Original Article

# “Budding”—an early MRI feature established in a case-control study of perianal fistula mucinous adenocarcinoma

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**Background:** Perianal fistula mucinous adenocarcinoma (FMA) usually presents at an advanced stage, necessitating extensive surgical resection. Symptoms of perianal pain and discharge are indistinguishable from fistula sepsis. Absence of defined features on magnetic resonance imaging (MRI) precludes early diagnosis. This study aims to validate MRI features that should increase suspicion of early mucinous transformation, prompting urgent examination and targeted biopsies.

**Methods:** Retrospective review of MRI studies was conducted in 9 patients with FMA in Crohn’s perianal and non-Crohn’s ileoanal pouch fistula between 2015–2019. Radiological features were assessed. Fine T2-weighted high signal lobulation of the fistula tract on MRI, described as ‘budding’, was retrospectively noted on historic studies in all cases of FMA and was determined a feature distinct from expected T2-weighted high signal appearance of bland fistula sepsis. The significance of these features in early diagnosis of FMA was assessed using a case control study.

**Results:** ‘Budding’, mass-like expansion of the tract, and septation of T2-weighted high signal components of the fistula were significantly associated with FMA using Fisher’s exact test (P<0.001). The presence of T2-weighted high signal “budding” predated the histological confirmation of FMA by a median 36 months (range, 12–156 months). One control patient was diagnosed with FMA during the study as ‘budding’ was retrospectively detected, triggering urgent targeted biopsy.

**Conclusions:** Radiological awareness of early features of FMA may improve outcomes by reducing the morbidity of exenterative surgery with delayed diagnosis. The presence of T2-weighted high signal ‘budding’ on MRI should prompt urgent targeted biopsy.

**Keywords:** Adenocarcinoma; mucinous; fistula; ileoanal pouch

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## Introduction

Fistula mucinous adenocarcinoma (FMA) was first reported in 1934 in idiopathic chronic perianal fistula (1). In the literature, FMA has been mostly reported in patients with Crohn's perianal fistula and less so in idiopathic chronic perianal fistula (2-6). Prevalence varies in studies and has been reported at 0.004–0.7% in the presence of Crohn's disease with no clear prevalence data available for patients with idiopathic chronic perianal fistula (2,6). FMA in idiopathic chronic perianal fistula and Crohn's perianal fistula are usually described together due to the rarity of the disease (6), although a recent study suggests that there may be histopathological differences between patients with FMA from Crohn's and idiopathic fistula aetiology (7). Clinical characterisation of FMA is based on observational studies, often reporting fistulising adenocarcinomas and anal squamous cell cancers together (3). FMA is usually diagnosed at a median 10 years (2,8) following fistula diagnosis. The actual time to malignant transformation is difficult to ascertain as diagnosis is delayed given the extraluminal site of malignancy developing within the fistula tract and by inconclusive or inadequate biopsy of low volume extraluminal lesions. This can be further complicated when sampling returns acellular mucin in a known septic tract.

It is common for a mucinous tract malignancy to be over-looked and deemed 'fistula related sepsis' given the overlapping T2-weighted high signal features on magnetic resonance imaging (MRI). By the time a diagnosis of malignancy is made, patients often present with a locally invasive mass requiring more extensive surgical resection including vaginal wall resection, pelvic exenteration and even bony excision in order to obtain complete tumour resection (4,6).

MRI is used to assess fistula healing, sepsis and disease activity (9-11) providing an opportunity for early detection of features of extraluminal mucinous tract malignancy. Establishing imaging red-flags might help to trigger urgent targeted biopsy or enable enhanced surveillance of high-risk patients (12,13). Septic fistulae and FMA both display high signal on T2-weighted imaging due to fluid content. The mucinous component of the tumour is at times mistaken for worsening sepsis. While the literature has described post-contrast enhancement of FMA (14), in our experience fistula MRI is not always performed with the addition of post-contrast sequences, limiting the real-world usefulness of this feature. These tumours are often locally extensive at the time of diagnosis, emanating from an extra-luminal site and therefore involving standard abdomino-perineal excisional margins, but rarely present with metastatic disease, reflecting an indolent nature.

