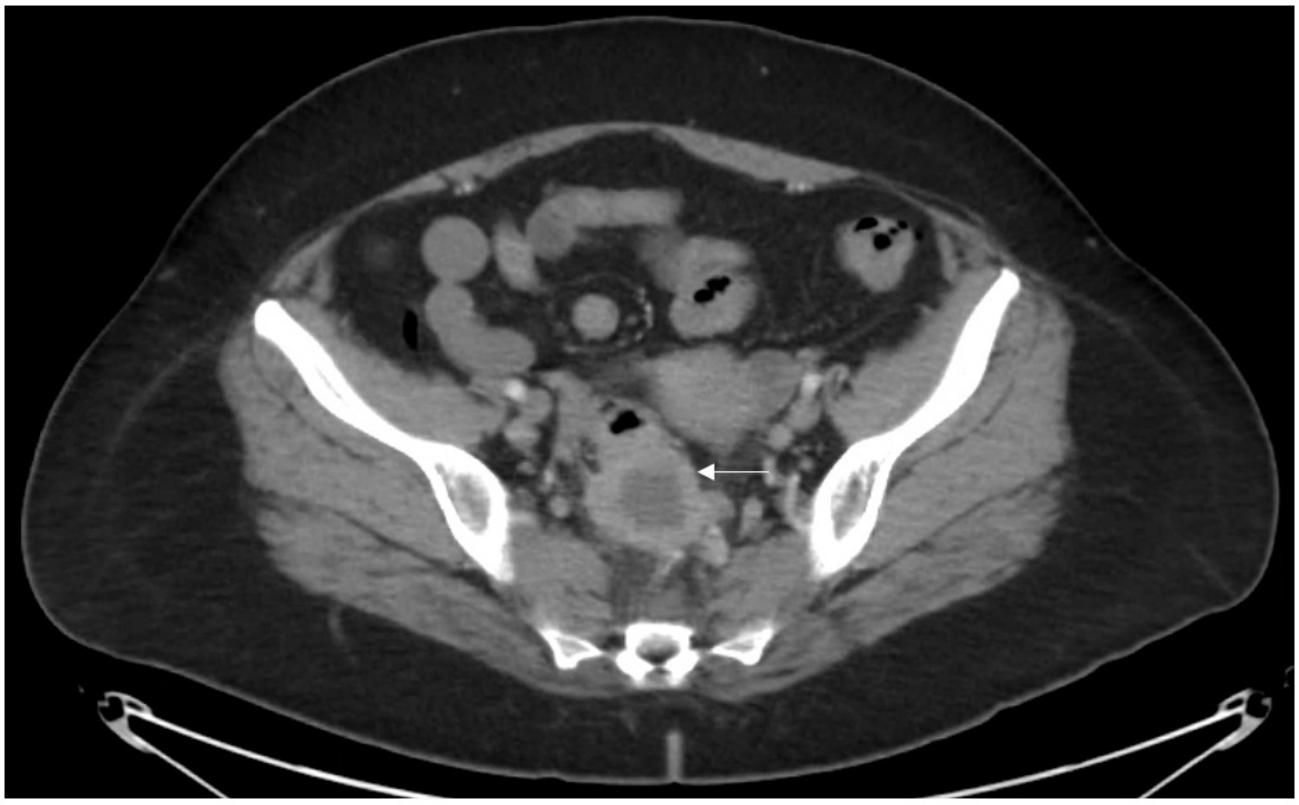

Figure 1. Abdominal imaging demonstrates a low-density mass involving the rectosigmoid colon. The rounded thick-walled structure measures approximately 4 cm (*arrow*). There is some adjacent inflammation in the presacral space as well as prominent lymph nodes. Given the radiological findings the differential diagnosis includes transmural abscess versus inflammatory carcinoma of the sigmoid colon.

