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Case Report

Asymptomatic Mesenteric Desmoid Fibromatosis: A Diagnostic and Therapeutic Challenge

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ABSTRACT

Background: Desmoid fibromatoses are rare, benign neoplasms of myofibroblast origin that lack metastatic potential but can be locally invasive. Diagnosis and management are challenging as these are based on a multitude of factors such as symptomatology, tumor location, risk of recurrence, and the possibility of treatment-induced morbidity.

Case Presentation: A healthy 48-year-old Filipino woman presents with an 2x3 cm incidental jejunal mesenteric mass found intraoperatively during the excision of her choledochal cyst. Histopathology of the core-needle biopsy revealed desmoid fibromatosis. An initial watchful waiting approach was employed since the patient was asymptomatic and resection would cause significant bowel loss. After three months, her abdominal CT scan shows that the mass had progressed, to 4.7 x 4.5 x 4.7cm. Anti-hormonal therapy with high-dose Tamoxifen (120mg daily) was initiated due to its limited toxicity and low cost. The patient is currently asymptomatic, on her sixth month of treatment. The tumor remained stable at 4.5 x 4.6 x 4.7cm, on repeat abdominal imaging.

Conclusions: Desmoid fibromatosis represents a benign histology with a malignant and unpredictable course. It warrants a multidisciplinary team approach upfront. Watchful waiting is an appropriate first line option, especially in asymptomatic tumors and those found in non-critical locations. In case of progression, management should be site specific and via a stepwise approach. Therapeutic toxicities, such as significant intestinal loss upon resection, should be carefully weighed before choosing treatment. Preferred management for patients with intra-abdominal desmoid tumors that progress after observation has shifted towards non-surgical approaches or systemic therapies, including anti-estrogens, NSAIDs, tyrosine-kinase inhibitors (sorafenib, pazopanib and imatinib) and chemotherapy (methotrexate and vinblastine, and vinorelbine). A stepwise escalation of therapy from less to more toxic agents are a reasonable approach. It is also possible to discontinue treatment and resume watchful waiting for patients not progressing for two years.

Keywords: desmoid fibromatosis, mesenteric, fibrous tumor, case report

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Corresponding Author:*FRANCO Asymptomatic Mesenteric Desmoid Fibromatosis: A Diagnostic and Therapeutic Challenge*

Background

Desmoid tumors, otherwise known as aggressive fibromatoses, are rare, histologically benign neoplasms that develop as a result of abnormal monoclonal myofibroblast proliferation. They lack metastatic potential but are infiltrative and locally invasive, resulting to significant morbidity, especially if located intra-abdominally. It accounts for <3% of all fibrous tissue neoplasms, and 0.03% of malignant tumors, with a peak age of 30 – 40 years old [1,2]. Associated risk factors include the female gender, a history of abdominal surgery or trauma and oral contraceptive use [3]. It may occur sporadically or in the context of familial adenomatous polyposis (FAP) in 5-10% of all cases[1]. The location and presentation of these masses vary, with tumors arising from the abdominal wall, in extremities and approximately 70% occurring intra-abdominally[4].

Intra-abdominal desmoids may present as asymptomatic masses or with non-specific symptoms that may signify intestinal or urinary obstruction, vascular or neural involvement[4]. Its clinical course is also unpredictable, with approximately 20% capable of spontaneous stabilization or regression. Management is often challenging and based on a multitude of factors such as symptomatology, tumor location, risk of recurrence and the possibility of treatment-induced morbidity[1,4,5]. Historically categorized as a low-grade sarcoma[6], desmoid tumor were treated primarily through surgical resection[1,2,5]. However, aggressive attempts at achieving complete resection were found to cause significant morbidity with no improvement in recurrence rates[4,5]. There now appears to be a shift towards more conservative, non-surgical approaches[1,5,7]. With the variety of treatment options available including watchful waiting, resection, radiotherapy, and a combination of systemic therapies (chemotherapy, anti-inflammatories, hormonal therapy, and tyrosine kinase inhibitors), an upfront multidisciplinary team approach is recommended[1,5].

We report this unique medical entity, presenting as an incidental, asymptomatic jejunal mesenteric mass found intraoperatively in a middle-aged female.

Case Presentation

A fit-and-well 48-year-old Filipino woman was referred to us after an intraabdominal mass, measuring approximately 3cm x 2cm, was incidentally found at the root of the jejunal mesentery during her scheduled operation for a choledochal cyst (Figure 1).