This study aims to validate MRI features that should increase suspicion of early mucinous transformation, prompting urgent examination and targeted biopsies. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-562/rc).

### Highlight box

**Key findings**

- Features of 'budding' on magnetic resonance imaging (MRI) predated histological confirmation of fistula mucinous adenocarcinoma (FMA) by a median 36 months.

**What is known and what is new?**

- FMA is reported in patients with chronic idiopathic and Crohn's perianal fistula. It is difficult to distinguish from sepsis. Diagnosis is delayed due to its inconspicuous location, and patients usually present with locally advanced malignancy requiring extensive surgical resection.
- We describe an MRI feature called 'budding' which has been identified on retrospective review of a local series. This feature appeared at a median 36 months prior to clinically obvious FMA. A case-control study showed that 'budding' was significantly associated with a diagnosis of FMA.

**What is the implication, and what should change now?**

- MRI in patients with chronic anal fistula should be assessed for 'budding'.
- 'Budding' on MRI should trigger examination under anaesthetic and targeted biopsy for early diagnosis of FMA.
- Inconclusive histology should prompt repeat biopsy +/– enhanced surveillance with MRI.

## Methods

This is a retrospective case control study. FMA cases presenting between 1st January 2015 and 31st December 2019 were identified from the cancer database at St Mark's Hospital. Clinical notes, colonoscopy, and histology reports were reviewed in potential cases for inclusion to ensure that the carcinoma had originated from the fistula tract and did not represent a fistulising rectal cancer. Data were extracted on patient demographics, duration between the time of diagnosis of Crohn's disease (if present) and diagnosis of perianal fistula to first suspicion of FMA on MRI leading to histological confirmation of FMA. In ileoanal pouch

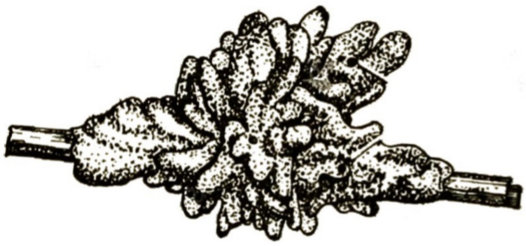

**Figure 1** Schematic representation of a budding sponge.

fistula, the extracted data also included pouch fistula classification (15), duration between pouch creation and fistula diagnosis, duration between fistula diagnosis and first suspicion of FMA on MRI leading to histological confirmation of FMA.

### *Selection of controls*

A research fellow without formal experience in MRI reporting performed the selection of controls to reduce bias. Five controls were matched to each known case of FMA from a prospectively maintained fistula database by age, gender, fistula anatomy, complexity (16), duration of fistula persistence and presence of perianal Crohn's disease or pouch fistula of non-Crohn's aetiology. A 5:1 ratio of controls to cases were selected based on guidance in existing literature for case control studies in rare disease (17). The MRI study selected for assessment in the Crohn's perianal fistula controls was matched in terms of fistula duration and complexity.

### *Retrospective review of sequential MRI studies*

Historic MRI fistula studies were reviewed in cases and controls by two consultant radiologists who work in a tertiary gastrointestinal centre, with 14 and 11 years of experience. The two reviewers evaluated magnetic resonance images independently and reached a consensus. All available images for each case were reviewed and included standard sagittal T2-weighted and multiplanar heavily T2-weighted short tau inversion recovery (STIR) sequences as a minimum. Imaging was acquired from a heterogenous pool of external centres of referral as well as the study site, largely on 1.5 Tesla scanners. MRI based fistula morphological classification was defined using established MRI criteria (16).

