Case Report

Mucinous adenocarcinoma arising from chronic perianal fistula—a multidisciplinary approach

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Abstract: Mucinous adenocarcinoma (MA) is a rare entity. Indeed, the pathogenesis of fistula-associated perianal MA is still controversial. Due to the lack of informed evidence regarding this malignancy, no guidelines have been established concerning diagnostic and treatment strategies. The aim of this article is to report our experience and outcomes after three cases of large perianal MA treated in our center. From our retrospective chart review, we identified three male patients with chronic perianal fistula-in-ano who progressively developed perianal MA, confirmed by pelvic magnetic resonance (MRI) and histopathological examination performed on biopsy. We hereby, in accordance with the Surgical CAse REport (SCARE) guidelines, describe the management and further follow-up of each patient. The three patients underwent preoperative chemoradiation therapy, followed by ischioanal abdominoperineal resection (APR). Perineal reconstruction was needed in every case, using a vertical rectus abdominis myocutaneous (VRAM) flap and, punctually, a left fasciocutaneous flap was used too. Also, two of three patients completed the treatment with adjuvant chemotherapy. Neither recurrences nor distant metastases have been observed during the follow-up in both cases that finished the multimodal treatment. MA arising from chronic perianal fistula has an indolent growth with locoregional aggressiveness and a high risk of local recurrence. Therefore, although an ischioanal APR remains the surgical treatment of choice, an aggressive multimodal approach combining preoperative chemoradiation and adjuvant chemotherapy may achieve favorable effectiveness and promising response rates.

Keywords: Mucinous adenocarcinoma (MA); perianal fistula (PF); fistula-in-ano; abdominoperineal resection; chemoradiotherapy

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Introduction

Perianal fistula (PF) is a common entity in the proctology area. However, the development of a mucinous adenocarcinoma (MA) arising from chronic anal fistula is extremely rare. The relation between both entities was first described by Rosser *et al.* in 1934, who reported seven cases of fistula that had undergone malignant transformation (1). The pathogenesis of this malignancy is still controversial. MA has an indolent growth and, although metastases to inguinal lymph nodes may be present in advanced cases, distant metastases are uncommon (2-4). However, these locally aggressive neoplasms entail a high probability of local recurrence. The subtle symptoms that resemble a fistula-associated perianal MA to an inflammatory benign pathology make an early diagnosis difficult (5).

There is no uniform consensus until date regarding diagnosis and/or therapeutic strategies due to the lack of randomized prospective trials embracing this rare malignancy. Multimodality therapies for locally advanced anorectal cancer are currently well recognized treatment

options that improve the outcomes. Pre- and postoperative combined chemoradiation therapy (CRT), in association with surgery and wide resection margins is, up until now, the best available alternative, achieving better survival rates (4,6,7).

Unfortunately, as the diagnosis is often delayed, some of these patients have locally advanced cancer at the time of surgery, which results in poor prognosis (3).

Due to the lack of available data and definitive therapeutic guidelines, the aim of this study is to present our experience based on the outcomes after combining preoperative concurrent chemoradiotherapy, ischioanal APR and eventual adjuvant chemotherapy, and discuss the clinical features with respect to safety and efficacy of the multimodality therapy.

Case presentation

Patient A

A 66-year-old male, without medical records, complained about pain and perianal oozing for one month. The patient referred a growth in the perianal region with no history of any altered bowel habits. Physical examination revealed multiple deformities of the perianal region, with surrounding induration and the presence of several external fistula openings (*Figure 1A*).

Anorectal digital examination evidenced a stony and fixed to deep planes extramucosal mass, occupying the half posterior of the inferior rectum and anal canal. Colonoscopy confirmed the integrity of the rectal mucosa, and histological examination of the biopsy taken from the fistula tract showed epithelial cells and well differentiated dilated tortuous glands with lakes of mucin, consistent with the diagnosis of MA. Pelvic MRI showed a large mass with high signal intensity in T2 sequency extending to both ischioanal fossas, without any pelvic or inguinal lymph nodal involvement (*Figure 1B*). Thoraco-abdominal computed tomography scan (CT) did not reveal distant metastases.