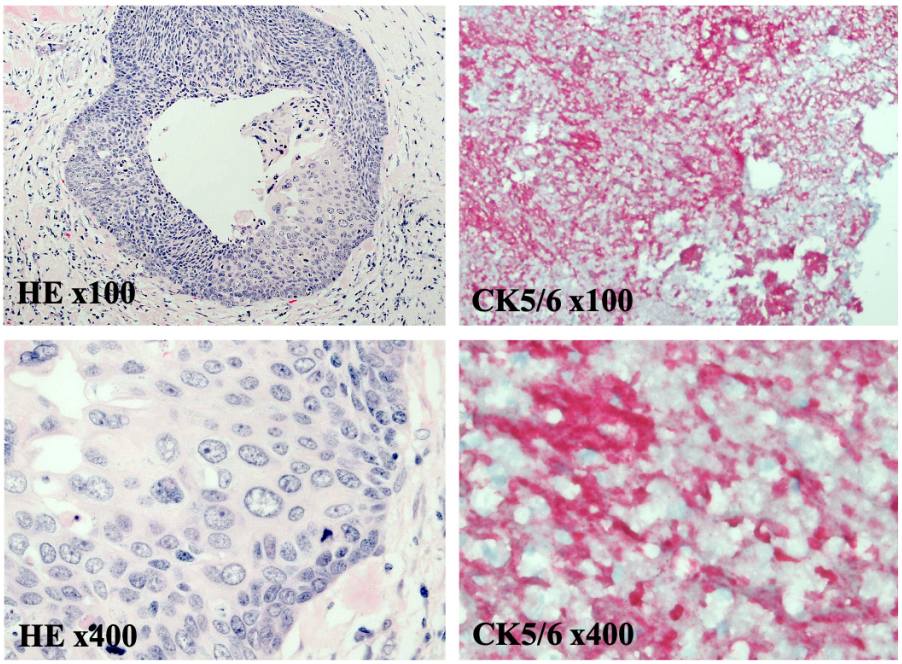

Figure 2. Pathology of the rectal mass demonstrates a squamous carcinoma. At medium and high power magnification, hematoxylin and eosin (HE) staining reveals sheets of poorly differentiated squamous cells invading the surrounding submucosal tissue (HE x40 and x100). Immunohistochemical staining for the squamous cell marker CK5/6, visualized by a cytoplasmic red-chromogen reaction, is positive (CK5/6 x40 and x100). Together histopathology and immunostaining show a poorly differentiated squamous cell carcinoma originating from rectal tissue.