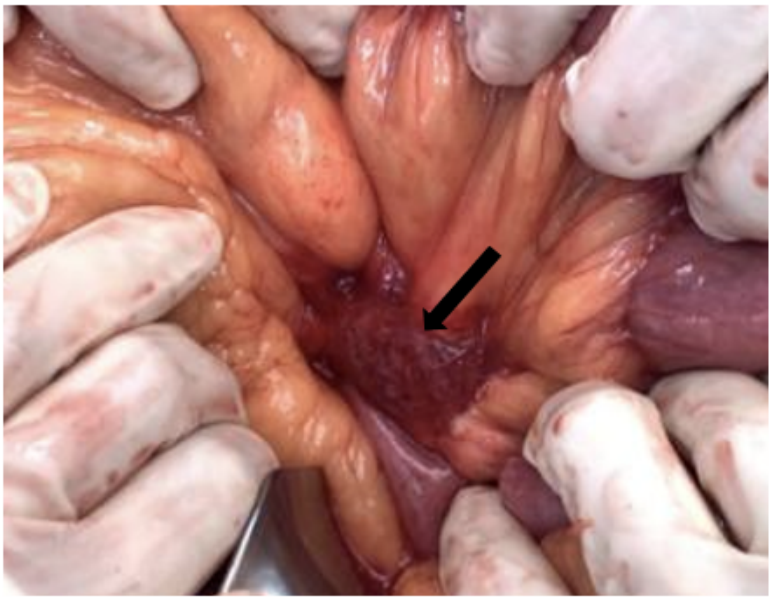

Figure 1. Incidental fibrous mass at the root of the jejunal mesentery

She underwent an excision of the choledochal cyst and cholecystectomy with a roux en y hepaticojejunostomy. While preparing the roux limb, her surgeons noted a firm, mobile mass at the root of the jejunal mesentery, to the left of the ligament of Treitz. The mass was not resected at the time due to its highly vascular location which, consequentially, may cause an unplanned and extensive bowel loss. Hence, only a core biopsy of the mass was done. Histopathology revealed a low-grade spindle cell neoplasm, with immunohistochemical analysis favoring desmoid fibromatosis. There was immunoreactivity to SMA and desmin, as well as nuclear and cytoplasmic expression of beta-catenin (Figure 2A-D). Meanwhile, negative staining for DOG1 and CD117, S100 and ALKD5F3 dissuaded differentials such as a

gastrointestinal stromal tumor (GIST), peripheral nerve sheath tumor or an inflammatory myofibroblastic tumor, respectively.