Given these findings, management options were discussed by a multidisciplinary team, and the patient was proposed to undergo preoperative chemoradiation followed by surgery. Neoadjuvant treatment consisted in chemotherapy with capecitabine, and concurrent 3-dimensional conformal radiotherapy to a dose of 50.4 Gy in 28 fractions. Post-CRT re-staging MRI did not show a decrease in the tumor size. Twelve weeks after preoperative CRT, the patient underwent an ischioanal APR, and a VRAM flap was used for the perineal reconstruction (*Figure 1C,D*). Histological findings confirmed the mucinous nature, with only 3% of malignant cellularity and wide free-tumor margins. The perineo-gluteal wound healed completely and he was discharged on postoperative day 16.

Subsequently, the patient completed the treatment with adjuvant oral capecitabine for four months. No evidence of local recurrence or distant metastases has been observed after 28 months of follow-up.

Patient B

A 71-year-old male with a 10-year history of complex anal fistula for which he had undergone a fistulotomy and three previous drainages, complained about persistence of symptoms and a recurrent posterior horseshoe-shaped abscess. Physical examination revealed chronic inflammatory perineal tissue, with two external openings found at both buttocks. Colonoscopy showed no abnormality. Histological examination of the biopsy performed revealed a low grade signet-ring cell MA (*Figure 2*). Pelvic MRI evidenced a 95 mm length tumor present in the pelvis, extending from the posterior wall of the lower third of the rectum to the external anal margin (*Figure 2A,B*). Contrast-enhanced thoraco-abdominal CT scan revealed multiple inguinal lymph nodes, with no evidence of distant metastases.

Based on these findings, the patient was first subjected to neoadjuvant chemoradiotherapy. Post-CRT re-staging MRI examination on the fifth week showed a moderate response of the tumor (grade 3). Ten weeks later, the patient underwent an ischioanal APR, and perineal reconstruction was made using a right VRAM flap. Also, a left fasciocutaneous flap was advanced into the wound defect for a better covering (*Figure 2D*). Histopathological examination of the specimen confirmed a low-grade MA with few malignant cellularity, adequate tumor-free margins and the absence of lymph nodal involvement. Unfortunately, the patient developed a viral pneumonia that prolonged his length of stay for 66 days. No other complications were observed, and the patient was discharged in good condition and with suitable healing of the perineum. Because of the extended length of stay, the patient did not receive adjuvant chemotherapy.

The patient had remained free from disease for 26 months follow-up. At that time, an abdominal CT scan revealed an enlarged left inguinal lymph node, which malignancy was confirmed on biopsy; yet no local recurrence has been observed until date.

