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Case Report

Anal fistula associated mucinous adenocarcinoma with anal fissure: a case report

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ABSTRACT

Perianal abscesses and anal fistulas are interconnected phases of an infectious process. Persistent irritation and inflammation around an anal fistula can cause cellular changes that increase the risk of cancerous transformation. A long-standing anal fistula, persisting for over 10 years, has been recognized as a potential precursor to fistula-associated mucinous adenocarcinoma (FAMC). A 67-year-old male patient presented with complaints of intense anal pain and a palpable tumor last year. Examination revealed a gluteal abscess, fistula-in-ano and an anal fissure. The patient gave a history of perianal abscess and anal fistula treated three years ago with fistulectomy, pus drainage, and lateral anal sphincterotomy. MRI revealed a horseshoe-shaped, multiseptate abscess in the intersphincteric plane (1 to 9 o'clock, predominantly left-sided), displacing the anal canal to the right, with three intersphincteric fistulas connected to the tumor. Histopathological examination revealed well to moderately differentiated mucinous adenocarcinoma in the distal aspect of the fistula suggesting a direct link between the chronic inflammatory process and development of malignancy. FAMC is a rare but serious complication of chronic anal fistulas. The diagnosis was made three years after treating a perianal abscess, indicating that epithelial dysplasia and carcinogenesis may have begun before the abscess developed. Consequently, FAMC can arise from anal fistulas in fewer than 10 years. This case underscores the importance of careful monitoring of patients with a history of perianal abscesses or anal fistulas for signs of malignant transformation, as early detection can significantly impact prognosis and treatment outcomes.

Keywords: Perianal abscesses, Anal fistulas, Fistula-associated mucinous adenocarcinoma, Anal sphincterotomy, Chronic inflammation, Dysplasia, carcinogenesis

INTRODUCTION

While chronic inflammation is known to create an environment conducive to cancer development and proliferation, the exact mechanisms linking inflammation to cancer aren't fully understood. But in some cases, especially in the context of inflammatory conditions like perianal abscesses and anal fistulas it is surprising how quickly cancer can develop. Perianal abscesses and anal fistulas are interconnected phases of an anorectal infectious process. Perianal abscesses result from the accumulation of pus in the tissues surrounding the anus and are typically caused by bacterial infections. If left untreated or inadequately treated, a perianal abscess can lead to the formation of an anal fistula, which is a small tunnel that forms between the anal canal and the skin near the anus. This tunnel allows the ongoing drainage of pus or fluid from the abscess.[1] Anal fistulas can also result from chronic inflammatory conditions, such as Crohn's disease or recurrent infections. Over time, the continuous irritation and inflammation of the tissues surrounding the fistula can lead to cellular changes that increase the risk of

cancerous transformation over time.[2] A long-standing anal fistula, especially one persisting for over 10 years, has been recognized as a potential precursor to fistula-associated mucinous adenocarcinoma (FAMC). Fistula-associated mucinous adenocarcinoma is a rare but serious complication of chronic anal fistulas. Mucinous adenocarcinoma is a type of cancer that originates from glandular cells and produces mucin, a jelly-like substance. This association highlights the significance of chronic inflammation and its role in promoting cancer development. The exact mechanisms by which a long-standing anal fistula progresses to FAMC likely involves a combination of factors including persistent inflammation, genetic mutations, and possibly infection with oncogenic viruses.[3]

In this paper we present a patient with FAMC arising 3 years after the treatment of a perianal abscess. The transition from perianal abscess to FAMC within just three years is unusual and raises questions about the underlying processes driving carcinogenesis.

CASE REPORT

A 67-year-old male patient presented to the hospital with complaints of intense anal pain and a palpable tumor last year. On examination a gluteal abscess and fistula-in-ano with anal fissure was detected. He gave a previous history of perianal abscess and anal fistula 3 years ago for which fistulectomy was carried out along with pus drainage and lateral anal sphincterotomy. The timing when the anal fistula developed was unclear.

Present MRI studies revealed a horse shoe shaped multiseptated heterogeneously enhancing abscess in the intersphincteric plane from 1 o'clock to 9 o'clock position predominantly on the left side and displacing the anal canal to the right side. The abscess caused thinning of bilateral external sphincter and bulging of the left Levator ani muscle as shown in Figure 1.