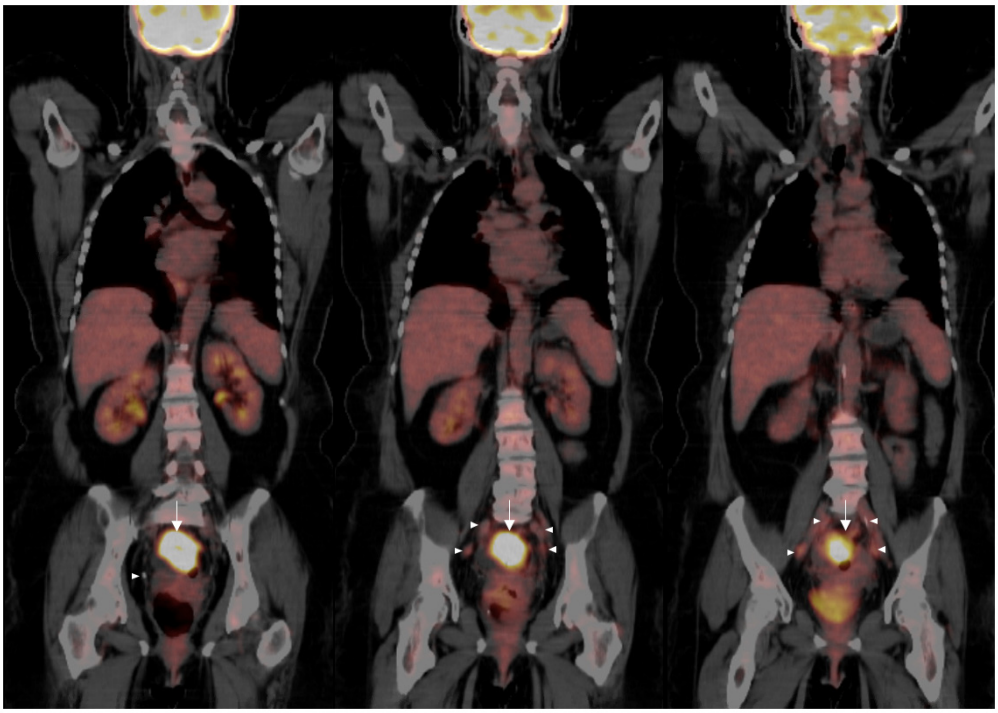

Figure 3. PET scans demonstrate a rectal malignancy. Imaging reveals a large focus of hypermetabolic activity in the rectosigmoid colon with a SUV of 16 and diffuse stranding in the region (*arrows*). There are multiple slightly prominent perirectal lymph nodes with the maximal SUV of 3.3 (*arrowheads*). There is presacral fat stranding and retroperitoneal lymphadenopathy, none of which exhibit hypermetabolism. No evidence of malignancy is noted above the diaphragm. Expected physiologic uptake of F-18 fluorodeoxyglucose is observed in the kidneys and brain. Given these findings, the rectal tumor was determined to be stage III rectal squamous cell carcinoma.

neoadjuvant chemoradiation with radiation followed by surgical intervention was recommended. She was started on neoadjuvant chemotherapy with continuous-infusion 5-flurouracil (5-FU) with concomitant radiation. She received radiation therapy (28 treatments; total dose of 180 centiGrays) to her entire pelvis. Follow-up CT scans showed an excellent response and near resolution of the tumor. Subsequent PET scans displayed a low SUV in the primary tumor site with no additional uptake. She proceeded with sigmoid colon resection, with minimal residual carcinoma. Given the patient's good response to chemotherapy and radiation, she was started on adjuvant chemotherapy with FOLFOX (leucovorin, 5-FU, and oxaliplatin) (Figure 4).

Following adjuvant FOLFOX chemotherapy for six months, all of the patient's consecutive surveillance CT scans have showed a complete resolution. This is consistent with a durable and long-lasting response to therapy for a rectal tumor that unusually originated from a poorly differentiated squamous cell carcinoma. The patient remains alive, healthy, and in complete remission following cessation of FOLFOX chemotherapy three years ago (Figure 4).

Discussion

Although RSCC has a similar presentation to rectal adenocarcinoma, its pathogenesis remains unclear and response to treatment is highly variable. Some of the most prominent risk factors include tobacco use, inflammatory bowel disease, radiotherapy and infections such as human immunodeficiency virus, human papilloma virus, amebiasis, and schistosomiasis[4,5]. Compared to adenocarcinoma of the rectum, RSCC occurs more often in younger Caucasian women with an average age of 60 years[6,7]. Patients clinically present with one or more of the following: gastrointestinal bleeding, changes in stool shape, diarrhea, constipation, tenesmus, weight loss and lower abdominal pain[5].

When histopathology is suggestive of RSCC, other more common etiologies such as anal squamous cell carcinoma, gynecological malignancy, and bowel fistula should be ruled out prior to establishing a definite diagnosis[8]. Further evaluation