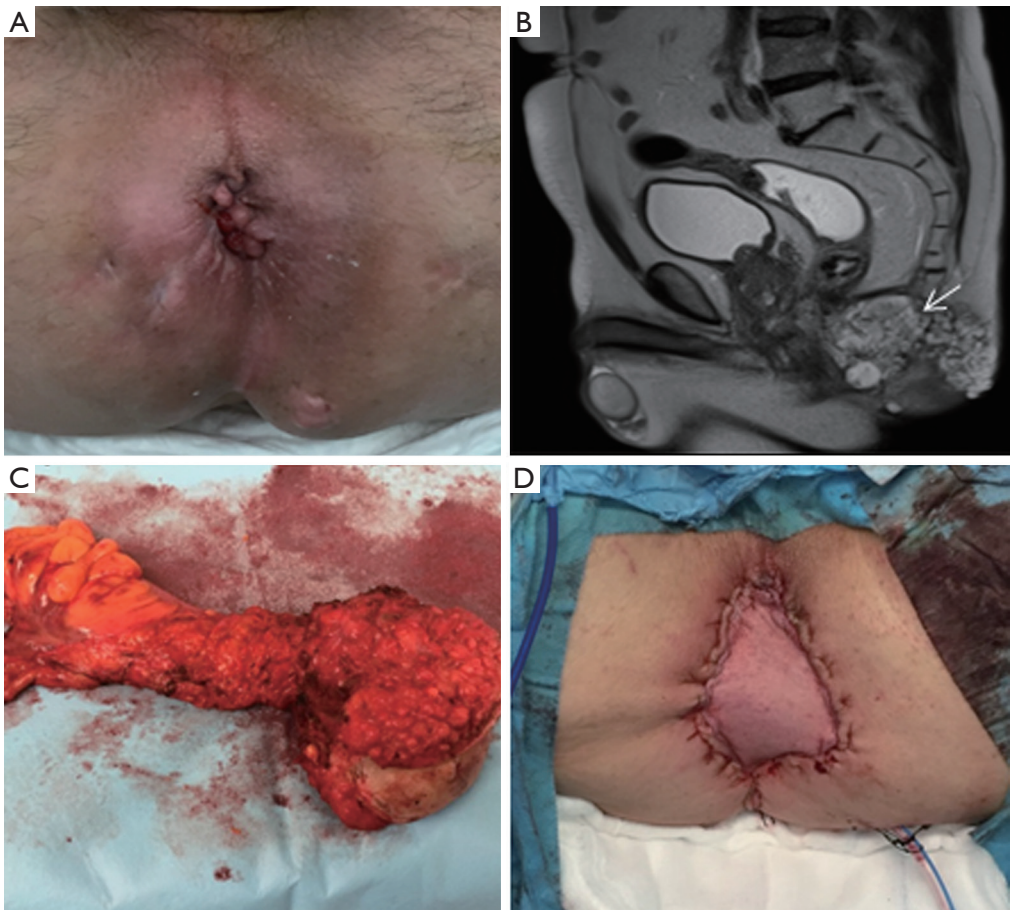

Figure 1 Physical examination, magnetic resonance imaging (MRI) and abdominoperineal resection. (A) Perianal swollen area, with several external openings; (B) MRI shows hyper signal in T2, suggesting mucinous adenocarcinoma (arrow); (C) abdominoperineal resection, surgical specimen; (D) perineal reconstruction with VRAM flap. VRAM, vertical rectus abdominis myocutaneous.

Patient C

A 62-year-old male presented with history of painful defecation and bleeding per rectum, in association with mucinous perianal drainage for 3 years. He gave a past history of complex anal fistula for which he had undergone an excision of the fistula tract and two additionally abscess drainages. Inspection of perineal region revealed an indurated area with several external anal fistula openings with spontaneous discharge of mucinous material. Colonoscopy showed circumferential ulceration of the mucosa in the lower anal canal, and a 2 cm length infiltrative tumor just proximal to the anal verge. Histological examination of a biopsy taken from one of the fistula tracts confirmed infiltration by a well differentiated MA (*Figure 3*). Pelvic MRI revealed a large demarcated mucinous lesion, measuring 49 mm × 42 mm × 71 mm. The tumor occupied the left elevator muscle of the anus with cranial extension to the left mesorectal fat (*Figure 3A*). Preoperative contrast-enhanced CT scan evidenced one enlarged left external iliac lymph node. No distant metastases were observed. The treatment outcome with preoperative chemoradiation therapy followed by ischioanal APR, nine weeks later. Post-CRT re-staging MRI examination did not show any evidence of tumor regression. A VRAM flap was used for perineal reconstruction (*Figure 3D*). Pathological response was evaluated using the tumor regression grading system criteria of the Japanese Society for the Cancer of Colon and Rectum (8), confirming the absence of primary tumor and a complete response (G0) after preoperative chemoradiotherapy (ypT0N0).