Additional features were also evaluated: mass effect of the fistula on adjacent structures; the presence of an internal 'matrix' within the fistula tract, described in this study as 'mesh-like' internal signal on T2-weighted sequences; enhancement where applicable; and the presence of tract 'budding'. On retrospective review of serial MRI studies in FMA, a feature was noted and termed 'budding' due to its morphological similarity to a budding sponge, a spatiotemporal morphological pattern of reproduction in an aquatic invertebrate (18) (*Figure 1*). 'Budding' describes the micro-lobulated border of a mucinous tumour growing outward from an epicentre within the fistula tract. The time between the scan that first demonstrated 'budding' and the time of histological diagnosis of FMA was noted. *Figure 2* demonstrates the evolution of budding on MRI over a 4 year period in a patient between these time points. Additional examples of cases can be found in the supplementary file as Figures S1,S2.

### *Research ethics review*

Institutional ethics committee review did not require ethical approval for this study. This study was a service delivery evaluation of the use of MRI in FMA. Patient consent was not required. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

### *Statistical analysis*

Statistical analysis was performed using Stata (version 15.1). Continuous data such as age, were presented with a median value and a range. Duration between diagnoses of Crohn's disease and a fistula, fistula and cancer on MRI were presented in months. The time interval between the historical MRI that first demonstrated 'budding' and histological diagnosis of cancer has also been presented in months with a median value and range. Absolute and relative frequencies of each radiological feature were described in case and controls. Analysis focused on assessing the association between each radiological feature noted on MRI and case/control status. Conditional logistic regression was used to allow for the matching of cases and controls. Case/control status was considered an outcome variable while the MRI features were predictor variables. Fishers exact test was used to account for small sample size where some radiological features were present in all cancer cases. An effect was considered statistically significant at $P<0.05$.

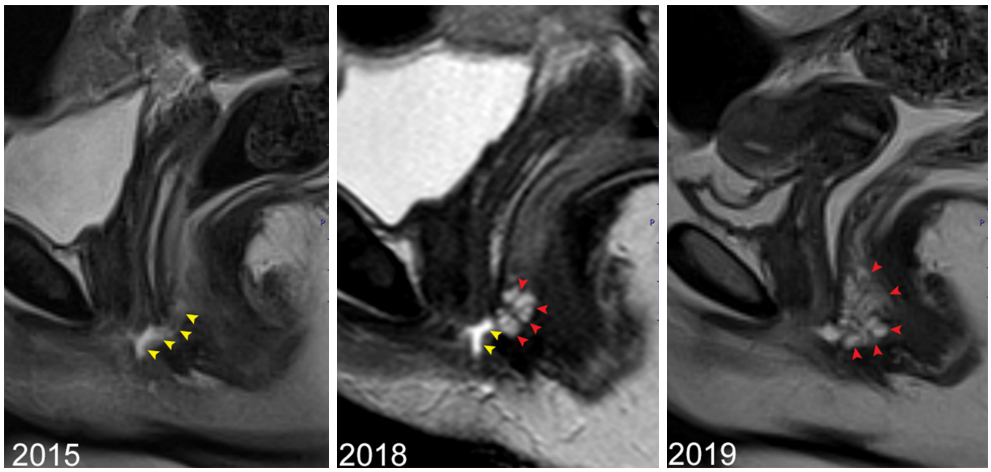


**Figure 2** T2-weighted sagittal STIR MRI sequences in a male patient between 2015–2019. A micro-lobulated contour akin to 'budding' (red arrows) has developed over time from the fistula tract (yellow arrows). Clinical diagnosis of FMA was made in 2019. FMA, fistula mucinous adenocarcinoma; MRI, magnetic resonance imaging; STIR, short tau inversion recovery.

## Results

Review of the institutional cancer database between 2015–2019 identified 12 potential cases of FMA. Three patients with fistulising primary luminal adenocarcinoma were excluded as they were deemed to not emanate from a true primary fistula tract. Nine patients (four female) with FMA were included in further analysis; six arose in perianal Crohn's fistula and three were diagnosed in ileoanal pouch fistula in patients. Of the external referrals (n=6), one patient was referred with an incidental finding of FMA following intersphincteric proctectomy for severe Crohn's perianal disease. The median age at histological diagnosis of FMA was 49 years (range, 32 to 66 years). At the time of diagnosis, digital rectal examination in seven patients was suspicious for malignancy, with a hard lump. Patients reported perianal pain with copious discharge, managed with seton drainage (n=5), biologics (n=4), defunctioning colostomy (n=2) and proctectomy (n=1).

