CASE REPORT – OPEN ACCESS

International Journal of Surgery Case Reports 6 (2015) 175–178

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.casereports.com

Metachronous adenocarcinoma of the anal canal after anterior resection for sporadic primary rectal adenocarcinoma: A rare case report

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ARTICLE INFO

Article history:
Received 7 July 2014
Accepted 28 July 2014
Available online 11 December 2014

Keywords:
Anal canal
Adenocarcinoma
Case report
Treatment

ABSTRACT

INTRODUCTION: Anal canal adenocarcinoma is an extremely rare malignancy with poorly defined diagnostic and treatment criteria.
PRESENTATION OF CASE: A 42-year-old women was diagnosed with primary anal canal adenocarcinoma 11 months after undergoing anterior resection for primary sporadic rectal adeocarcinoma. Transanal excision was performed and additional adjuvant chemotherapy was given. Immunohistology showed positivity for cytokeratin (CK) 20 and CDX2, and negative CK7, which is compatible with colorectal subtype anal adenocarcinoma. At 6 months follow-up the patient has no evidence of recurrent or metastatic disease.
DISCUSSION: Diagnosis of primary anal adenocarcinoma is typically delayed because of its rarity, and vague clinical presentation. Exact histologic criteria remain poorly defined but the use of immunohistology has improved the overall diagnostic accuracy of anal adenocarcinoma and it also helps define its correct origin. Reports on the management and outcomes of this cancer consist mainly of retrospective studies with no consistent treatment strategy and limited comparison data. Most authors currently recommend neoadjuvant chemoradiotherapy and radical resection. Despite aggressive therapy, rates of local failure and distant recurrence remain high.
CONCLUSION: Diagnosis of adenocarcinoma of the anal canal is difficult but specific immunohistolgic patterns help to correctly identify its correct origin and subtype. Defining the correct subtype of anal adenocarcinoma may impact treatment strategies of this rare cancer.

1. Introduction

Anal canal adenocarcinoma is a rare gastrointestinal tumor; comprising 5–19% of all anal canal malignancies.[1] Standard treatment for adenocarcinoma of the anal canal has not been clearly defined, mainly because of the rarity of this malignancy. Treatment modalities include combined chemoradiotherapy, local excision, and radical excision with abdominoperineal resection. Treatment outcomes are scarce and limited to small retrospective studies and case reports, with no prospective and limited comparative data. We present a case of metachronous anal canal adenocarcinoma occurring after anterior resection and adjuvant chemoradiotherapy for a primary rectal adenocarcinoma.

2. Presentation of case

A 42 year old women with no significant past medical history presented with intermittent hematochezia of 1 month duration. She denied abdominal pain, constipation, or family history of colorectal cancer. Physical examination revealed mild hemorrhoidal disease and a normal digital rectal exam. Colonoscopy was performed and demonstrated a 4-cm long circumferential and ulcerated rectal mass, 12 cm from the anal verge. These findings were confirmed with rigid proctoscopy; and endoscopic biopsies confirmed adenocarcinoma and high-grade dysplasia arising in a tubulovillous adenoma. Pelvic magnetic resonance imaging (MRI) showed a tumor confined to the rectal wall with no evidence of adenopathy or a threatened circumferential resection margin. Further oncologic work-up, including a positron emission tomography – computed tomography (PET-CT) did not show evidence of locally invasive or metastatic disease.

After preoperative clearance, the patient underwent a hand-assisted laparoscopic anterior resection of the rectum without complications. The patients' postoperative course was uncomplicated and she was discharged on postoperative day seven. Final

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http://dx.doi.org/10.1016/j.ijscr.2014.07.021

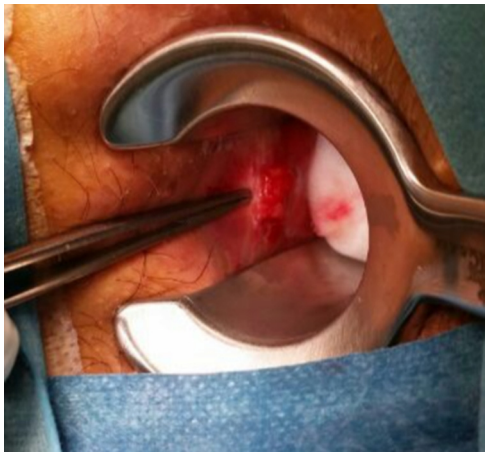

Fig. 1. Intraoperative photograph showing a nodular lesion at the left lateral position of the upper anal canal.