Postoperative course was uneventful. The patient had a

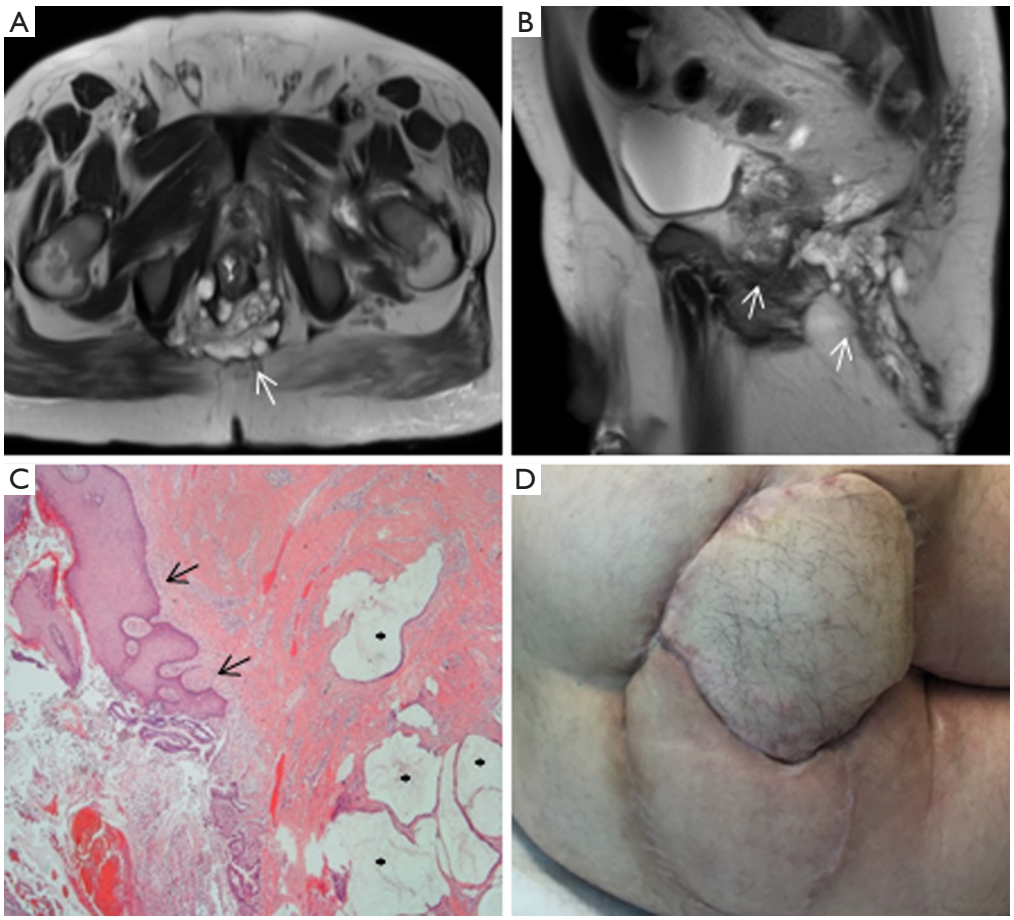

Figure 2 MRI T2-weighted images in (A) axial and (B) coronal plane showing the tumor involving the left elevator muscle of the anus and the mesorectum on either sides (arrows), piercing into the intersphincteric space, as well as the left ischioanal fossa; (C) biopsy from pelvic mass shows lakes of mucin (*) and tumor glands invading surrounding squamous epithelium (arrows) from fistulous tract (200×, H&E); (D) perineal reconstruction.

suitable wound healing, and was discharged on postoperative day 14. He received postoperative chemotherapy with oral capecitabin for four months. No recurrences or distant metastases have been observed after 19 months of follow-up.

Discussion

According to the World Health Organization (WHO), MA is an invasive adenocarcinoma consisting of malignant glandular cells which contain intracytoplasmic mucin. Usually, the infiltrating glandular structures are associated with mucoid stromal formation (9).

MA can appear not only in multiple locations of the digestive tract (colon, stomach, pancreas, gallbladder, etc.), but also in other placements like breast, thyroid, or even skin. However, perianal location of MA is very uncommon. It has been suggested that malignant degeneration of a long-standing PF is often associated with mucosal regeneration, while other authors believe malignant cells settle in the fistulous granulation tissue arising from proximal gastrointestinal neoplasms (10). Repeated friction, scarring and inflammatory reactions may be predisposing risk factors for development of perianal MA (5,11). The association of Crohn's disease with MA has been widely established, and a high suspicion has to be maintained in the presence of perianal fistulas (12-14).

Symptoms at presentation usually include perianal pain, itching, mucinous discharge and/or abscess, in association with an ulcero-proliferative growth or palpable mass in the