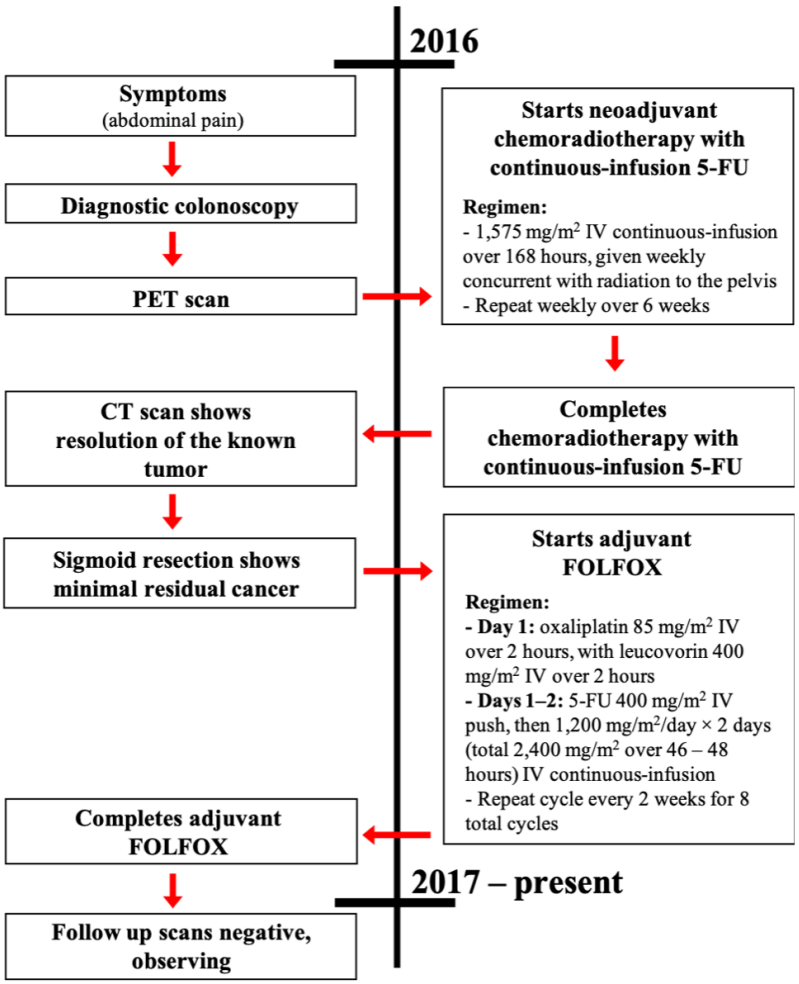

Figure 4. Case report timeline. Presented according to CARE guidelines.

and sampling can be achieved by colonoscopy and colposcopy. IHC plays an important role in differentiating RSCC from other histological subtypes. Although this specific IHC stain was not utilized in this case due to availability, cytokeratin CAM5.2, an epithelial marker, immunoreactivity suggests rectal tissue as the primary tumor site, rather than anal[4]. Cytokeratin 7 and 20 stain glandular epithelia in the upper and lower gastrointestinal tract, respectively[4,9]. While these markers identify adenomatous malignancies, both are expected to be negative by IHC in tumors with a squamous cell origin.

Historically, radical surgery was recommended for RSCC. However, more recent analyses have shown improved outcomes following chemoradiation only in localized disease or preceding salvage surgical resection in advanced disease to reduce tumor burden[2–4,6,7,10]. One of the main factors contributing to the discrepancy among the results and conclusions drawn is the lack of consistency in staging criteria used among all studies. This raises concern since management is based on tumor staging. Another factor that led to the paradigm shift was the amount of complications that arise following surgical intervention. Resection reduces the risk of death from the cancer itself. Patients often have worse outcomes and reduced overall survival due to the debilitating issues secondary to invasive interventions[5]. Review of the literature reveals treatment choice can also be influenced by the perceived severity of the illness. As a result, patients with advanced disease and a poorer prognosis were often offered surgical resection rather than conservative management with chemotherapy. However, poor outcomes following surgical resection could have been attributed to complications rather than the extent of the disease itself. The current understanding is based on case series, and results are highly biased. This in turn raises the need for a standardized staging system. Furthermore, randomized controlled trials would help outline an effective management strategy based on disease severity.

It has been postulated that staging based on size rather depth of invasion is a better predictor of prognosis[6]. Chemotherapeutic options for RSCC include 5-fluorouracil in combination with capecitabine or cisplatin. A five-year disease-free survival of 86% with chemoradiation only and 93% with chemoradiation plus salvage surgery has helped establish a benchmark for other therapeutic options[11]. Four other case series involving patients with advanced RSCC have shown improved overall survival with chemoradiation as definitive management, as well as alternative salvage surgery[2,10,12,13]. However, these retrospective observations are derived from small cohort studies that reported multiple limitations. Thus, it would be difficult to determine if the findings can be generalized.

Conclusion

This report presented a unique and rare case of a primary squamous cell carcinoma of the rectum. Most likely due to the extraordinarily low incidence of colorectal tumors having squamous cell origins, the etiology, pathogenesis, and risk factors for RSCC remain poorly understood. As a result, no standardized therapeutic regimen exists. Historically successful regimens for more common colorectal cancers, such as adenocarcinomas, will likely continue to be widely used in practice until additional therapeutic options are elucidated. Recently, overall survival has been shown to be improved for RSCC patients when certain regimens are used. However, this data comes from retrospective small cohort studies. Much work remains to be accomplished for patients with RSCC.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Consent

Written informed consent for publication of their clinical details and clinical images was obtained from the patient.

