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The surgical management of metastatic pancreatic acinar cell carcinoma and associated pancreatic panniculitis—A case report and literature review

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ABSTRACT

INTRODUCTION: Pancreatic panniculitis is a rare manifestation of benign and malignant pancreatic disease. The presentation of pancreatic panniculitis is non-specific and thus diagnosis is often delayed. When associated with malignancy, pancreatic panniculitis confers a poor prognosis. This case demonstrates the successful surgical management of this paraneoplastic phenomenon following resection of the underlying pancreatic acinar cell carcinoma and associated liver metastasis.

PRESENTATION OF CASE: A 71-year-old female with debilitating subcutaneous lower limb lesions had a delayed diagnosis of pancreatic panniculitis. A formal diagnosis of pancreatic acinar cell carcinoma with liver metastasis was established and the disease was determined to be resectable. Pre-operatively, serum lipase measured 10,825 U/L. The patient proceeded to an open left hemihepatectomy and radical distal pancreatectomy with complete resection of malignant disease. Six days post-operatively the serum lipase levels normalised, and the panniculitis began to settle. The patient proceeded to adjuvant FOLFIRINOX chemotherapy. Twenty months post-surgery, the patient remains disease-free and without any evidence of panniculitis.

DISCUSSION: Due to the rarity of pancreatic acinar cell carcinoma, guidelines based on prospective data do not exist. Most management is based on retrospective analyses. A survival benefit may be achieved with more aggressive surgical management compared to other pancreatic cancer types. Pancreatic acinar cell carcinoma may show a slower rate of disease progression, an increased likelihood of resectability of disease at presentation and is more likely to undergo potentially curative resection.

CONCLUSION: Aggressive surgical management of resectable metastatic pancreatic acinar cell carcinoma can treat pancreatic panniculitis and provide sustained disease-free survival from pancreatic cancer.

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1. Introduction

Pancreatic panniculitis is a rare manifestation of pancreatic disease in which inflammation occurs in subcutaneous tissues. It manifests as tender, erythematous lesions which, in severe cases, may discharge necrotic material or ulcerate. The mechanism of the condition is incompletely understood however the hypersecretion of pancreatic enzymes is thought to be related [1]. When present in the setting of pancreatic acinar cell carcinoma (ACC) it confers a poor prognosis [2]. Approximately 95% of pancreatic malignancies arise from the exocrine pancreas with pancreatic neuroendocrine

tumours accounting for the remainder. The vast majority (>95%) of malignancies from the exocrine pancreas are pancreatic ductal adenocarcinomas (PDAC) [3]. In contrast, pancreatic ACC is a rare type of malignancy of the exocrine pancreas, accounting for less than 1% of all pancreatic cancers. Acinar cells make up the bulk of the pancreas and are responsible for producing pancreatic enzymes that are packaged into zymogen granules. In 10–15% of patients, ACCs are associated with a lipase hypersecretory syndrome characterised by elevated lipase, panniculitis and polyarthralgia.

Treatment algorithms for malignancies of the exocrine pancreas are largely based on experiences with PDAC. Traditionally, only surgical management of these cancers offers a possibility for cure. However, when patients have metastatic pancreatic cancer, which most patients do at the time of presentation, surgery is usually considered futile [4]. We report a case of pancreatic panniculitis with associated metastatic pancreatic ACC where complete surgical

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resection of malignant disease successfully treated the debilitating pancreatic panniculitis and provided sustained disease-free survival from pancreatic cancer. This case has been reported in line with the SCARE 2018 criteria [5].

2. Presentation of case

A 71-year-old female presented to her family physician with dyspnoea, cough and a fever – consistent with a lower respiratory tract infection. She improved after antibiotics and a short course of steroids, though a month after this initial presentation, developed painful, erythematous, lesions bilaterally over her lower limbs with pedal oedema. It was clinically consistent with erythema nodosum. There also existed tenderness of the hands, wrists and ankles. No formal skin biopsy was completed. For this presentation, the patient was referred to a rheumatologist. The patient described concurrent worsening hearing impairment which led to an audiogram, MRI head and an otolaryngology review which does not reveal a pathological process. There was no abnormality on routine bloods (including liver function) on initial presentation. The patient's past surgical history was significant for a laparoscopic cholecystectomy, and a total abdominal hysterectomy and bilateral salpingo-oophorectomy at age 35 for which she remained on hormone replacement. She took pantoprazole for GORD, though had no history of diabetes or heart disease, nor a family history of pancreatic or liver disease. She was a distant ex-smoker and drank alcohol occasionally.

