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Title: Extensive resection for treatment of locally advanced primary mucinous adenocarcinoma arising from fistula in ano.

Running Title: Extensive resection for perianal adenocarcinoma

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Signed informed consent was gain from the patient involved prior to the write up of this report.
Abstract

We report a case of a 66-year-old male who presented with a locally advanced primary mucinous adenocarcinoma arising from a fistula-in-ano. The presentation was typical for perianal sepsis and fistula-in-ano with anal pain and chronic discharge. Initial treatment with fistula debridement and seton were performed. Subsequent review of histology revealed underlying adenocarcinoma, while MRI imaging showed local invasion into the prostate. The patient received neoadjuvant chemoradiotherapy followed by pelvic exenteration to maximise the chance of achieving cure. Features of this case are discussed together with its implications, including treatment guidelines and typical MRI findings.

Keywords

General Surgery
Colorectal
Fistula-in-ano
Mucinous adenocarcinoma
**Introduction**

Perianal sepsis and development of fistula-in-ano are common surgical problems, often having a significant impact on patients’ quality of life and proving challenging to manage. Rare cases may be associated with malignancy, with the fistula-in-ano either arising as a result of a primary anorectal malignancy, or primary fistula tract malignancy occurring as a consequence of the prolonged inflammatory nature of the fistula. Thus, we report a rare and interesting case of locally advanced mucinous adenocarcinoma arising from fistula-in-ano. In addition, we discuss the decision-making process and management pathway adopted.

**Case Report**

A 66 year-old male presented for treatment of fistula-in-ano. His medical history was significant for type II diabetes and previous ankle fracture. He had a 25 pack-year smoking history and his only medication is metformin. Over the 4 months preceding this presentation, he suffered recurrent perianal sepsis requiring multiple incision and drainage procedures. Examination of the perineum showed extensive scarring and multiple external openings on the left side, extending toward the left buttock. Ongoing purulent discharge was noted.

Pelvic magnetic resonance imaging (MRI) showed a complex tract in the left ischioanal fossa with an extension superiorly towards the left-lateral margin of the prostate. T2 high signal intensity was seen within the tracts (Figure 1).

An examination under anaesthetic was performed, the fistula was debrided and a seton was placed. Histopathology of the tissue debrided revealed anal mucosa with underlying infiltrating mucinous adenocarcinoma extending into the ischiorectal adipose tissue. The tumour was MMR proficient and BRAF wild-type on immunohistochemistry. It was CK20, CDX2 and CK19 positive, but negative for CK 7, GATA 3, ER and PR. Computer tomography (CT)
staging showed no distant metastasis to chest or abdomen. Subsequent colonoscopy showed no visible mucosal primary lesion (Figure 2).

Decision regarding progression of management was based on a number of factors discussed in the context of a colorectal cancer multidisciplinary team meeting. Namely, confirmation of adenocarcinoma upon biopsy, the absence of distant metastasis on staging and the presence of prostatic invasion on MRI imaging. As such, it was felt that administration of neoadjuvant chemoradiotherapy followed by pelvic exenteration was the only viable management option to achieve potential cure.

He commenced neoadjuvant chemoradiotherapy with capecitabine, completing 50 Gy over 25 fractions. Repeat MRI showed no significant response. He proceeded to pelvic exenteration with abdominoperineal resection (APR), uretherectomy, cystoprostatectomy with ileal conduit formation, partial excision of left obturator internus, S5 sacrectomy and excision of medial head of gluteus maximus. The perineum was reconstructed using a transverse rectus abdominus musculocutaneous (TRAM) flap (Figure 3).

Histology showed a well differentiated mucinous adenocarcinoma arising from a fistula-in-ano, confined to the surrounding tissues (Figure 4). No anorectal mucosal involvement was evident. The component of the fistula-in-ano adjacent to the prostate was free of malignancy. No regional lymph node metastases were identified.

Post-operatively he developed a pelvic collection which was treated with radiologically-guided drainage and intravenous antibiotics. Otherwise his recovery was uneventful. Multidisciplinary team decision was for adjuvant chemotherapy.