References

1. Fléjou JF: **WHO Classification of Digestive Tumors: The Fourth Edition.** *Ann Pathol.* 2011; **31**(5 Suppl): S27–31.
PubMed Abstract | Publisher Full Text

2. Yeh J, Hastings J, Rao A, *et al.*: **Squamous Cell Carcinoma of the Rectum: A Single Institution Experience.** *Tech Coloproctol.* 2012; **16**(5): 349–54.
PubMed Abstract | Publisher Full Text

3. Musio D, De Felice F, Manfrida S, *et al.*: **Squamous Cell Carcinoma of the Rectum: The Treatment Paradigm.** *Eur J Surg Oncol.* 2015; **41**(8): 1054–8.
PubMed Abstract | Publisher Full Text

4. Nahas CS, Shia J, Joseph R, *et al.*: **Squamous-cell Carcinoma of the Rectum: A Rare but Curable Tumor.** *Dis Colon Rectum.* 2007; **50**(9): 1393–400.
PubMed Abstract | Publisher Full Text

5. Guerra GR, Kong CH, Warrier SK, *et al.*: **Primary Squamous Cell Carcinoma of the Rectum: An Update and Implications for Treatment.** *World J Gastrointest Surg.* 2016; **8**(3): 252–65.
PubMed Abstract | Publisher Full Text | Free Full Text

6. Goffredo P, Robinson TJ, Frakes JM, *et al.*: **Comparison of Anal Versus Rectal Staging in the Prognostication of Rectal Squamous Cell Carcinoma: A Population-Based Analysis.** *Dis Colon Rectum.* 2019; **62**(3): 302–308.
PubMed Abstract | Publisher Full Text

7. Dutta SW, Alonso CE, Waddle MR, *et al.*: **Squamous Cell Carcinoma of the Rectum: Practice Trends and Patient Survival.** *Cancer Med.* 2018; **7**(12): 6093–6103.
PubMed Abstract | Publisher Full Text | Free Full Text

8. Williams GT, Blackshaw AJ, Morson BC: **Squamous carcinoma of the colorectum and its genesis.** *J Pathol.* 1979; **129**(3): 139–47.
PubMed Abstract | Publisher Full Text

9. Selves J, Long-Mira E, Mathieu MC, *et al.*: **Immunohistochemistry for Diagnosis of Metastatic Carcinomas of Unknown Primary Site.** *Cancers (Basel).* 2018; **10**(4): 108.
PubMed Abstract | Publisher Full Text | Free Full Text

10. Rasheed S, Yap T, Zia A, *et al.*: **Chemo-radiotherapy: An Alternative to Surgery for Squamous Cell Carcinoma of the Rectum--Report of Six Patients and Literature Review.** *Colorectal Dis.* 2009; **11**(2): 191–7.
PubMed Abstract | Publisher Full Text

11. Sturgeon JD, Crane CH, Krishnan S, *et al.*: **Definitive Chemoradiation for Squamous Cell Carcinoma of the Rectum.** *Am J Clin Oncol.* 2017; **40**(2): 163–166.
PubMed Abstract | Publisher Full Text

12. Clark J, Cleator S, Goldin R, *et al.*: **Treatment of Primary Rectal Squamous Cell Carcinoma by Primary Chemoradiotherapy: Should Surgery Still Be Considered a Standard of Care?** *Eur J Cancer.* 2008; **44**(16): 2340–3.
PubMed Abstract | Publisher Full Text

13. Loganadane G, Servagi-Vernat S, Schernberg A, *et al.*: **Chemoradiation in rectal squamous cell carcinoma: Bi-institutional case series.** *Eur J Cancer.* 2016; **58**: 83–9.
PubMed Abstract | Publisher Full Text

Open Peer Review

Current Peer Review Status: ? ? ✓

Version 1

Reviewer Report 24 August 2020

https://doi.org/10.5256/f1000research.26511.r67425

✓ **Mukesh S. Paudel**
Gastroenterology, Lumbini Medical College, Palpa, Nepal

The paper describes a rare case of squamous cell carcinoma of the rectum, which was diagnosed by colonoscopy and histopathological examination. The write-up is good and this paper will be a valueable addition to the current existing literature on this topic. The methodology of diagnosis and the treatment protocol have been well explained in the current paper.