On rheumatological review three months after first presentation, she was found to have tender, oedematous and erythematous ankles, as well as; tenderness of the metatarsal phalangeal joints, tenderness of the metacarpal phalangeal joints, and nodal arthritic changes in the hands. The suspected erythema nodosum lesions were not initially evident initially. Significant bloods results demonstrated an eosinophilia of $1.7 \times 10^9/L$ (0.0–0.6) as well as; ALP 205 U/L (50–140), GGT 112 U/L (<38), ALT 50 (<34), total bilirubin 5 (<20). Inflammatory markers were elevated; ESR 69 mm/hr (<20), CRP 26 mg/L (<5). Autoimmune and infectious screen was normal. Chest Xray was normal and an Xray of the hands demonstrated erosive arthritis within most of the interphalangeal joints. The rheumatologist's provisional diagnosis was sarcoidosis and the patient commenced on oral prednisolone 15 mg with review in a month. The deranged liver function was of uncertain significance as was the eosinophilia, thought possibly due to vasculitis (though ANCA was negative). Other differentials considered included allergy or a hepatic parasite.

Another month passed, and the patient was clinically deteriorating on rheumatology review. She had lesions resembling erythema nodosum as well as a discharging lesion from her left heel (Fig. 1A, B). The ankle arthralgia was worsening, and the prednisolone dose was increased to 50 mg daily. Urgent ultrasound to investigate the deranged liver function was organised which demonstrated a complex liver mass. The liver mass was further characterised with CT revealing a heterogeneous irregular mass filling segment 2, extending into segment 3 and bulging into segment 4A of the liver. The lesion involved the left hepatic vein, abutted the middle hepatic vein and did not definitely contact the inferior vena cava (See Fig. 2A, B). The tail of the pancreas appeared bulky on the CT, though enhanced uniformly.

The patient was urgently referred to a hepatopancreatobiliary (HPB) surgeon who ordered tumour markers and an MRCP to further characterise the liver lesion and the pancreas. Chromogranin A was raised at 844 ug/L (<102) suggestive of a neuroendocrine tumour, though the patient was on a proton pump inhibitor at the time. Lipase measured 10,825 U/L. MRCP demonstrated a T1 hypointense well circumscribed hypervascular mass present

within Segment 2 (See Fig. 2C). A lobulated well-circumscribed mass was demonstrated at the pancreatic tail which was also hypervascular (See Fig. 2D). It was T1 hypointense, mildly T2 hyperintense and demonstrated restricted diffusion. CT demonstrated no other distant disease in the head, neck, thorax, abdomen or pelvis. PET revealed a poorly FDG-avid and DOTATE-negative pancreatic tail mass and liver lesion. No other metabolically active lesion was detected. Liver biopsy was taken from the segment 2/3 mass without complication and confirmed the diagnosis of pancreatic ACC.

The initial diagnosis was made by needle core biopsy of segment 2/3 of the liver mass showing a carcinoma with distinctive features of polygonal cells with granular cytoplasm arranged in acinar structures (Fig. 3A, B). Differential diagnoses of a well differentiated neuroendocrine tumour and hepatocellular carcinoma was excluded by lack of immunohistochemical staining for synaptophysin, chromogranin, hepar-1, and polyclonal CEA, the latter showing no evidence of a canalicular staining pattern. The tumour cell granules were PAS positive, and immunohistochemistry for chymotrypsin showed diffuse cytoplasmic staining (Fig. 3C).

Following discussion in an HPB multi-disciplinary team meeting (MDM), the patient was recommended for resection of the pancreatic primary and associated liver metastasis. She was admitted to hospital early due to severe pain and worsening appearance of the lower limb lesions requiring analgesia, IV antibiotics for a possible superimposed cellulitis component and leg elevation (Fig. 1A, B). Pre-operative splenectomy vaccines were administered. The patient proceeded to theatre under and experienced hepatobiliary surgeon, who operates in a high-volume referral centre. The patient had a midline laparotomy which did not reveal any peritoneal disease. Intraoperative ultrasound of the liver did not demonstrate any other intrahepatic metastases. The surgeon performed a left hemihepatectomy (including resection of the middle hepatic vein) using the Erbe waterjet and staples for vascular structures (Fig. 4A). Then the primary tumour was resected with a distal pancreatectomy and splenectomy. The operative course was uneventful. Post-operatively, the patient was commenced on insulin and on day six the lipase measured 14U/L. In preparation for adjuvant chemotherapy a baseline CT chest, abdomen and pelvis was ordered, and the patient was discharged home day eight.

