Rare disease

Carcinoma arising within an anal gland

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Summary

Anal gland carcinoma (AGC) is rare, and its innocuous presentation and developing immunohistochemical profile make the diagnosis of it challenging. Predominant presenting symptoms include anal pain, rectal bleeding and the presence of a perianal mass in advanced stages of the disease. Histological profile commonly reveals an intramural adenocarcinoma with normal unaffected overlying anorectal mucosa. Immunohistochemical analysis shows positive staining for cytokeratin (CK) 7 and negative staining for CK20. MUC5AC expression with CK5/6 and p53 negativity has been reported. The authors report a case of a 68-year-old woman with a rapidly advancing AGC and review the current literature with respect to diagnosis and current consensus on therapeutic management.

BACKGROUND

The literature on anal gland carcinoma (AGC) is scarce and the only published cases are case reports or case series. We report a case along with a review of the current literature in order to gain a better understanding on the consensus for adjuvant therapy of this rare disease.

CASE PRESENTATION

A 68-year-old woman presented with a 2-month history of painful rectal bleeding. Flexible sigmoidoscopy revealed a subcentimetre, non-ulcerating painful lesion in the anal canal. Initial tissue biopsies were inconclusive. Subsequent examination of anus and rectum under anaesthesia revealed rapid progression of the lesion with a threefold increase in size over a 6-week period (figure 1). Multiple deep tissue biopsies were taken, which were positive for adenocarcinoma.

The primary tumour was not identified by MRI, however, there was eccentric mural thickening at the anorectal junction with associated local lymphadenopathy. Consensus from the multidisciplinary meeting was that the lesion represented a primary adenocarcinoma of the anal canal. A wide abdominoperineal resection (APR) incorporating a cuff of vaginal wall was performed without complication followed by a long course of adjuvant chemotherapy. As this is a rare tumour with very little evidence to support or refute any adjuvant therapy for any stage of the disease, we undertook an informed discussion with the patient. The patient preferred the option of long course chemotherapy after taking into account the evidence provided and the circumferential resection margin (CRM) not being involved by the tumour. The resection was classed as R0 using the principles of staging of rectal and anal carcinomas.¹

INVESTIGATIONS

Gross examination of the resection specimen showed a circumferential tumour involving the rectum and anal canal, measuring 4 cm in maximum dimension, with

ulceration of the overlying mucosa 1.5 cm above the dentate line. The tumour was completely excised as there was no macroscopic or microscopic involvement of the margins in the specimen. Microscopically, the tumour was a moderately differentiated adenocarcinoma, with extensive infiltration into the wall of the rectum and anal canal. There was focal invasion into the external anal sphincter and into the adherent vaginal flap (pT4a). Focal colonisation of glandular mucosa was seen along with perineural invasion. The background large bowel mucosa and squamous mucosa of the anus appeared normal; no adenomatous polyps were identified (figure 2). Two of 12 local lymph nodes identified contained metastatic tumour deposits; the apical node was free from tumour and no other lymph nodes (groin/inguinal region) were obtained.

Immunohistochemistry was performed. The tumour stained positive for cytokeratin (CK) 7 and negative for CK20, CK5/6 and p63 (figures 3 and 4). No definite origin from the native anal glands could be identified. Given the immunohistochemical profile, the absence of surface dysplasia and an extrarectal primary tumour, we concluded that the appearances were consistent with an anal gland adenocarcinoma. The tumour was staged as pT4a pN1 M0 and potentially curative resection (R0 resection) with no involvement of the CRM in accordance with the International Union Against Cancer classification.¹

DISCUSSION

AGCs remain a challenge; they have an innocuous presentation, non-specific morphology, are often in proximity to other glandular tissue associated with more common malignancies and have a developing immunohistochemical profile making them a testing diagnosis. Due to their scarcity, incidence is not widely reported but they are believed to account for less than 5% of all anal canal malignancies and have been shown to have a slightly higher male predominance. Predominant presenting symptoms of AGCs include anal pain, rectal bleeding and the presence of a

Figure 1 Retroflexed view of the rectum during flexible sigmoidoscopy. Inflammatory lesion is shown at the anorectal junction.

Figure 2 H&E staining showing adenocarcinoma with normal overlying squamous epithelium.

Figure 3 Adenocarcinoma staining positive for CK7.