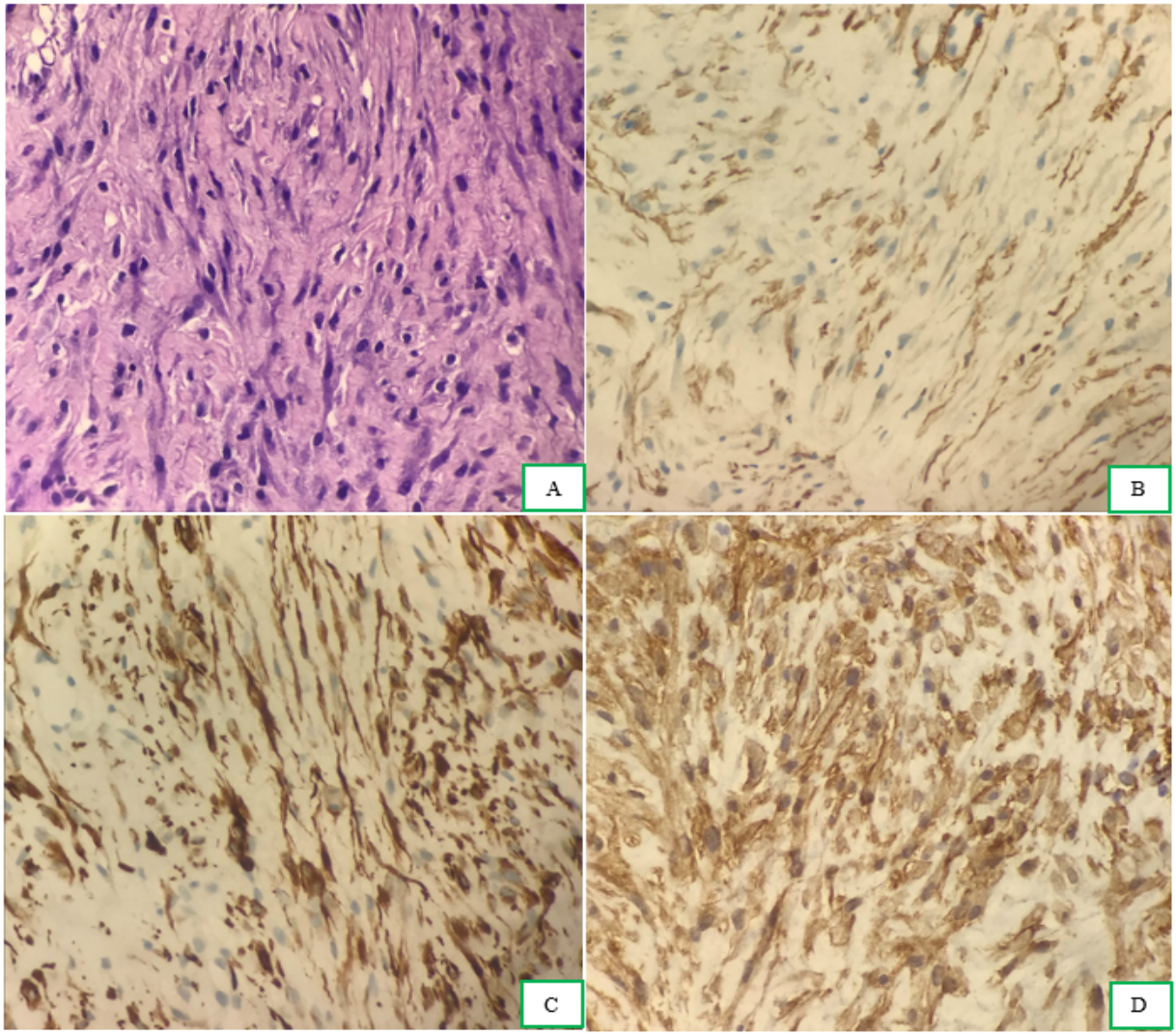

Figure 2. A: A low-grade spindle cell neoplasm with long fascicles of elongated and slender spindle cells in collagenous stroma with minimal atypia and low to no mitotic figures. B: SMA is positive and patchy. C: Desmin is positive. D: β-Catenin is positive with nuclear and cytoplasmic staining

The patient's family history was unremarkable. She has no comorbidities, had two previous cesarean sections more than a decade prior, and had no history of oral contraceptive pill use. She had been experiencing intermittent bouts of epigastric pain, radiating to the back, for more than a year prior her operation. On examination, there were no abdominal masses palpable. Her previous symptoms were attributed to an extra-hepatic choledochal cyst, initially diagnosed through a dynamic pancreas CT which showed a large, fusiform dilatation of the extrahepatic ducts up to the distal common bile duct. Upon retrospective review of this scan, a 1.5 x 1.5cm mass can also be visualized near the jejunal segment, consistent with the desmoid tumor's intraoperative location (Figure 3A).

In the interim, the patient has been asymptomatic. A surveillance contrast-enhanced abdominal CT scan done three months post-operatively showed progression of the mass, measuring 4.7 x 4.5 x 4.7cm, with no encasement of superior mesenteric vessels and with normal bowel gas pattern throughout the intestinal tract (Figure 3B). To assess for FAP, a colonoscopy was also done, yielding normal findings.