*Tables 1*,*2* demonstrate the demographic and disease characteristics of the case series. In six patients with Crohn's perianal fistula, the median interval between diagnosis of Crohn's disease and a perianal fistula was 294 months (range, 12 to 408 months). Ulcerative colitis was the primary diagnosis for pouch creation in three patients with ileoanal pouch fistula. Prior to diagnosis of FMA, three patients had at least one false negative biopsy result. The median time to histological confirmation of cancer from fistula diagnosis was 72 months (range, 36 to 156 months). Pelvic exenteration was required in eight patients. Palliative chemotherapy was offered to one patient due to extensive tumour invasion.

### *Controls*

The control group consisted of 45 patients (20 female) with a median age of 42 years (range, 17 to 61 years). The median interval between diagnosis of Crohn's disease and fistula was 126 months (range, 12 to 516 months). The median duration of fistula persistence at the time of MRI included in the study was 60 months (range, 12 to 312 months). Perianal Crohn's fistula controls were predominantly managed with biologics, immunomodulators and setons (n=29) while two patients were defunctioned and one had a proctectomy. In ileoanal pouch fistula controls, management included permanent seton (n=5), laying open of fistula (n=2), biologics (n=1), pouch advancement (n=1), defunctioning colostomy (n=2) and pouch excision (n=4). A summary of demographic characteristics of controls are provided as supplementary data.

### *Detection of 'budding' on MRI of case series*

Retrospective review of sequential MRI studies in the case series found that 'budding' was identifiable on MRI at a median 36 months (range, 12 to 156 months) before a histological diagnosis of FMA.

**Table 1** Patient demographics of FMA in Crohn's peri-anal fistula

| Patient | Gender | Age at diagnosis of FMA (years) | Duration between diagnosis of Crohn's disease and fistula (months) | Duration between MRI with 'budding' and histological diagnosis of FMA (months) |
|---|---|---|---|---|
| 1 | Female | 32 | 144 | 36 |
| 2 | Male | 66 | 312 | 156 |
| 3 | Female | 54 | 276 | 48 |
| 4 | Male | 56 | 408 | 36 |
| 5 | Male | 57 | 348 | 48 |
| 6 | Male | 35 | 12 | 36 |

FMA, fistula mucinous adenocarcinoma; MRI, magnetic resonance imaging.

**Table 2** Patient demographics of FMA in ileoanal pouch fistula

| Patient | Gender | Age at diagnosis of FMA (years) | Duration between pouch creation and diagnosis of a fistula (months) | Duration between MRI with 'budding' and histological diagnosis of FMA (months) |
|---|---|---|---|---|
| 7 | Female | 48 | 108 | 12 |
| 8 | Male | 47 | 72 | 36 |
| 9 | Female | 49 | 240 | 48 |

FMA, fistula mucinous adenocarcinoma; MRI, magnetic resonance imaging.

### *Statistical analysis of MRI features identified in case and controls*

Retrospective review of sequential MRI studies in cases and controls found that the presence of 'budding' (P<0.001), 'mass-like' (P<0.001) and 'septae' (P<0.001) were significantly associated with FMA. 'Budding' demonstrated the largest difference between cases and controls. 'Budding' was present in all cases of FMA but only recorded in 7% of controls (n=3). Heterogeneous T2-weighted tract signal (P=0.02), matrix (P=0.03) and collection (P=0.04) also demonstrated a positive association with FMA. 'Heterogenous signal' was present in over a third of the MRI studies in the control group, diminishing their relevance in identifying early mucinous change. The presence of inter-sphincteric horseshoe, more than two tracts, increasing tract length, interstitial signal described as signal changes in the adjacent soft tissues, enlarged pelvic lymph nodes and proctitis were not associated with a diagnosis of FMA. The results are summarised in *Table 3*.

