CASE 2

Perianal (extramucosal) mucinous adenocarcinoma arising in anorectal fistula

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Pathology

The mass was localised to one quadrant of the anal canal and radical local excision was attempted to preserve continence. There was an ellipse of mucosa and anal skin with deep tissues. The mucosal surface was scarred from the chronic fistula, but had no mass lesion evident. Sectioning showed a loculated mucinous lesion. Histologically, the tumour was a very well differentiated mucinous adenocarcinoma. In many areas acellular mucin dissected through the tissues. When present, the epithelium lining the mucin-filled spaces was atypical, ranging from only subtle nuclear crowding and mild loss of polarity to more obvious but still relatively mild pleomorphism. The epithelium was predominantly flat or was thrown into low amplitude papillary folds. The stroma was bland collagenous tissue. The tumour cystic spaces extended into the muscularis propria, and focally reached the peripheral resection margin.

Discussion

Carcinomas of the anal canal are rare lesions, accounting for only 1.5% of all gastrointestinal cancers[1]. At this site, squamous cell carcinoma is the most common diagnosis with adenocarcinomas representing only a minority of tumours. Because of their rarity and heterogeneity, anal canal adenocarcinomas present a number of diagnostic challenges including under-diagnosis.

Adenocarcinoma of the anal canal is defined as one arising in the anal canal epithelium. This includes surface epithelium, the epithelium of anal glands and their draining ducts, or the lining of chronic fistulae.[2] Importantly, tumours arising from each of these structures may have differing pathological features and behaviour. The current WHO classification recognises three forms of adenocarcinoma at this site[2]:

1. Adenocarcinoma arising in the distal rectal mucosa. This usually represents direct extension of a rectal adenocarcinoma into the anal canal. The histological features are the same as conventional colorectal adenocarcinoma. Importantly, some rectal cancers can express Keratin (Ker)-7 as well as the more usual Ker-20.
2. Adenocarcinoma arising in a chronic anorectal fistula. As in the current case these are often of mucinous type and may occur with an underlying disorder such as Crohn disease[3, 4] or a congenital rectal duplication.[5, 6] These tumours do not have a mass lesion on the mucosal surface unless advanced.

3. Adenocarcinoma of anal glands (or anal ducts[1]). Again these generally lack a surface component, instead forming small infiltrative glands extending into the perianal tissues.[7]

Patients from the second group, the subject of this case, often have a long history of perianal disease, including discharging fistulae or abscess; symptomatically they may have anal discharge or pain, although acute presentation including obstruction has been described.[6, 8, 9] Generally no mucosal lesion is appreciated grossly although scarring and irregularity from previous fistula healing and surgery is common. The tumours are typically mucinous, which can be suspected at macroscopic handling.

Histologically, like the current case, the mucin-filled spaces are either acellular or are lined by atypical epithelium that is very low grade and forms low papillae, with a pattern very reminiscent of low grade appendiceal mucinous neoplasm (LAMN).[10, 11] Also similarly to LAMN, features of invasion are subtle. Instead of stromal desmoplasia and other usual changes of malignant invasion, these tumours often extend subtly into the muscle and soft tissues. Granulomas have been noted in some patients in association with extravasated mucin[6], a feature that may raise the possibility of Crohn disease.

Importantly, the low grade appearance of these lesions can make the diagnosis of adenocarcinoma more challenging. In a similar fashion to appendiceal LAMN and to a subgroup of rectal low grade villous adenocarcinomas[12], the diagnosis of malignancy relies heavily on the combination of an atypical glandular arrangement with location of the low grade atypical glands and cystic spaces in muscle or deeper. The epithelium has a colonic immunophenotype with positive staining for Ker-20 and, in most cases, CDX2.[4] There may be positive staining for Ker-7 [7] although this was seen in only 1 of 7 cases in a recent series.[4]

Mucin lakes are also an important feature of this tumour. It has been suggested that the finding of acellular mucin globules within granulation tissue in an anal fistula biopsy should alert pathologist and clinician to the possibility of mucinous adenocarcinoma.[13] However, Jones and Morson described mucin pools in some patients with chronic anal fistulae secondary to benign rectal duplications with no evidence of carcinoma in the resected specimen.[6] Thus, the finding of acellular mucin alone is suspicious but not sufficient to diagnose adenocarcinoma.

Jones and Morson, as well as earlier authors, have proposed an association between these tumours and the presence of a congenital rectal duplication.[5, 6] Rectal duplication is diagnosed by the presence of benign crypts surrounded by lamina propria deep to the mucosa, often with an associated muscularis mucosae. The presence of dysplastic foci in some cases at the transitional areas between the duplication and adenocarcinoma points to a chronic inflammation – dysplasia – carcinoma sequence.

The differential diagnosis includes the other types of anal canal adenocarcinoma. Anal involvement by extension of a rectal adenocarcinoma is associated with an obvious mucosal component (unless there has been pre-operative neoadjuvant chemo-radiation with regression, in which case an ulcer will be seen). Paget disease obviously shows classical in

situ change of the surface epithelium and is unlikely to be confused with this entity. Anal gland adenocarcinoma, possibly more correctly recognised as arising from the ducts draining the anal glands[1], is the most problematic differential. This is usually a more aggressive tumour and shows more conventional features of adenocarcinoma including small, infiltrative glands, desmoplastic stroma and lack of mucinous differentiation.[7] However, some cases have shown a mucinous appearance, indicating some morphological overlap.[1] The immunophenotype is different and mirrors that of anal glands/ducts (Ker-7+, and Ker-20- in over 80%) without colorectal differentiation.

Benign conditions also need to be considered in the differential diagnosis. In chronic fistula secondary to a rectal duplication there is rectal mucosa deep in the wall of the anal canal, but these glands are not atypical cytologically, lamina propria is present and muscularis mucosae may be evident in some areas. If dysplasia develops, the distinction between non-invasive and invasive well differentiated adenocarcinoma can become difficult or even impossible.[6] The presence of granulomas, often around mucin, can suggest the possibility of Crohn disease.[6]

The prognosis of these lesions where complete excision can be achieved seems to be good.[6] Just like the morphologically similar appendiceal lesions, these tumours are slow growing and have a low propensity for nodal or distant metastatic spread (although cases with nodal metastasis are described[14]).

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