Pathological examination demonstrated the pancreas containing a 6 cm primary tumour which appeared to infiltrate the peripancreatic adipose tissue (Fig. 4B). The liver contained an 11 cm solid, fleshy tumour consistent with a metastasis (Fig. 4C). Histology from both tumours confirmed features of ACC with identical histological features to the original liver biopsy (Fig. 4D). No metastatic tumour was identified in twelve lymph nodes. After another MDM, the patient was referred to an oncologist and was treated with twelve cycles of FOLFIRINOX and referred for genetic testing and found to have a somatic BRCA2 mutation.

Over the proceeding months the patient's lower limb skin lesions slowly resolved. There was one necrotic area over the lateral ankle which required an incision and drainage two months post-operatively and took several months to improve. For surveillance the patient had LFTs, CEA, Ca19.9, lipase levels and a CT chest, abdomen and pelvis requested 3-monthly after the completion of chemotherapy. The most recent investigations at the end of July 2020 – twenty months post-surgery – demonstrate no evidence of recurrent disease.

3. Discussion

Panniculitis refers to a group of varying inflammatory disorders of the subcutaneous fat. The histopathological classification is that of septal panniculitis or lobular panniculitis. The clinical presentation of the panniculitides is similar, with erythematous



Fig. 1. Clinical Images. A. Pre-operative discharging necrotic material from a lower limb lesion of the patient. B. Pre-operative peri-ankle erythematous lesions.