Three blind tracts were visible, a linear intersphincteric tract on the right side with internal opening on the abscess at 7 o'clock position, extending inferiorly in the subcutaneous plane and external opening at 9 o'clock position in the skin. A second tract arising from the abscess at 6o'clock position extending posteriorly in the right paramedian aspect with external opening at 7 o'clock position, 2.3 cm from the anal verge. A third tract arising from the abscess at 8 o'clock position on the right extending laterally in the gluteus maximus muscle 5 cm from the anal verge. Colonoscopic evaluation revealed two ulcers along with fistulous openings just above the anal canal. Rectum up to terminal ileum did not reveal any abnormality as shown in Figure 2.

Histopathological examination of the tissue from the fistula tract revealed well to moderately differentiated mucinous adenocarcinoma. Tumor marker carcino-embryonic antigen was 8.43ug/l, higher than the reference range. Patient was diagnosed with FAMC with sphincter involvement at T3d stage, CRM status positive and mesorectal node involvement (N1a status). PET scan revealed heterogeneous metabolism in an ill-defined predominantly hypodense mass at cutaneous and subcutaneous aspect of perianal region and extending superiorly as hypodense thickening of anal canal and left mesorectal space. No distant organ metastases were observed. Patient underwent fistulectomy and fissurectomy with drainage of perianal abscess and was also administered chemotherapy. Patient received CTRT with concurrent capecitabine.

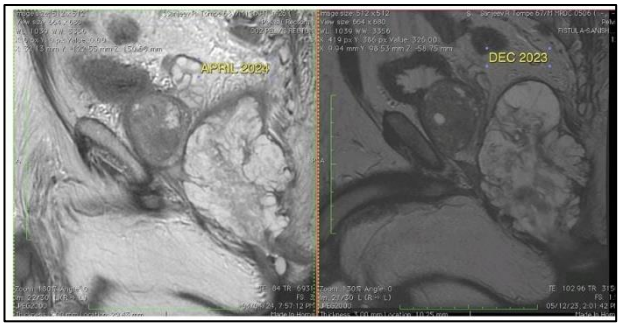

Figure 1: MRI showing size of growth before and during chemotherapy.

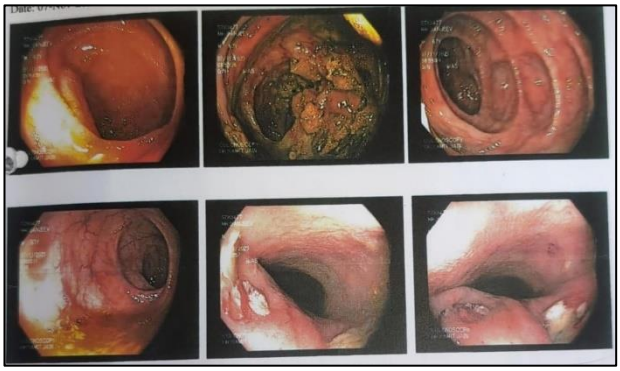

Figure 2: Scope passed up to terminal ileum. Entire visualised colonic mucosa from upper rectum up to terminal ileum is normal. Two ulcers along with fistulous opening seen just above the anal canal.

DISCUSSION

In 0.1 % of all persistent anal fistulae with recurrent inflammation, a primary cancer can develop if there is recurring inflammation of the fistula for at least 10 years with increasing pain and induration at the fistula and mucus secretion, such a fistula has an opening in the anal canal or an anal crypt.[4] Chronic inflammation is a cause of cancer development. More than 10 years after the onset of anal fistula, the risk of developing FAMC increases. However, the present case of FAMC was diagnosed three years after the treatment of a perianal abscess and fistula, implying that dysplasia of the epithelial cells with resulting carcinogenesis may have already developed prior to the

perianal abscess. Thus, an FAMC can arise from anal fistulas in less than 10 years.[5] According to Japanese multi-institutional research which examined 164 patients with anal fistula-associated carcinoma, 60 patients (37%) had a history of anal fistula of less than 10 years.[6] A single-institutional review in the US showed that three (21%) of 14 anal fistula-associated carcinomas developed within 10 years after the diagnosis of anal fistula.[7]

Delayed diagnosis of the anal fistula may account for the short disease period in patients with FAMC. Some patients might take a long time to present because of unawareness of symptoms. Other patients might hesitate to visit the hospital because of anxiety or shame, even if they were already aware of symptoms. Even if the duration of the anal fistula is fewer than 10 years, the possibility of FAMC should not be excluded. The bias that anal fistula-associated carcinoma always arises from a long-standing anal fistula can risk losing an opportunity for early diagnosis of FAMC.

