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ORIGINAL ARTICLE

Do Acellular Mucin Pools in Resection Margins for Rectal Cancer Influence Outcomes?

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Abstract

Positive resection margins predict poor prognosis in rectal cancer (RC). Literature on the impact of acellular mucin (ACM) in circumferential resection margin (CRM) or distal resection margin (DRM) of proctectomy specimens on RC recurrence and outcomes is lacking. The retrospective study was conducted to determine the oncological outcomes of the RC patients with ACM in or within 1 mm of margins of the rectal resection specimens. Histopathology reports of RC resection specimens dated from June 2013 till May 2016 were reviewed to identify cases with ACM in CRM ($n = 10$) and DRM ($n = 2$). Relevant details of these patients were gathered from the electronic medical record. Pattern of recurrence was studied. In cases with only ACM in CRM ($n = 10$), disease (primary tumor or nodes) was radiologically reaching the mesorectal fascia except two, who had extra mesorectal nodes. Median distance of tumor from anal verge was 2 cm. All patient received neoadjuvant therapy: four patients received chemoradiotherapy (NACTRT), one received short-course radiotherapy, and five received NACTRT followed by neoadjuvant chemotherapy. Abdominoperineal resection, intersphincteric resection and total pelvic exenteration were done for six, three, and one patient, respectively. In two additional cases of anterior resection with ACM in DRM, one underwent upfront resection while the other received NACTRT. Over a mean follow-up period of 43 months, four patients developed recurrences. Two of them had local recurrence and only one had isolated local recurrence. ACM in resection margins of RC resection specimens does not seem to increase likelihood of local recurrence.

Keywords Rectal cancer · Mucin · Resection margin · Cancer recurrence

Introduction

It is not uncommon to find acellular mucin (ACM) pools in resection specimens of rectal cancer (RC) treated with neoadjuvant chemoradiation (NACTRT). The current recommendation by the College of American Pathologists is to regard ACM as a type of treatment response and not as a residual tumor [1]. However, robust evidence for or against it is lacking [2]. The recommendation seems to aim at achieving a standardized reporting. A retrospective study concluded that ACM pools in RC resection specimen may suggest aggressive disease biology [3] whereas others concluded that it does not

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impact outcomes [2, 4]. It is now established that positive circumferential resection margin (CRM) or longitudinal resection margin predicts poor prognosis. With frequent use of NACTRT, there are instances when ACM is detected in the CRM of rectal resection specimens. This particular finding raises concern in the mind of the treating surgeon as well as the patient. There is dearth of literature on the impact of ACM pools involving resection margins on RC recurrence and outcome. This series aims to throw light on outcomes of this rare patient subset.

Aim

The study was conducted to determine the oncological outcomes of the RC patients with ACM in or within 1-mm margins of the rectal resection specimens.

Methodology

Histopathology reports of RC resection specimens dated from June 2013 to May 2016 at our institution were retrieved. As a standardized pathology evaluation protocol (for post-neoadjuvant-treated RC specimens), in cases with histologic presence of "ACM only," complete tumor bed is sampled with step-serial evaluation at our center. A total of 219 reports recording the presence of "ACM pools" on microscopy were reviewed. Of these, all cases with presence of ACM pools at or within 1 mm of the resection margins were retrieved. These broadly included two types of cases: (1) cases with complete pathologic response (pCR) containing only ACM pools that were completely devoid of viable cancer cells and (2) cases with variable amounts of residual cancer cells, however containing isolated ACM lakes (discrete and separate from foci bearing residual viable tumor cells) reaching the resection margin (Fig. 1). Cases where resection margins were involved by mucin pools bearing residual cancer cells were excluded. Pertinent details including preoperative tumor (T), node (N), and metastasis (M) staging; radiological imaging reports; neoadjuvant therapy; operative details; histopathology reports; adjuvant therapy; and follow-up visit details of these patients were gathered from the electronic medical record. Follow-up visit notes and investigations were