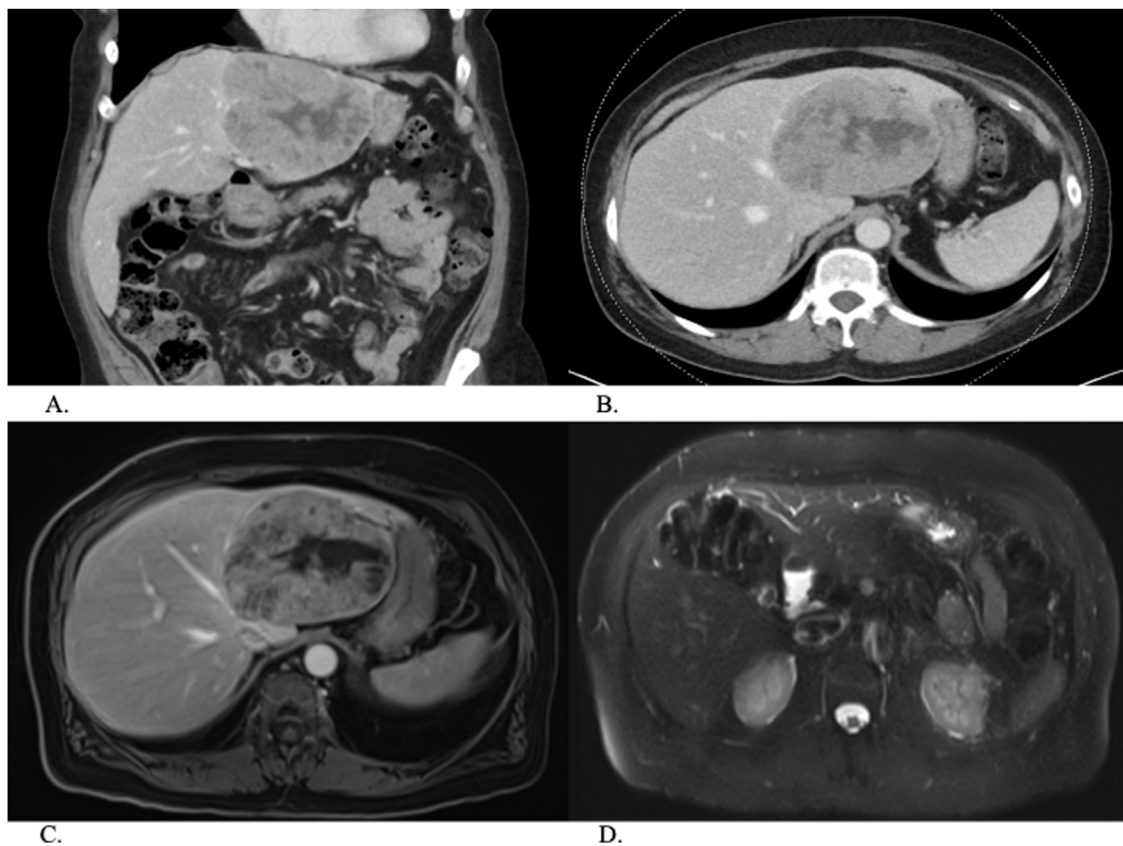


Fig. 2. Radiology.

A. Coronal CT showing irregular liver mass with approximate dimensions $8.7 \times 11.0 \times 8.8$ cm.

B. Axial CT showing irregular liver mass with approximate dimensions $8.7 \times 11.0 \times 8.8$ cm.

C. Axial T1 MRI Liver well circumscribed liver mass.

D. Axial T2 MRI demonstrating a lobulated well-circumscribed mass.

lesions mostly on the lower limbs. Pancreatic panniculitis is one of the subtypes of lobular panniculitis, it often charades as one of the more common forms of panniculitis, erythema nodosum – a form of septal panniculitis, of which this patient was initially diag-

nosed. Pancreatic panniculitis occurs in approximately 2–3% of all patients with pancreatic disease [6]. It is most commonly associated with pancreatitis (both acute and chronic), and is a known association with ACC. Panniculitis is rarely associated with PDAC,

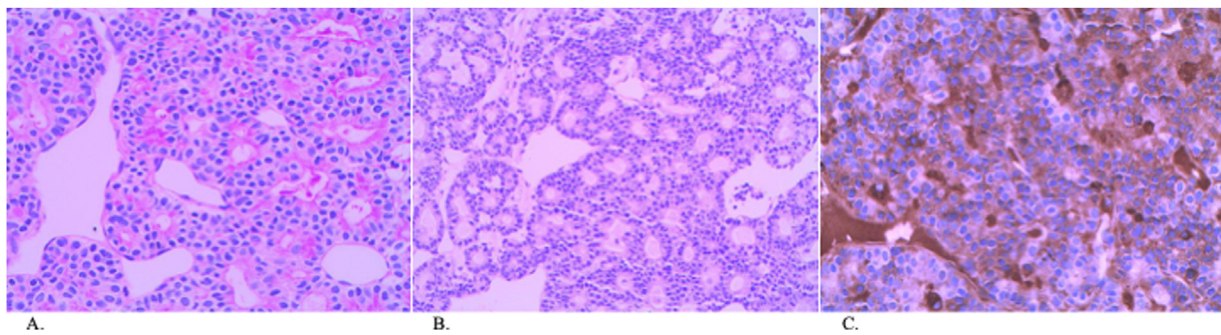


Fig. 3. Histopathology (Liver Biopsy).