During the study period, four patients from the control group were found to have features of 'budding' on retrospective MRI review. Three patients from this group subsequently had repeat MRI or examination under anaesthetic (EUA) to exclude FMA. One patient was urgently recalled for imaging with MRI triggering targeted biopsy of the fistula tract using video-assisted anal fistula treatment. Histology confirmed FMA, leading to curative resection. This patient was removed from the control group and not included in the analysis.

## Discussion

First described in 1934 by Rosser (1), FMA has been reported in Crohn's and chronic idiopathic perianal fistula mostly in mixed case series including fistulising anal squamous cell carcinoma and non-mucinous adenocarcinoma of the rectum (19-24). As a result, pathogenesis remains unclear, particularly as large population-based studies are not possible due to the rarity of FMA, which comprises less than 1% of anal cancers (2,24). Several hypotheses for mucinous transformation exist including carcinoma originating from chronic inflammation in Crohn's and chronic idiopathic anal fistula, or primary anal gland neoplasia (6). A diagnosis of FMA is usually made following 5–10 years of fistula persistence suggesting an indolent growth, similar to our cohort with a median duration of fistula persistence of 6 years (14,24). A long duration of Crohn's activity preceding fistula is usually

**Table 3** A summary of the significance of radiological features in cases and controls

| Radiological feature | Controls (n=45) | Cases (n=9) | Odds ratio (95% CI) | P value |
|---|---|---|---|---|
| Budding | 3 [7] | 9 [100] | (+) | <0.001 |
| Mass-like | 7 [16] | 8 [89] | (+) | <0.001 |
| Septae | 7 [16] | 9 [100] | (+) | <0.001 |
| Heterogeneous | 17 [38] | 8 [89] | 12.1 (1.42, 104) | 0.02 |
| Matrix | 8 [18] | 5 [56] | 5.07 (1.15, 22.3) | 0.03 |
| Collection | 13 [29] | 6 [67] | 4.65 (1.05, 20.62) | 0.04 |
| Horseshoe | 19 [42] | 7 [78] | 4.46 (0.85, 23.4) | 0.08 |
| 2+ tracts | 18 [40] | 5 [56] | 1.96 (0.44, 8.68) | 0.37 |
| Tract length[†] (mm) | 49±27 | 56±27 | 1.14 (0.84, 1.55) | 0.40 |
| Interstitial signal | 9 [20] | 1 [11] | 0.47 (0.05, 4.54) | 0.51 |
| Enlarged nodes | 8 [18] | 1 [11] | 0.51 (0.05, 5.70) | 0.58 |
| Proctitis | 19 [42] | 4 [44] | 1.10 (0.26, 4.70) | 0.90 |

Statistics are presented as number [percentage] or mean ± standard deviation. [†], odds ratios given for a 10-mm increase in maximum tract length. (+), analysis using Fisher's exact test. CI, confidence interval.

reported as described in our cohort (median 294 months) (3,23,24). Early diagnosis of FMA is challenging as there are overlapping features with perianal sepsis: patients commonly present with worsening perianal pain and discharge, mistaken for perianal sepsis, and at diagnosis already have a clinically detectable perianal mass (3,23,24).

FMA develops from the fistula tract and is extraluminal therefore evading early clinical detection on digital examination. This makes adequate biopsy challenging, yielding false negative histology, or retrieval of acellular mucin (23). Positive histological diagnosis on first biopsy has been reported in only 20% of patients (3). Three cases in this cohort had one or more false negative biopsy results prior to diagnosis. To improve clinical diagnosis, several studies have described MRI features of FMA but none have attempted to identify features of early disease to aid in surveillance or early detection (14,25,26). FMA has been described on MRI as 'infiltrative' with 'mesh-like enhancement' and large tract width (14) or 'progressive septal enhancement' (26) that is 'heterogeneously hyperintense on T2-weighted images' (25). Others have described FMA as a 'mass between fistula and anal canal' that has 'peripheral ring enhancement' (27) and may appear 'multilocular or lobular' (28). Zhu *et al.* described 10 cases of FMA on MRI as 'cauliflower-like with internal septa' that was a 'heterogenous mass' usually between anal canal and a fistula (26). Mucin pools associated with FMA have been described as a 'collection' (14).