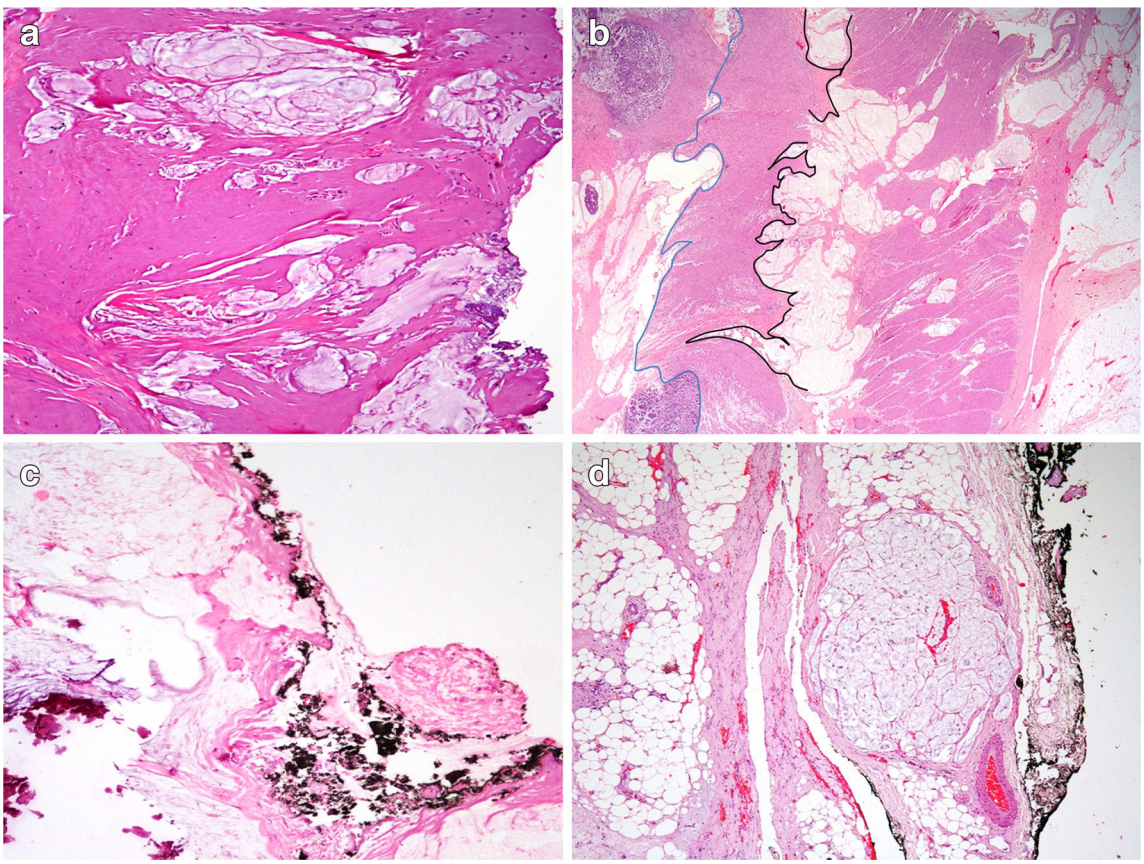

Fig. 1 **a** A tumor showing complete pathologic response with acellular mucin pools only (magnification, × 100). **b** Pools of acellular mucin on the right side of the image, separate and well demarcated (black line) from areas bearing residual cancer cells on the left side (delineated with blue line) (magnification, × 10). **c** Inked circumferential resection margin involved by acellular mucin (magnification, × 100). **d** Acellular mucin pools reaching within 1 mm of the inked margin (magnification, × 40)

studied to identify sites of recurrence. Follow-up period was calculated from the date of surgery to the date of last visit to the hospital. Recurrences were categorized as local, regional, or distant. Recurrence pattern was assessed. All details were recorded and analyzed using SPSS software (SPSS Inc.).

Results

There were ten cases with ACM pools reaching CRM and two cases with ACM reaching distal resection margin (DRM). Four patients had complete pathologic response (yT0) whereas eight patients had residual cancer cells (ypT1–3 and one pT4); however, the mucin pools that involved the margins were acellular and devoid of cancer cells.

A. CRM involvement ($n = 10$)

All 10 cases had low RCs. Age ranged from 25 to 57 years. All patients had disease (primary tumor or nodes) radiologically reaching the mesorectal fascia (MRF) except two who had extra mesorectal nodes. The median distance of the primary tumor from anal verge was 2 cm (range 1–4 cm). All patient received neoadjuvant therapy: four patients received NACTRT, one received short-course radiotherapy, and five received NACTRT followed by neoadjuvant chemotherapy. After NACTRT, these cases were evaluated with magnetic resonance imaging (MRI) of the pelvis and further neoadjuvant chemotherapy was administered in those in whom R0 rectal resection was unlikely.

Abdominoperineal resection (APR), intersphincteric resection, and total pelvic exenteration were conducted for six, three, and one patients, respectively. Complete pathological response was achieved in four cases (Table 1).

Over a mean follow-up period of 40.8 months (range 5–153, months), two patients had distant recurrences, one had locoregional as well as distant site recurrence, and one had a local anastomotic site recurrence (Table 2).