pathology reported a 6/4.5/1.7 cm moderately differentiated adenocarcinoma arising in a tubulovillous adenoma with positive lymphovascular and perineural invasion, as well as intra and peritumoral lymphocytic infiltrate. Twelve of 29 perirectal lymph nodes showed evidence of metastatic disease (TNM classification T3N2b, stage IIIC). Mesorectal grading for completeness of resection was "good" and all resection margins were negative for malignancy. Given the patients' pathologic staging and the recommendations by medical oncology, she received adjuvant chemotherapy (leucovorin, fluorouracil, and oxaliplatin [FOLFOX]), and long-course radiotherapy (total of 45 Gy fractioned over five weeks). She tolerated her adjuvant therapy well with no severe complications or need for hospital admission.

During post-treatment follow-up, the patient remained asymptomatic. Eleven months after surgery she underwent a follow-up colonoscopy that showed a normal appearing and patent colorectal anastomosis at 15 cm from the anal verge. The rest of the colonoscopy was normal. Digital rectal exam showed a mobile, pale-yellow, 1-cm nodular lesion at the left lateral position of the upper anal canal with a smooth surface (Fig. 1). There was no evidence tumor fixation, tethering, or ulceration. There was no evidence of inguinal adenopathy. Biopsy of the anal canal lesion showed poorly differentiated adenocarcinoma. Endoanal ultrasound demonstrated a 1 by 0.6 cm nodule at the left lateral position of the upper anal canal without evidence of sphincter involvement or adenopathy (Fig. 2). Pelvic MRI and PET-CT did not show evidence of locally invasive or metastatic disease. Shortly thereafter, the patient underwent a transanal excision of the lesion with 1-cm margins of normal-appearing tissue (Figs. 3 and 4). Additional margins were excised and evaluated intraoperatively and showed no evidence of malignancy. The patient tolerated the procedure well and there were no complications. Final pathology showed a high-grade poorly differentiated adenocarcinoma with positive lymphovascular and perineural invasion (TNM classification T1N0, stage I). No lymphocytic infiltrate was noted and all margins were negative for malignancy. Tissue staining showed positivity for cytokeratin (CK) 20 and CDX2, and negative CK 7. Additional adjuvant chemotherapy was recommended and the patient tolerated this well. Six months after surgery, the patient is asymptomatic with no evidence of recurrent or metastatic disease.

3. Discussion

Carcinomas of the anal canal are rare malignancies comprising approximately 1–2%of all gastrointestinal carcinomas.[1] Most anal canal carcinomas are squamous cell carcinomas, with less than

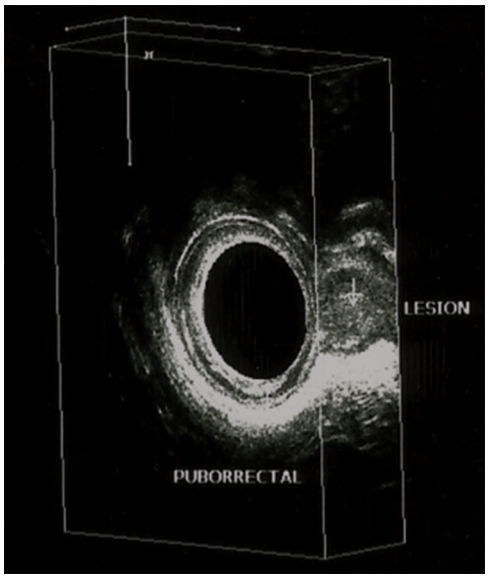

Fig. 2. Endoanal ultrasound demonstrating the location and position of a metachronous adenocarcinoma of the anal canal.