It's possible that genetic predispositions with or without active environmental factors can accelerate the progression of cancer. Understanding the molecular and cellular mechanisms that participate in the progression from inflammation to cancer is an active area of research.[8,9] Factors such as the presence of immune cells, cytokines, and genetic mutations within the inflammatory microenvironment may contribute to the transformation of normal cells into cancerous ones.[10] A handful of studies have reported primary cancer arising from a chronic anal fistula, but implantation of tumor cells from a distant site, in an anal fistula is rare.

Cancer implantation in an anal fistula from a colon cancer was first reported by Guiss et al. Only 27 cases of this condition have been reported since the report by Guiss et al.[11] According to Umpleby et al, the primary tumor being found in the sigmoid colon or the rectum (2 in the descending colon, 13 in the sigmoid colon, 10 in the upper rectum, and 2 in the lower rectum).[9,12] Cells from this primary tumour may shed into the intestinal lumen and get implanted in injured mucosa. An inflammatory response to a bacterial infection or wound healing activates cancer cell growth, presumably resulting in cancer implantation in an anal fistula.[13,14] Similar implantation of colorectal cancer cells in a hemorrhoidectomy wound and implantation of rectal cancer in the anal canal due to anal injury occurring during insertion of a circular stapler have also been reported.[15,16]

Thus, the potential for cancer implantation must also be taken into account in patients with colon cancer who develop an anal fistula and in patients who have undergone surgery for an anal disorder. Such patients must be carefully followed prior to surgery. In the present case, a fistula had already existed at the time of development of perianal abscess, 3 years prior, indicating that latent chronic inflammation had also been there, though the patient did not have any symptoms of the disease. Dysplasia and carcinogenesis may have proceeded in the context of that latent chronic inflammation. It is possible that FAMC cells arise among these dysplastic cells, and were transplanted to the drainage site of the perianal abscess where they proliferated.[17] When cancer arising from an anal fistula is diagnosed, the proximal intestine should be examined with metastasis of colon cancer in mind. The basis for this diagnosis is immunohistology, when implanted cells have the same histologic type as the primary tumor. A combination of CK7 and CK20 can facilitate this determination. Loy et al reported that the vast majority of colon cancers (80 %) are CK7 (−)/CK20 (+) while some (16 %) are CK7 (+)/CK20 (+) and a few (4 %) are CK7 (−)/CK20 (−).[7] In six of seven cases of primary cancer arising from an anal fistula, those cancers were CK7 (+)/CK20 (−).[18]

Ninety percent of anal fistulas are considered to arise from cryptoglandular infection. Hence, cryptitis followed by perianal abscess and anal fistula are continuous processes in the same infectious disease. The progression of each step is different depending on the case. Proctologists often encounter patients who develop anal fistula after experiencing several episodes of perianal abscess formation over the years. Those patients have had chronic inflammation before the development of anal fistulas, which can lead to malignant transformation of perianal epithelial cells.[19]

Histopathological evidence of carcinoma is essential for preoperative assessment. However, concerning FAMC, documenting carcinomatous cells via biopsy is often difficult because of the relatively small size of the carcinomatous component in the tumor compared with the huge amount of the mucinous component.[20] Even when the first biopsy is negative, a repeat biopsy is recommended to avoid misdiagnosis. Meticulous examinations should be conducted when the anal fistula is suspected of being associated with FAMC. Unhealed wounds, mucinous secretion, and early induration, observed in the surgical site of the perianal abscess and anal fistula, might be related to FAMC. Following up patients until complete wound healing after treatment for a perianal abscess is necessary to avoid missing an opportunity to detect latent FAMC.[21]

Where colon cancer and cancer arising from an anal fistula are both present, the primary cancer must be differentiated from metastases. Further studies are needed to understand the processes involved in rapid cancer development in such cases so that more efficient strategies can be developed for prevention, diagnosis, and treatment.

CONCLUSION

Fistula-associated mucinous adenocarcinoma is a rare but serious complication of chronic anal fistulas. A long-standing anal fistula, especially one persisting for over 10 years, has been recognized as a potential precursor to FAMC. The present case of FAMC was diagnosed only 3

years after the treatment of a perianal abscess suggesting that epithelial cell dysplasia and subsequent carcinogenesis might have already progressed prior to the development of the perianal abscess. Consequently, FAMC can arise from anal fistulas in fewer than 10 years as chronic inflammation caused by a long-standing anal fistula can predispose to carcinogenesis. This case underscores the importance of vigilance in monitoring patients with a history of perianal abscesses or anal fistulas for signs of malignant transformation, as early detection and intervention can significantly impact prognosis and treatment outcomes.

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