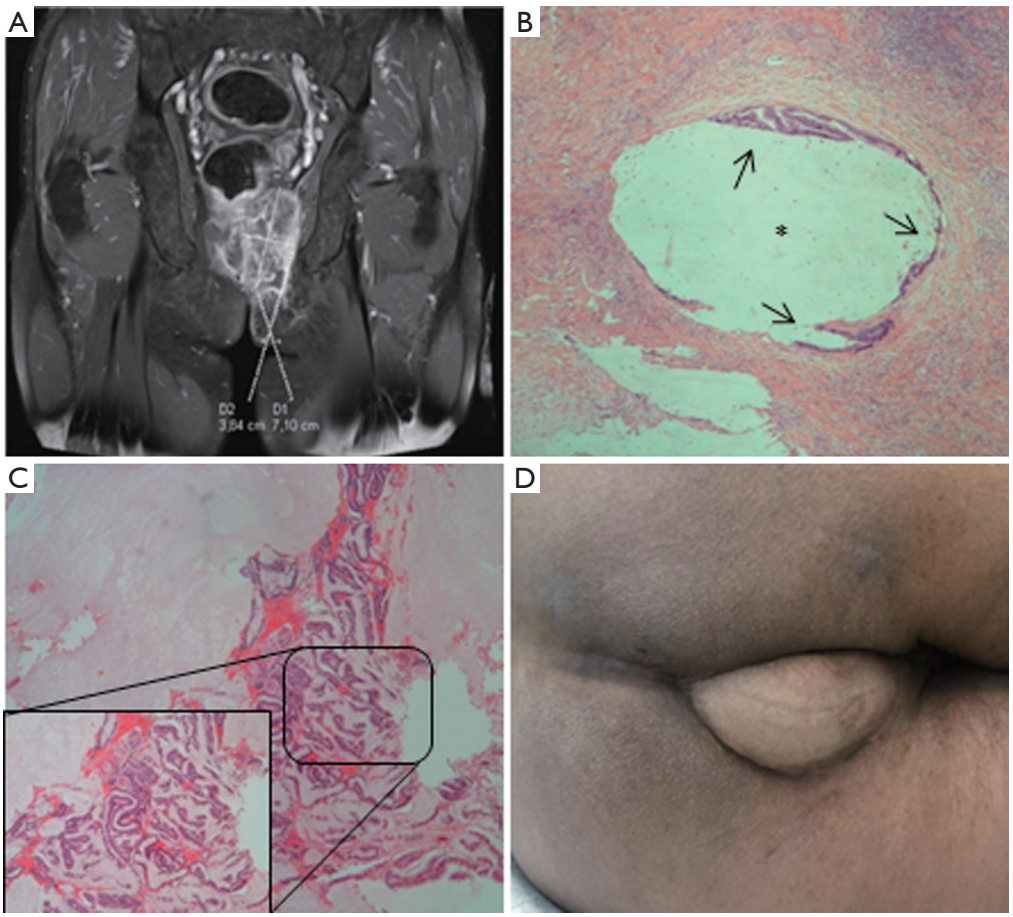

Figure 3 Diagnosis, histological examination, and postoperative result. (A) Oblique coronal MRI T2-weighted image showing a large mucinous tumor arising from perianal fistula, measuring 49 mm × 42 mm × 71 mm; (B) biopsy from the lesion showing lakes of mucin (*) and intervening stroma (arrows) showing chronic inflammatory changes (H&E, 400×); (C) tortuous glands with lakes of mucin consistent with mucinous adenocarcinoma (H&E, 200× and 400×); (D) perineal reconstruction using VRAM flap. MRI, magnetic resonance imaging; VRAM, vertical rectus abdominis myocutaneous.

perianal region (3). Considering the unusual infiltration of rectal mucosa, neither intestinal obstruction nor rectal bleeding are very common symptoms (5,15,16). The most frequent clinical presentation is related to long-standing fistula-in-ano (1); tumor progression may imply tissue destruction, resulting in perianal abscesses and anal fistulas, with the consequent development of symptoms as perianal oozing and/or mucinous discharge (6).

Early diagnosis of perianal adenocarcinoma is difficult as the tumor does not pierce the rectal mucosa and its course is usually indolent. Therefore, clinical suspicion is of paramount importance in the diagnosis, as the symptoms often mimic benign inflammatory conditions. In our series, patients' symptoms were attributed to their perianal benign diseases, and neither previous biopsy samples nor clinical suspicion of malignant carcinoma were performed. Thus, further colorectal investigation was not achieved, and an early diagnosis was missed.