20% being adenocarcinomas.[2] There are two subtypes of anal canal adenocarcinomas: (1) Colorectal (mucosal-based), and (2) Extramucosal (fistula-associated or anal gland). The colorectal subtype originates in the mucosa of the anal canal and is histologically identical to colorectal adenocarcinomas. The extramucosal subtype has no overlying mucosal lesion and arises from the columnar epithelium lining of anal glands. These glands open into the transitional zone of the anal canal through the internal anal sphincter.[3,4] This subtype is more aggressive and has been frequently reported in association with chronic anorectal fistulas and Crohn's disease.[5,6] Adenocarcinomas extending down from the rectum are considered rectal adenocarcinomas. Risk factors for the development of anal canal adenocarcinoma include cigarette smoking, human immunodeficiency virus infection, human papilloma virus infection and anal intercourse.[1,7–9]

The differentiation of anal canal adenocarcinoma from other adenocarcinomas is difficult and diagnostic criteria have not been well established. The utility of immunohistochemistry has been

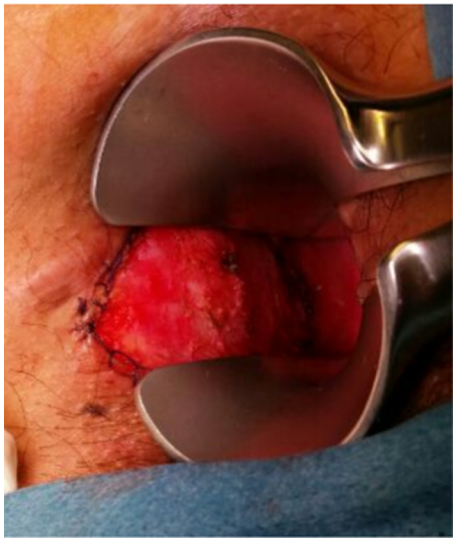

Fig. 3. Intraoperative photograph after wide local excision of a metachronous adenocarcinoma of the anal canal.

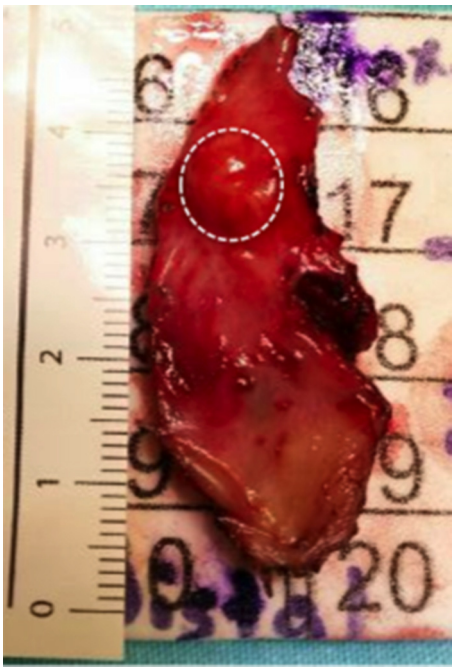

Fig. 4. Gross pathologic specimen after transanal excision of a metachronous adenocarcinoma of the anal canal.

reported in primary anal adenocarcinoma and specific markers include p63, CK 5/6, CDX2, CK 7, CK 20.[8] Specific immunohistochemical patterns have been useful to distinguish anal canal adenocarcinoma subtypes (Table 1), and may play a role when choosing a treatment strategy.