B. ACM in DRM involvement ($n = 2$)

We also identified two patients who had ACM in DRM and are disease-free on follow-up. The details of these patients are given in Table 3.

Eventually, we noticed 17% (2 out of 12 patients) local recurrence rate and 28.5% (4 out of 12 patients) of overall recurrence rate (local and/or systemic recurrence) over a mean follow-up period of 43 months. Only one patient of the total 12 cases (8.3%) had isolated local recurrence.

Table 1 Clinico-pathological profile of the cases

Case	Age in years and sex	cT[a] stage	Disease extent	Neoadjuvant therapy [c]	Surgery	Pathological staging	ACM in relation to CRM	TRG[d]	Follow-up in months
A	57 male	T4	Disease reaching the lateral pelvic wall	NACTRT +8 # CAPOX	Total pelvic exenteration	ypT2N0	Upto CRM	5	13
B	25 female	T3	Primary tumor reaching CRM	NACTRT	APR	ypT0N0	< 0.1 cm from CRM	1	54
C	32 male	T3	Presence of Extramesorectal nodes and suspicious peritoneal metastasis [b]	NACTRT +6 # CAPOX	Prone APR	ypT3N1b	Upto CRM	4	5
D	48 male	T4	Primary tumor reaching CRM	NACTRT +8 # FOLFIRINOX	Prone APR	ypT3N0	Upto CRM	2	11
E	26 male	T3	Primary tumor reaching CRM	NACTRT +4 # FOLFIRINOX	Extralevator APR	ypT0N0	Upto CRM	1	45
F	50 male	T3	Mesorectal node reaching CRM	NACTRT	Intersphincteric resection	ypT2N1b	< 0.1 cm from CRM	3	153
G	28 male	T3	Primary tumor reaching CRM	SCRT	Intersphincteric resection	ypT3N1	< 0.1 cm from CRM	2	45
H	31 male	T3	Mesorectal nodes reaching CRM	NACTRT +4 # FOLFIRINOX	APR	ypT0N0	Upto CRM	1	36
I	29 male	T3	Presence of extramesorectal nodes	NACTRT	Intersphincteric resection	ypT0N0	Upto CRM	1	35
J	49 female	T4	Primary tumor reaching CRM	NACTRT	APR	ypT3N2b	Upto CRM	2	11

[a] cT is clinical T stage

[b] Staging laparoscopy before definitive surgical resection revealed no evidence of distant disease in this case

[c] Abbreviation # chemotherapy cycle

[d] Abbreviation TRG, tumor regression grade

Table 2 Details of rectal cancer cases with recurrence

Case	Stage	Neoadjuvant treatment	Site of recurrence	Disease-free interval (months)	Follow-up period (months)
B	cT3	NACTRT	Breast	23	54
C	cT3	NACTRT +6 # CAPOX	Pararectal soft tissue mass and para-aortic nodes, bone	5	5
D	cT4	NACTRT +8 # FOLFIRINOX	Liver	7	11
G	cT3	SCRT	Local anastomotic site	45	45

Discussion

Dworak et al. [5] first defined the presence of mucin pools in RC resection specimens after chemoradiotherapy. Various other studies have correlated prior treatment with radiotherapy to induction of mucinous changes in the rectal tumors [6, 7]. The impact of ACM in rectal resection specimen on RC outcomes is not exactly known. There are many case studies looking at the significance of ACM in rectal resection specimen, some of them suggest that its presence does not affect outcomes [2, 4].

A positive CRM confers a poor prognosis [8] and indicates a high likelihood of local recurrence, more so in cases who have received neoadjuvant therapy [9]. CRM-positive resection rates vary from 1 to 28% [9]. Additional neoadjuvant chemotherapy in unresectable RCs post NACTRT has been evaluated in a study by Ostwal et al. [10]. Five of our patients did receive further such therapy in an effort to downsize the tumor.

This study deals with a very peculiar subset of unfortunate RC patients with "CRM-positive" resection specimens but fortunate enough to have only ACM in the CRM and hence reported to have negative CRM. This is likely to be a very rare subset and hence the number of cases in our study is low. None of the studies till date have reported outcomes of patients with ACM reaching or close to CRM, making our series unique.

In our study, overall recurrence rate was 28.5% and only one had isolated local recurrence (8.3%). The German randomized trial of preoperative versus postoperative chemoradiotherapy published a local relapse rate of 7.1% in the preoperative chemoradiotherapy group [11]. Another large study evaluating the patterns of failure in patients with locally advanced RC revealed an overall recurrence rate of 25.9% and local recurrence rate of 7.4% [12]. Hence, rate of recurrence in this study seems acceptable.