**Discussion**
Primary mucinous adenocarcinoma of the perianal region is an exceedingly rare condition [1]. A subset of these are found to be associated with chronic fistula-in-ano making early diagnosis difficult. As Rosser first established in 1934, these cancers are often associated with a prolonged history of chronic fistula disease greater than 10 years [2]. Recently however, cases where the fistula has been present for less time are being reported, in some cases being diagnosed after 2 months [3]. In this particular case, mucinous adenocarcinoma was diagnosed only 4 months after the fistula. The histopathology findings of the exenteration specimen suggest that this was a primary adenocarcinoma originating within the fistula tract, as no anorectal mucosal involvement was evident. It is however peculiar that this occurred in the context of a relatively short history of fistula-in-ano (4 months), as primary fistula tract tumours would typically require a prolonged period of inflammation to prompt metaplastic change [4].

The MRI findings are non-specific. The most common finding is hyperintense content on T2 imaging, representing mucin pooling [5]. This can be difficult to distinguish from an abscess, however this malignancy tends to show heterogenously with a grape-like appearance [5]. No thick fibrous capsule is seen [5]. Diffusion-weighted imaging (DWI) showed increased signal intensity in keeping with pus, however the apparent diffusion coefficient (ADC) showed increased signal intensity, likely representing less restricted diffusion of mucin versus pus with T2 shine-through confusing the DWI image [6] (Figure 1).

Literature reviewed revealed similar cases of adenocarcinoma arising from fistula-in-ano being treated with APR. These suggest that most cases are locally aggressive, with a low risk of lymph node involvement or distant metastasis [1]. However, evidence-based treatment guidelines are limited. Anecdotally, APR may be effective for non-malignant localised disease. Chemoradiotherapy may be beneficial but there is a lack of data to supportive or deny its use. Some have reported successful treatment of local disease with surgery only [7]. In our case there was no significant response to chemoradiotherapy, whilst others report significant
reduction in tumour size [5]. Given the current uncertainty, our multidisciplinary team opted for neoadjuvant therapy to maximise likelihood of cure.

This case was unique for several reasons. Firstly, mucinous adenocarcinoma arising within a fistula-in-ano is a rare occurrence. Secondly, the fistula-in-ano associated with this primary malignancy tracked via a complex course towards and abutting the prostate, raising concern of local invasion into the prostate. As such, multidisciplinary decision was for more radical resection to acquire clear margins and maximise the likelihood of cure. To our knowledge, this is the first case where tracking of the fistula-in-ano associated with a malignancy was so extensive, thus warranting a more radical resection to ensure complete resection. Thirdly, this case emphasizes the limitations of preoperative imaging and examination under anaesthetic in ascertaining the extent of malignant involvement in the presence of a fistula-in-ano.

This case presentation highlighted the difficulties associated with diagnosis, staging and treatment of primary malignancies arising from within a fistula-in-ano. Guidance of a multidisciplinary team is imperative in this condition, due to challenging interpretation of preoperative imaging to assess extent of tumour involvement and sparsity of evidence to guide treatment decisions.

Informed consent was gained prior to writing. This study was approved by the Institutional Review Board (IRB) of North Shore Hospital (Auckland, New Zealand)
References


**Figure Legend**

Figure 1 – MRI pelvis showing axial T1 and T2 fat suppressed images (a,b), with granular appearance and lack of thick fibrous capsule around mucin pools. DWI showing restricted diffusion, but apparent diffusion coefficient reveals a relatively non-restricted pattern (c,d).

Figure 2 – Colonoscopic images showing: (a) Rectum, (b) Sigmoid colon with diverticulosis, (c) Caecum and ileocaecal valve, (d) Terminal ileum.

Figure 3 – Intraoperative images showing: (a) Perineum with seton in place, (b, c) Resection of the tumour and surrounding structures, (d) Flap reconstruction.

Figure 4 – Histopathology slides: (a) Macroscopic image of pelvic exenteration specimen, (b) Low power image of the fistula-in-ano and tumour, (c) High power image at the junction of the skin and the tumour, (d) High power image of the tumour within the skeletal muscle,
Figure 1
Figure 2
Figure 3
Figure 4