The management of adenocarcinoma of the anal canal remains controversial. High rates of pelvic failure and distant metastasis among patients with anal adenocarcinoma treated with surgery alone or chemoradiotherapy have been reported.[10,11] A retrospective review from the Rare Cancer Network in Europe reviewed the outcomes of 82 patients with anal adenocarcinoma treated with multiple different modalities.[10] Disease-free and overall survival were improved with chemoradiotherapy *versus* radiotherapy plus surgery or surgery alone (risk ratio, 0.31 and 0.28; $P < 0.001$). Multivariate analysis showed that T and N stage, histologic grade, and treatment modality were significant prognostic factors. The authors therefore recommended that definitive chemoradiotherapy should be considered for these patients and radical resection should be reserved for salvage. From a 20-year experience at the MD Anderson Cancer Center, Chang et al.[11] reviewed the outcomes of 28 patients with anal canal adenocarcinoma treated with local excision ($n = 13$), and radical excision ($n = 15$). Thirteen patients received neoadjuvant chemoradiotherapy, 10 adjuvant chemoradiotherapy, and 3 adjuvant radiotherapy alone. At a median follow-up of 37 months, median disease-free survival was 13 months after local excision and 32 months after radical surgery ($P = 0.055$). Overall survival at 5 years was 43% for patients treated with local excision and 63% for patients treated with radical surgery ($P = 0.3$). Tumor grade was predictive of overall survival and recurrence. Based on this experience, the authors recommended neoadjuvant chemoradiotherapy and radical excision. At Memorial Sloan-Kettering Cancer Center, 13 patients with primary anal adenocarcinoma were followed for a median of 19 months after treatment with neoadjuvant chemoradiotherapy plus abdominoperineal resection ($n = 5$), local excision plus adjuvant radiotherapy or chemoradiotherapy ($n = 5$), or abdominoperineal resection plus adjuvant chemoradiotherapy ($n = 3$).[12] Median survival was 26 months and local recurrence occurred in 37% of patients. Patients treated with abdominoperineal resection plus pre or postoperative radiation or combined modality therapy had a 37% local recurrence rate, and three of eight showed no evidence of disease at last follow-up. Patients who underwent local excision plus adjuvant radiation or combined modality therapy had a 40% local recurrence rate with one local failure salvaged by abdominoperineal resection, and one of the five patients had no evidence of disease upon follow-up.

Table 1
Immunohistology patterns used to differentiate subtypes of primary anal canal adenocarcinoma.

	Colorectal type	Extramucosal type
p63	Negative	Negative
CK 5/6	Negative	Negative
CDX2	Positive	Negative
CK 7	Occasionally positive	Positive
CK 20	Positive	Negative

CK: cytokeratin.

The therapeutic approach and oncologic results of studies evaluating the management of primary anal adenocarcinoma invariably reflect surgeon and patient preference, as well as tumor stage. Furthermore, the limited experience with a single therapeutic approach is likely related to the rarity of this malignancy. Our case report of primary anal canal adenocarcinoma is unique because it was diagnosed 11 months after treatment of a primary rectal adenocarcinoma. Adjuvant chemoradiotherapy had already been given after her prior anterior resection; therefore, additional neoadjuvant therapy was contraindicated. Local excision was performed largely because of patient preference but immunohistology was taken into account as well. Immunohistology was indicative of a colorectal subtype anal adenocarcinoma, which has been reported as less aggressive compared to the extramucosal subtype. Although specific immunohistochemistry patterns may play a role in the treatment of anal adenocarcinoma, treatment outcomes based on immunohistology have not been reported. The decision to give further adjuvant chemotherapy was based on the poor histologic findings seen on final pathology. The patient understands the inherent risk of local and distant recurrence of disease and the questionable role of salvage therapy. Currently, she is committed to a rigorous follow-up and screening program which involves endoanal ultrasound, colonoscopy, and PET-CT.

4. Conclusion

In this rare case report, we present a metachronous anal canal adenocarcinoma diagnosed 11 months after treatment of a sporadic primary rectal adenocarcinoma. Immunohistology was essential to establish the diagnosis of a colorectal subtype anal adenocarcinoma. Based on clinical and histologic characteristics of the tumor, and imaging studies; transanal excision was performed.

Reports of anal canal adenocarcinoma in the current literature consist of small case series and retrospective reviews with no clear consensus regarding the ideal treatment option. Despite high local and distant failure rates with most available treatment options, neoadjuvant chemoradiotherapy and radical resection are recommended. The use of immunohistology to establish the correct subtype of anal adenocarcinoma is essential, and in the future, certain immunohistologic patterns may influence treatment strategies of this rare cancer.

Funding

None.

Conflicts of interest

The authors have no financial disclosures to report.

Patient consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Authors' contributions

All the authors have contributed equally in study design, data collection, data analysis, and manuscript preparation.

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