A. PAS stain, showing positive staining of fine cytoplasmic granules.

B. H&E stain, showing the typical acinar cell pattern.

C. Chymotrypsin: Immunohistochemical stain for chymotrypsin showing granular pattern of cytoplasmic staining.

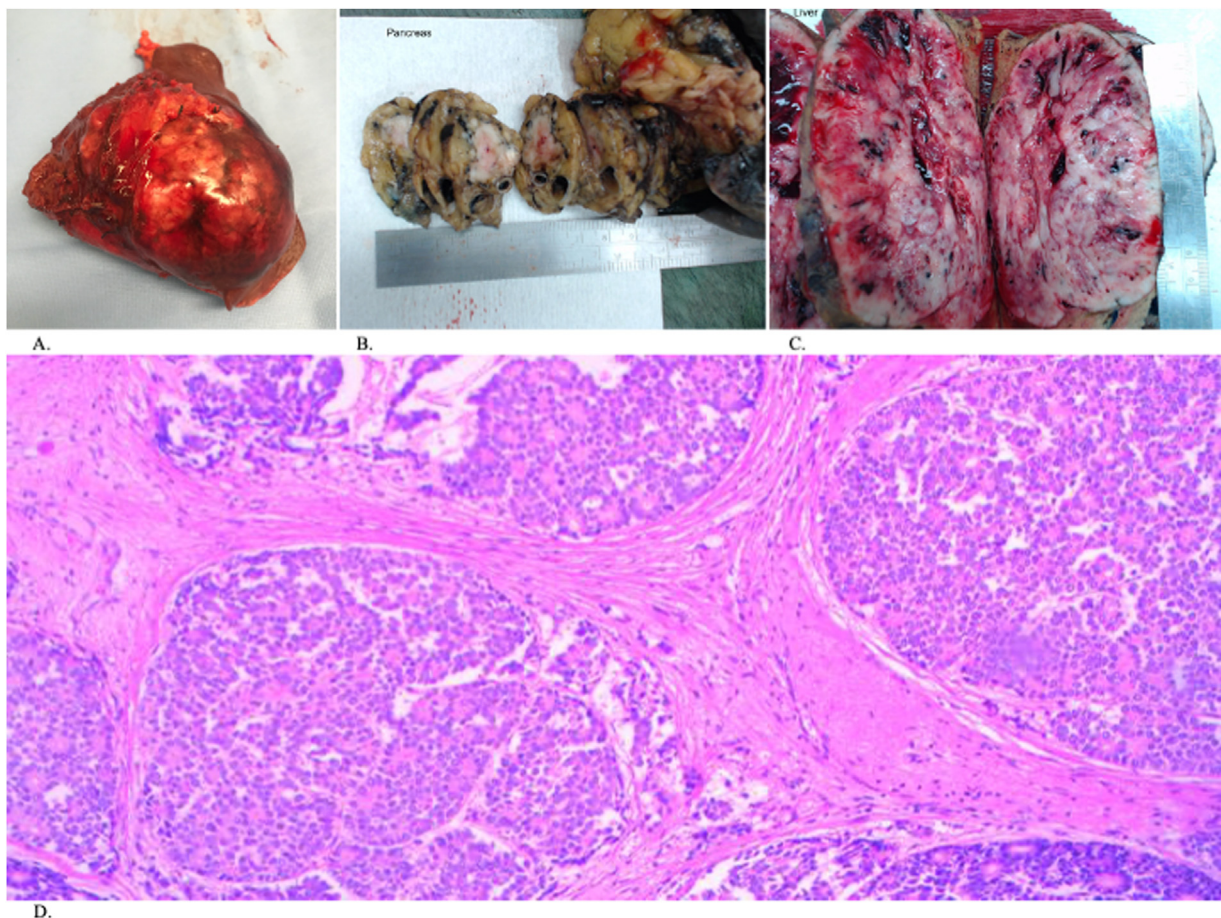


Fig. 4. Histopathology (Post-operative specimens).

A. Left hemihepatectomy specimen with tumour evident.

B. Distal pancreatectomy specimen showing primary ACC.

C. Large solitary liver metastasis.

D. Distal pancreatectomy specimen showing primary ACC.

islet cell carcinoma, pancreas divisum, pancreatic pseudocysts, and vasculo-pancreatic fistulas [6]. Coexisting polyarthritides is a known association with pancreatic panniculitis believed due to necrosis of periarticular fat [1]. The patient in this case had presented with arthritic changes in her hands, feet and ankles. On retrospect, this patient fulfilled Schmid's triad (panniculitis, polyarthritides and eosinophilia), a clinical presentation indicative of a pancreatic tumour. Five months existed between onset of symptoms and formal diagnosis of pancreatic ACC.

The literature over the last several decades has described panniculitis presenting in the setting of pancreatic ACC [2,7–14]. Most of these case reports demonstrate the poor prognosis associated with the condition, though some reveal improvement of the panniculitis when treating the underlying pathology [10,14]. Few case reports have demonstrated successful surgical resection of the primary and metastatic lesions to treat pancreatic ACC [14,15]. Good outcomes can be achieved with multimodal therapy when treating panniculitis in both locoregional and metastatic ACC [2,10,14,15]. A

survival benefit has been demonstrated with surgery in both locally advanced and metastatic ACC [16,17]. This case report supports the literature that pancreatic panniculitis can be treated with the complete resection of the primary pancreatic ACC and associated metastases. Further still, this may improve survival.