Is the background of the case's history and progression described in sufficient detail?
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Yes

Is the case presented with sufficient detail to be useful for other practitioners?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Colonoscopy, IBS, Liver disease

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 30 June 2020

https://doi.org/10.5256/f1000research.26511.r65674

?

George S. Stoyanov
General and Clinical Pathology/Forensic Medicine and Deontology, Medical University of Varna, Varna, Bulgaria

- Based on the clinical description, the tumor seems to be in the sigmoid colon, which indeed is a rare localization. The authors however use the terms colon and rectum interchangeably. Rectal SCC carcinoma is common and the ethological factor there is most often HPV infection.

- Regarding patient information - it is too much revealing to indicate the profession of the patient. Please replace with the statement that her field of work is not associated with this kind of malignancy.

- On the diagnostic report, please specify TNM of the tumor and G as well. What did the gynecological report show, was there presence of HPV-associated changes in the cervical smear? That information could provide some information on the pathogenesis of the condition.

- On the report of the operative materials, please provide the TRG pf the tumor.

- In the discussion, RSCC does not share many of the hallmarks of AC - no mucus and obstructions are much less common.

- General comment on writing style: in some places the text is written very confusingly e.g.: "Although this specific IHC stain was not utilized in this case due to availability, cytokeratin CAM5.2, an epithelial marker, immunoreactivity suggests rectal tissue as the primary tumor site, rather than anal". The discussion needs to focus more on the analysis of the patient and the data you have stated in the introduction such as "no general consensus exists regarding the optimal treatment regimen due to the rarity of this cancer". Histology is of sub-par quality - in the H&E stained slides I am convinced that that is SCC, but I am not convinced on the location of the tumor, please provide a new slide which is more informative. The quality of the IHC is very bad, there is no counter staining on the cellular nucleus and the pattern on reactivity is more suggestive of tumor necrosis rather than that of any SCC - these need to be addressed. The abstract is way too short and seems a little bit detached from the article main text - please restructure it so be more coherent with the data provided in the manuscript.

Is the background of the case's history and progression described in sufficient detail?
Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
No

Is the case presented with sufficient detail to be useful for other practitioners?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: pathology, immunohistochemistry, oncology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 20 Jul 2020

Nathaniel Parker, Kansas University School of Medicine, 1010 N Kansas St, Wichita, USA

Based on the clinical description, the tumor seems to be in the sigmoid colon, which indeed is a rare localization. The authors however use the terms colon and rectum interchangeably. Rectal SCC carcinoma is common and the ethological factor there is most often HPV infection.
- This is to reflect the dynamic titles that were used in operative and pathology reports to describe this case (e.g. rectal vs. rectosigmoid). In terms of HPV, these details were not clinically significant to oncologist involved with the case, and thus were not reported.

Regarding patient information - it is too much revealing to indicate the profession of the patient. Please replace with the statement that her field of work is not associated with this kind of malignancy.
- This is a biased and non-constructive criticism However, if it satisfies the peer reviewer, this vocational information was made available at the request of the Editorial Board. Please ensure you are update on the peer review standards of F1000Research.

On the diagnostic report, please specify TNM of the tumor and G as well. What did the gynecological report show, was there presence of HPV-associated changes in the cervical smear? That information could provide some information on the pathogenesis of the condition.
- All relevant information has been provided in the case.

On the report of the operative materials, please provide the TRG pf the tumor.
- No TRG information was available to report.

In the discussion, RSCC does not share many of the hallmarks of AC - no mucus and obstructions are much less common.General comment on writing style: in some places the

text is written very confusingly e.g.: "Although this specific IHC stain was not utilized in this case due to availability, cytokeratin CAM5.2, an epithelial marker, immunoreactivity suggests rectal tissue as the primary tumor site, rather than anal". The discussion needs to focus more on the analysis of the patient and the data you have stated in the introduction such as "no general consensus exists regarding the optimal treatment regimen due to the rarity of this cancer". Histology is of sub-par quality - in the H&E stained slides I am convinced that that is SCC, but I am not convinced on the location of the tumor, please provide a new slide which is more informative. The quality of the IHC is very bad, there is no counter staining on the cellular nucleus and the pattern on reactivity is more suggestive of tumor necrosis rather than that of any SCC - these need to be addressed. The abstract is way too short and seems a little bit detached from the article main text - please restructure it so be more coherent with the data provided in the manuscript.
- These criticisms are biased and/or non-constructive.
- All available and relevant information has been reported in the case.