Figure 4 Adenocarcinoma staining negative for CK20.

perianal mass in advanced stages of the disease.^{2 3} Fistula formation has been noted in over half of all patients in the largest survey with a male preponderance.² Although adenocarcinoma can arise within a fistula secondary to a chronic inflammatory process, this must not be confused with primary AGC with associated fistula formation.^{4 5}

Often the symptoms do not distinguish AGC from other carcinomas. Detection is usually late as the symptoms often initially mimic benign inflammatory conditions of the anorectal region and biopsies fail to reveal the infiltrating carcinoma.^{6 7} Any chronic lesion of the perianal region that is resistant to routine therapeutic measures should be

scrutinised further with more invasive diagnostic measures including examination under anaesthesia and deep tissue biopsy. Metastatic disease has been reported at the time of first presentation in 15–60% of cases.^{2–3 8} In the largest reported series, tumour location was most commonly posterior (36.5%), followed by lateral (28.8%) and anterior (15.4%).²

Recent developments in the diagnosis of AGC have been in the immunohistochemical staining of these cancers. Several recent studies have shown that AGCs are commonly CK7 positive and CK20 negative, features in keeping with normal anal glands.^{9–11} This is in contrast to mucinous adenocarcinomas and most rectal type carcinoma that are commonly CK7 negative and CK20 positive. This, however, is not significantly discriminative as anal canal metastasis from distant adenocarcinomas may share this profile and a small proportion of rectal cancers are CK7 positive.¹⁰ However, Hobbs *et al*⁹ also suggest that even in the absence of the CK examination, the presence of a primary intramural anal canal tumour composed of small dispersed glands can be considered an AGC. A study by Lisovsky *et al*¹⁰ also found that their two cases of AGC stained negatively for p63 and CK5/6 suggesting that in AGC, the anal glands had lost intermediate and basal cell differentiation. Kuroda *et al*¹¹ have also recently shown normal and neoplastic anal glands to stain positive for MUC5AC expression (a marker more commonly associated with gastric foveolar epithelium).

Treatment is predominantly surgical. APR is advocated in the vast majority of patients to definitively remove the entire lesion and lessen the risk of local recurrence. Local resection is sometimes performed, but this is only in cases whereby the tumour margins can be confidently excised without damage to the anal sphincters. In the series of 52 cases reported by Abel *et al*,² 77% underwent APR. Fifty-three per cent of patients underwent adjuvant therapy with equal proportions undergoing either radiotherapy alone or in combination with chemotherapy. However, in this report and in a paper published by Cabrera *et al*,¹² there was no significant benefit in terms of survival rates with adjuvant therapy. Also, disease-free survival rates were similar between those patients undergoing local resection compared with those undergoing APR; therefore, the authors justified local resection as an acceptable alternative as long as an R0 resection was achieved and sphincter mechanism preserved. In the second largest series of 21 patients by Jensen *et al*,³ seven patients underwent APR (five described as radical resection) with apparently no patients receiving adjuvant therapy. Nine patients underwent palliative procedures due to advanced disease at initial presentation. The only patient still alive during the follow-up period had an AGC found incidentally during histological analysis of an excised haemorrhoid, emphasising the need to analyse all tissue removed from the anal/perianal region. Lisovsky *et al*¹⁰ published two cases of AGC, both of which underwent APR. One patient underwent adjuvant chemo/radiotherapy and unfortunately the second patient was lost to follow up. Biggs *et al*¹³ reported five cases of AGC following a survey of the members of the American Osteopathic College of Proctology, all of which underwent APR followed by adjuvant chemo/radiotherapy. In essence, no consensus exists

regarding adjuvant therapy following resection for AGC and the role of chemoradiotherapy in R0 resections remains unclear due to the lack of data. Chemoradiotherapy has proven benefit in squamous cell carcinoma but due to the low incidence of AGC, it is unlikely there will be a randomised trial. As such, most patients still appear to be offered adjuvant therapy.^{2 12 14 15}

Five-year survival rates of AGC appear to be varied. Abel *et al*² reported that of the 23 patients who were followed up for a period of 3 years, 17 (74%) were alive without disease, and of the 15 patients followed up for 5 years, 12 (80%) were alive without disease. The data are heavily skewed as only 29% of patients were followed up for the required 5 years, however, it may suggest that if local recurrence has not occurred within 3 years, it is unlikely to do so. Disappointingly, Jensen *et al*³ reported a less favourable combined 5-year survival rate of 4.8%. In this study, 62% of patients had metastatic disease at initial presentation, which may explain these findings. Overall, 5-year survival is generally accepted to be less than 20%.¹³

Learning points

- ▶ AGC is rare but necessitates a high index of suspicion due to its innocuous presentation and often rapid progression.
- ▶ The immunohistochemical profile of AGC is still in its infancy but AGC seems to have a relatively diagnostic immunohistochemical profile, staining positively for CK7 and negatively for CK20, CK5/6 and p63.
- ▶ Early immunohistochemical evaluation of deep tissue biopsies may accelerate diagnosis and earlier therapeutic intervention.

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Competing interests None.

Patient consent Obtained.

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