Our cohort demonstrated similar findings on early imaging, such as 'heterogeneous T2-weighted tract signal' (P=0.02), 'matrix' (P=0.03), 'mass-like' (P<0.001), 'septae' (P<0.001), and collection (P=0.04) prior to a clinically obvious mass. 'Budding' was only seen in 7% of controls but present in all cases of FMA and should be considered a red flag. Although T2-weighted high signal collection, heterogeneous T2-weighted tract signal, and matrix showed positive association with FMA, these features are not specific for FMA and are frequently described in perianal sepsis with a fistula tract. The presence of these features with 'budding', 'mass-like' and 'septae' should increase suspicion of FMA.

The retrospective appreciation of 'budding' on imaging significantly predated (median 36 months) the MRI study in which suspicion of malignancy was formally raised. Of significance, one patient from the control group was identified from review of their historic MRI studies with features of 'budding', and diagnosed with a new FMA following targeted biopsies of the fistula tract. This patient was removed from the study but powerfully illustrates the potential value of early radiological diagnosis.

'Budding' became more prominent over time on subsequent MRI studies. Clinical suspicion of early FMA development should increase in the presence of 'budding', prompting targeted excisional biopsy of the fistula tract.

 

Targeted biopsy should be undertaken under general anaesthetic and should involve a substantial biopsy of the area of 'budding' tissue. If negative, it should be repeated at least once, given the false negative rate. Communication between surgeon and radiologist may guide biopsy towards suspicious areas.

### *Limitations*

We identified a large number of controls in order to increase the power of the radiological findings, but case matching was imperfect. Factors such as duration of fistula persistence at the time of MRI study included for review and patient age was prioritised in case matching. It was challenging to identify control patients in the older age group with a long duration of luminal Crohn's disease preceding a complex perianal fistula with adequate duration of fistula persistence that matched the cases. Patients with Crohn's disease are increasingly escalated and optimised on anti-TNF therapy early in their diagnosis which may prevent later progression to complex fistulising disease, reducing the pool of such controls. The lack of adequate matching of fistula complexity in the controls may explain the positive associations such as T2-weighted high signal collection, heterogeneous T2-weighted tract signal, and matrix that are also found in complex perianal sepsis. The rarity of FMA poses a significant challenge in reassessing these findings in a single institution. These limitations can be corrected through further studies. The addition of post-contrast sequences for peri-anal fistula MRI is becoming more commonplace and future studies may show that this further aids timely detection of malignancy. Future studies should also aim to perform a double blinded radiologist evaluation of budding and other features of malignancy on MRI to evaluate inter observer variation. It was not possible to perform inter observer variation at this stage as the radiologists in the study were involved in establishing budding on MRI and had reviewed the scans together to reach a consensus on the features of budding.

## Conclusions

MRI has become an integral part of assessing fistula response to treatment. 'Budding' within a fistula tract described as a micro-lobulated expansion of T2-weighted high signal, detectable on at least two imaging planes is a significant feature that should be routinely reported, especially in the context of Crohn's disease and pouch fistulae. The presence of these features should trigger consideration of urgent targeted biopsy. Inconclusive or negative histology should be managed with interval surveillance MRI or repeated targeted biopsy given the risk of acquiring acellular mucin in these cases.

The detection of 'budding' on fistula protocol MRI outlined by this study should be validated by other centres in their own cohorts. Formalisation of imaging intervals may be warranted, with lowering of the threshold for re-imaging in the context of worsening or new symptoms of pain or discharge.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-562/rc

*Data Sharing Statement:* Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-562/dss

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Institutional ethics committee review did not require ethical approval for this

study. This study was a service delivery evaluation of the use of MRI in FMA. Patient consent was not required. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).



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