Competing Interests: No competing interests to report.

Reviewer Report 29 June 2020

https://doi.org/10.5256/f1000research.26511.r64793

?

Pratiksha Singh
Mercer County Community College, Trenton, NJ, USA

The case report is well described in terms of investigations performed and the treatment modality selected. It helps the practitioners by adding to the limited number of case reports and presentations available. However, the authors fail to describe the patient's symptoms and physical examination in sufficient detail:

1. The chief complaint in an emergency department as abdominal pain requires a further detailed description of presenting symptoms especially pertaining to relevant negative history about bowel habit changes, bleeding per rectum and weight loss.

2. It would help to describe smoking as pack years rather than chronic tobacco smoking for better interpretation.

3. The authors mention measurements that were unremarkable along with vital signs, it would be helpful to describe what these were (Guerra, 2006[1]).

During the staging process, it would be helpful to know the relevant system used (AJCC 7th or 8th edition staging for rectal carcinoma (Tong *et al.*, 2018[2]).

During discussion, the authors mention "Compared to adenocarcinoma of the rectum, RSCC

occurs more often in younger Caucasian women with an average age of 60 years". A recent update mentions the age of the patients usually range from 39-93 years with average 63 years with no apparent ethnic predisposition (Guerra, 2006[1]).

It would also help if in the discussion the authors could explain how this particular case was unique.

Thank you for giving the opportunity to review and learn from your case report.

References

1. Guerra GR, Kong CH, Warrier SK, Lynch AC, et al.: Primary squamous cell carcinoma of the rectum: An update and implications for treatment.*World J Gastrointest Surg*. 2016; **8** (3): 252-65 PubMed Abstract | Publisher Full Text
2. Tong GJ, Zhang GY, Liu J, Zheng ZZ, et al.: Comparison of the eighth version of the American Joint Committee on Cancer manual to the seventh version for colorectal cancer: A retrospective review of our data.*World J Clin Oncol*. 2018; **9** (7): 148-161 PubMed Abstract | Publisher Full Text

Is the background of the case's history and progression described in sufficient detail?
No

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Yes

Is the case presented with sufficient detail to be useful for other practitioners?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Limited by knowledge of immunohistochemistry.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 20 Jul 2020

Nathaniel Parker, Kansas University School of Medicine, 1010 N Kansas St, Wichita, USA

Thank you for the review. The authors responses are listed below peer review comments

The chief complaint in an emergency department as abdominal pain requires a further detailed description of presenting symptoms especially pertaining to relevant negative

history about bowel habit changes, bleeding per rectum and weight loss.
- All available details from the case presentation that were pertinent and/or positive have been listed.

It would help to describe smoking as pack years rather than chronic tobacco smoking for better interpretation.
- Smoking pack years was unknown to the authors.

The authors mention measurements that were unremarkable along with vital signs, it would be helpful to describe what these were (Guerra, 2006[1]).
- All available and relevant details from the case have been listed.

During the staging process, it would be helpful to know the relevant system used (AJCC 7th or 8th edition staging for rectal carcinoma (Tong *et al.*, 2018[2]).
- No formal staging process, such as the one mentioned, was not used during this case's work-up and management process. Thus, it would not be factual to present the case in such a manner.

During discussion, the authors mention "Compared to adenocarcinoma of the rectum, RSCC occurs more often in younger Caucasian women with an average age of 60 years". A recent update mentions the age of the patients usually range from 39-93 years with average 63 years with no apparent ethnic predisposition (Guerra, 20061).
- Please see reference numbers 6 and 7, which are more recent.

It would also help if in the discussion the authors could explain how this particular case was unique.
- Please see the Abstract and Conclusion sections.

Competing Interests: No competing interests to disclose