It is noteworthy that nine out of ten patients of this study with ACM in CRM had radiologically positive CRM at presentation. It may be right in judging that neoadjuvant therapy sterilized all these radiologically positive CRMs to yield acellular mucin at CRM. This finding suggests that tumors with mucinous component reaching till MRF, as seen on MRI (Figs. 2 and 3), may be resected after neoadjuvant therapy with acceptable rate of recurrence and avoidance of the morbidity of more extensive resections. Further consideration to factors that predict pathological complete response such as pretreatment CEA levels and interval between NACTRT and surgery [13] may help us guide in planning treatment, predicting negative CRM and selecting the type of surgery for RC cases with radiologically positive CRM. It is also imperative to counsel the patients and relatives regarding the likelihood of local as well as systemic recurrence in the context of locally advanced rectal cancer and ensure compliance to surveillance protocol. Timely diagnosis of any recurrence will help the multidisciplinary team to offer a curative treatment plan to the patient.

Do ACM pools really indicate complete pathological response? Additional multilevel sectioning and immunohistochemical processing have helped identify residual tumor cells in ACM pools in post-chemoradiotherapy proctectomy specimens of RC [14]. Use of such aggressive pathological processing before qualifying mucin pools as acellular will help to prognosticate accurately, but this approach needs further evaluation.

Table 3 Cases with ACM in DRM ($n = 2$)

	Case 1	Case 2
Site	Rectosigmoid	Rectum
Neoadjuvant treatment	Nil	NACTRT
Surgery	AR	AR
Stage	pT4 pN1b	pyT2 pyN2a
Adjuvant treatment	8 # CAPOX	8 # CAPOX
Follow-up (months)	46	62
Status	Alive and disease-free	Alive and disease-free

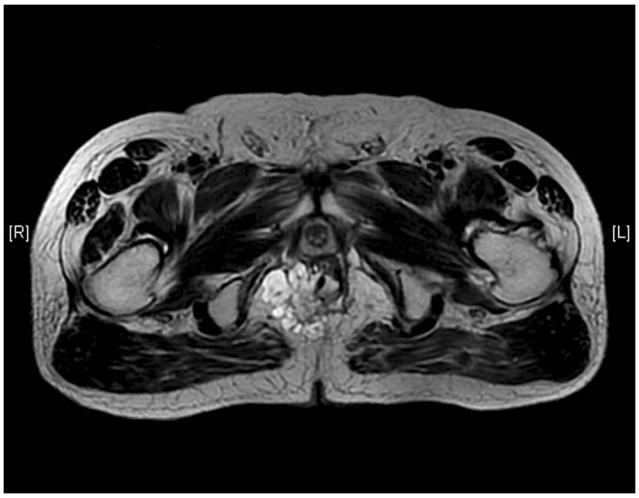

Fig. 2 MRI T2-weighted axial image showing mucin reaching CRM in a case of rectal cancer post NACTRT

Small case number and retrospective nature of the study precludes definite conclusion but generates interest in conducting further large sample size studies to evaluate outcomes and management strategy for this group of patients.

Conclusion

Though the small sample size of our study limits achieving any definite conclusions, ACM pools in resection margins do not seem to increase likelihood of local recurrence. Further prospective studies and collaborative research will enlighten us upon the prognostic implications of ACM in resection margins.

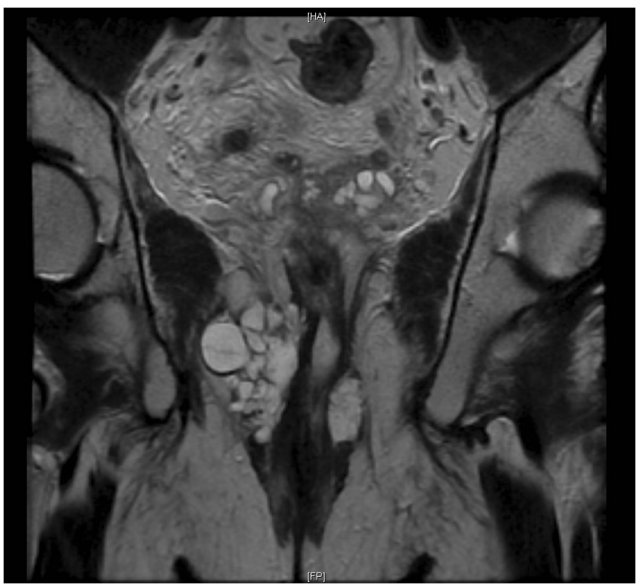

Fig. 3 MRI T2-weighted coronal image showing mucin reaching CRM in a case of rectal cancer post NACTRT

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