The guidelines for pancreatic cancer mostly focus on the management of PDAC. The NCCN guidelines for PDAC do not feature ACC. Standard management of *metastatic* PDAC is palliative chemotherapy. The presence of metastases in PDAC is generally considered a contraindication to surgical resection. The potentially curative benefit of surgery is limited to those with locoregional disease where complete surgical resection may be achieved [18]. Due to limitations in case numbers of ACC, studies of ACC are typically limited to retrospective analyses. However, there is evidence that in comparison to PDAC, ACC may show a slower rate of disease progression, an increased likelihood of resectability of disease at presentation and more likely to undergo potentially curative resection [16,19]. Further, when patients could be treated with surgery as first-line therapy they had increased survival [20]. These observations bring into question the appropriateness of treating patients with pancreatic ACC by following guidelines based largely experiences with PDAC. There appears to be significant differences between PDAC and pancreatic ACCs such that a separate treatment algorithm for pancreatic ACCs may be warranted.

Finally, pancreatic ACCs are well known to be associated with germline mutations of the BRCA2 gene [21]. Thus, patients diagnosed with pancreatic ACC should be referred for genetic counselling and tested for BRCA2 mutations. The patient in this case was seen by genetic counselling and found pathogenic variants in BRCA2 at allele frequencies >50%. However further germline sequencing from blood did not detect a germline mutation and instead were deemed to be somatic mutations. Therefore, no further genetic testing or screening was indicated for her family.

4. Conclusion

The primary aim of aggressive surgery in this case was to treat the morbidity associated with the debilitating pancreatic panniculitis. In doing so, a good oncological outcome has also been achieved and the patient remains in remission twenty months post-operatively, despite a delay in presentation and the presence of liver metastasis. This case provides evidence of the different behaviour of pancreatic ACC compared with PDAC. Further understanding of pancreatic ACC is required to ensure that the application of management guidelines based on PDAC do not unnecessarily restrict access to surgery for those with pancreatic ACC. Our current best practice is informed by retrospective analyses, case series, case reports and anecdotal experiences given the rarity of ACC. Prospective studies and collaborations will be required to inform consensus treatment guidelines customised for the management of ACC as distinct from other pancreatic exocrine cancers.

5. Patient perspective

I first started displaying unusual symptoms in my lower legs following a severe chest infection in May 2018. Although the chest infection eventually resolved, I didn't know then that this was the start of an extraordinary progress towards a permanently changed physical, mental and emotional self. A period of intense medical intervention, assistance and treatment followed which to a lesser extent continues to this day. However, both doctors, [my] rheumatologist and surgeon, have excellent communication, warm personalities and undoubted skills, which made the decision to trust their advice and to have surgery very straightforward.

Prior to the surgery I needed nursing assistance to dress the painful weeping lumps on my legs, caused I believe, by extremely high lipase levels. After the surgery I was rewarded with an excellent outcome. My surgeon's triumphant entry to my hospital room waving a test result showing that the lipase levels had returned to normal said it all. Success!

I recovered well and the lumps on my legs eventually disappeared. A fortnightly course of chemotherapy for 6 months was a difficult experience. I am a resilient person but loss of my sense of taste together with fatigue and a lack of physical strength still remain an issue for me despite my efforts to regain fitness. Unfortunately, but entirely predicably, this treatment has also resulted in neuropathy in my hands and feet and exacerbated the acute ankle problem, which led to many more interventions overseen by [my] rheumatologist.

Now I am getting the "all clear" from the follow up CT scans and blood tests from my highly skilled oncologist. Long may it last. This entire experience has taught me to accept patience, previously in short supply, the value of our health system, and a deep understanding of the value of exemplary professional and personal support.

Declaration of Competing Interest

The authors report no declarations of interest.

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Ethical approval

Not applicable.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Registration of research studies

Not applicable.

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Dr Edward M Clarke.

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CRediT authorship contribution statement

Edward M. Clarke: Conceptualization, Methodology, Project administration, Writing - original draft, Writing - review & editing. **Sean G. Stevens:** Writing - original draft, Writing - review & editing. **Tim Bennett:** Writing - review & editing. **Peter Crowley:** Writing - review & editing. **Graham Starkey:** Supervision, Conceptualization, Writing - review & editing.

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