Digital rectal examination evidences a thickened indurated area involving the fistula tract (6), while colonoscopic examination shows no growth in anorectum. Imaging modalities as CT scan, MRI and endoscopic ultrasound (EUS) establish the disease extension to adjacent tissues and help to plan the surgical strategy (7-11). Among them, pelvic MRI is the best image technique, since the abundance of mucin in these tumors gives them a unique radiological appearance, which results in a significant hyper-intense signal on T2-weighted images (17). However, MRI images can be difficult

to distinguish from other fluid-containing pathologies such as cysts, fluid collections, and even necrotic tumors. The presence of a fistula tract involved by the mass and the anal canal is a representative characteristic of MA over PF (18). Functional imaging technique like PET-CT is not a valid evaluation tool, since the presence of mucina may result in false negatives due to poor 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (FDG) uptake (19).

Histological diagnosis remains the gold standard. The presence of extracellular mucinous lakes surrounded by well differentiated dilated tortuous glands, nerves and vessels, confirms the diagnosis. In many cases, definitive diagnosis may be verified by the histopathological examination of the resected specimen because preoperative biopsies can fail to reveal an infiltrating carcinoma (2,20).

Surgery is considered the cornerstone in the management of this malignant entity. Most surgeons support the APR with wide local excision as the preferred therapeutic option, as it helps in removing the malignant tissue, while reducing the chances of local recurrence when negative margins are achieved (21). In locally advanced tumors, either an ischioanal APR or extralevator abdominoperineal excision (ELAPSE) is needed in order to decrease positive margins rates. In these specific situations, the reconstruction of the pelvic floor is required, meaning an increased operative time and a higher morbidity rate, too.

However, there is a high level of uncertainty surrounding the combination of chemo- and radiotherapy, either in preoperative or adjuvant setting, still unresolved. Yang *et al.* suggested that the combination of chemoradiotherapy is a valid and adequate option when the tumor is not completely resected or the patient refuses surgery (5). Also, Hongo *et al.*, in an 11-patient study, reported more disease-free survival in those cases where chemoradiotherapy was given prior to surgery (22). In a retrospective study including 82 patients, Belkacémy *et al.* conclude that the stage T and N, the histological grade, and the therapeutical modality are independent risk factors for survival rate, achieving better outcomes with chemoradiotherapy, and recommended surgery as a salvage approach (23). Hence, in locally advanced tumors, preoperative chemoradiotherapy causes downsizing of large neoplasms, contribute to eliminate disseminated tumor cells, thus increases the chances of R0 resection and decreases the incidence of local recurrences (21).

Besides that, it has been reported that mucinous status observed at pretherapeutic MRI was associated with a noticeably worse response to chemoradiation than non-mucinous tumors in rectal cancer (24).

In view of the extensive involvement of surrounding soft tissues and the histopathological reports evidenced in our cases, upfront surgery was not considered due to the possibility of a R2 resection. We particularly chose to treat our patients with preoperative chemoradiotherapy, followed by aggressive surgery such as ischioanal APR, and subsequently adjuvant chemotherapy. Also, post-CRT re-staging MRI did not show a significant tumor regression in any of our patients; however, far fewer active tumor cells were evidenced in the histopathological examination of the specimen, even though there was not a downstaging based on the tumor size.

Distant metastases are rare in MA, and tumor spread is usually lymphatic, being the inguinal nodes the most frequent site of metastases (21). According to the published data, prognosis seems to be worse when the tumor is larger than 5 cm size, carcinoembryonic antigen is elevated, or lymph nodal or haematogenous metastases are present at the time of diagnosis (25,26), finding reported survival rates of 2–48 months (27).

Long-term survival rates are not yet satisfactory if the patient has locally advanced stage disease.

Conclusions

Mucinous adenocarcinoma arising from chronic perianal fistula is an uncommon neoplasm with indolent growth and locoregional aggressiveness. As these tumors have a high risk of local recurrence, an aggressive and multimodal approach should be carried out to reduce positive surgical margin rates and increase R0 resection rates.

Despite the limited follow-up and the small sample size in the present series, we believe that combined chemoradiotherapy, followed by an aggressive surgery with ischioanal APR and adjuvant chemotherapy, are appropriate in locally advanced tumors, without major increased morbidity. However, further experience is required to establish the optimal management and accurate treatment in these uncommon malignancies.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from all individual participants included in the study for publication of this case report and any accompanying images.

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