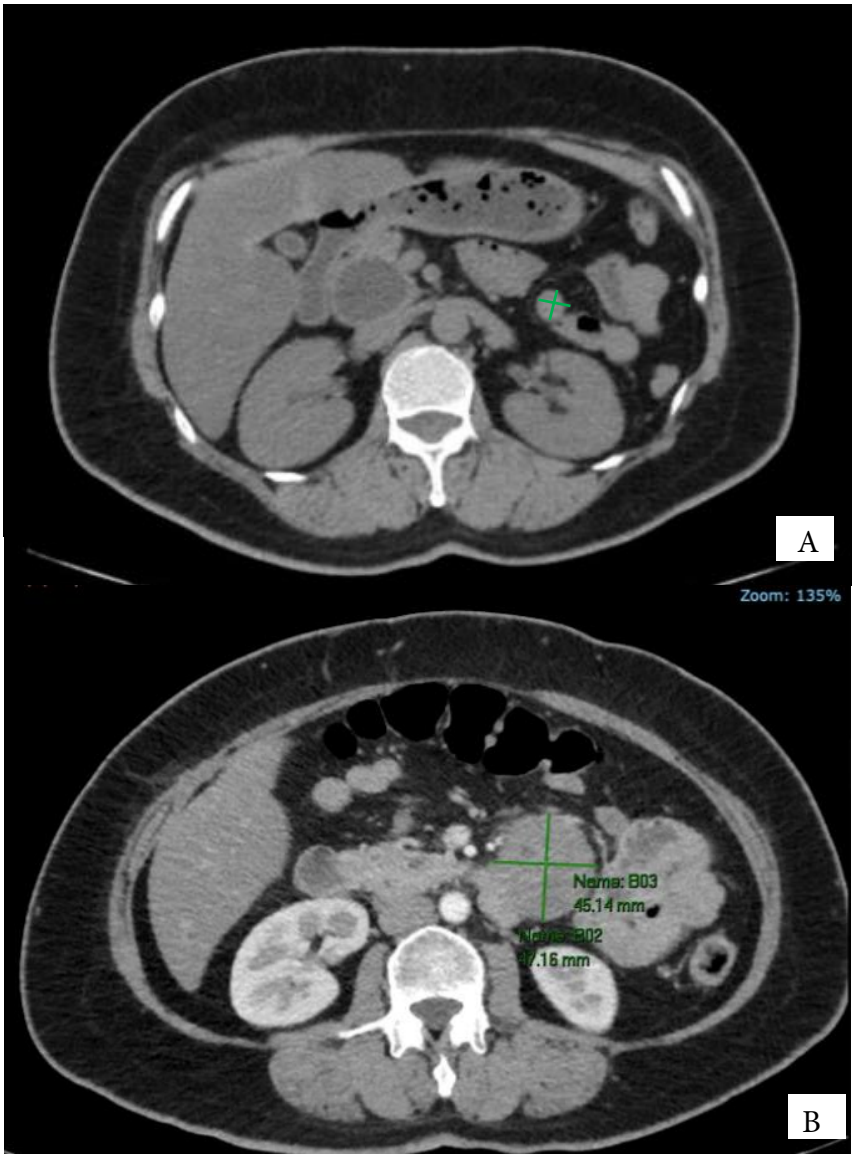

Figure 3. A: On dynamic pancreas scan, a 1.5 x 1.5cm mass can also be visualized near the jejunal segment, consistent with the desmoid tumor's intraoperative location. B: On an intravenous contrast-enhanced abdominal CT scan, there is progression of the mass to 4.7 x 4.5 x 4.7cm with normal bowel gas pattern.

A multi-disciplinary virtual tumor board was then conducted with a consensus of pursuing active medical therapy and surveillance because of the tumor's size progression and intra-abdominal location. Anti-hormonal therapy, particularly, high-dose Tamoxifen (120mg daily), was preferred for our patient considering the drug's limited toxicity and low cost.

At the time of writing this report, the patient was on her sixth month of high dose Tamoxifen with good compliance and no reported side effects such as menopause-like symptoms. She also denied experiencing gastrointestinal symptoms such as abdominal pain, bloating or early satiety. The tumor remained stable at 4.5 x 4.6 x 4.7cm, on repeat abdominal imaging.

Discussion

The occurrence of desmoid fibromatoses seem to be related to increased female sex hormone exposure as in females of reproductive age, in pregnancy and in patients with previous use of oral contraceptive pills. In fact, estrogen receptors in desmoid tumor tissues are higher than in normal tissues[8]. Other risk factors specifically for intraabdominal desmoid tumors include previous trauma or surgery[6,8,9]. Our patient had two previous cesarean sections, more than a decade prior to the occurrence of her desmoid tumor. The mechanism behind this remains unknown, but approximately 75-80% of patients with intraabdominal desmoid tumors have had previous operations[6].

Intra-abdominal desmoid fibromatoses are often locally aggressive and develop commonly in the mesentery or retroperitoneum[4,8]. Most intra-abdominal tumors (85%) are of the sporadic type, characterized by somatic activating mutations in the β-catenin gene, CTNNB1[8]. Mutation status for this gene may be tested via Sanger sequencing. In a

minority of patients, desmoid tumors result from loss of adenomatous polyposis coli (APC) gene. This is a germline mutation seen in patients with Gardner syndrome, an autosomal dominant disorder also known as a variant of FAP and associated with a triad of colonic polyposis, soft tissue tumors and osteomas[10]. Patients with FAP have a much higher relative risk of developing desmoid tumors and even accounts for 1% of cases of colorectal cancer. Patients with mesenteric and multiple desmoid tumors are more likely to have FAP[4,6]. The presence of CTNNB1 mutations or the loss of APC lead to the activation of the Wnt/β-catenin pathway, the primary oncogenic event behind the tumorigenesis of desmoid fibromatosis. β-catenin accumulates in the cellular nuclei and may be detected by immunohistochemistry. This serves as a diagnostic tool to differentiate desmoid tumors from other fibrous tumors[10]. CTNNB1 mutations and APC loss are also mutually exclusive events in desmoid tumors. With this, performing mutation analysis is strongly recommended to assess the need for more extensive diagnostic work-up, such as colonoscopy or germline testing for FAP[1]. Due to our patient's lack of necessary funds for CTNNB1 sequencing, we pursued a screening colonoscopy for her instead, which yielded normal results. It should be noted, however, that some retrospective studies conclude that routine colonoscopy of patients with desmoid tumors had a low diagnostic yield of FAP[11].

In recent years, significant steps by international societies have been made to standardize treatment strategies among clinicians. The Desmoid Tumor Working Group, a meeting of over 50 adult and pediatric sarcoma experts globally, has set consensus-based, evidence-driven guidelines for the management of desmoid tumors[1]. Active surveillance or watchful waiting is now an established primary approach for primary, recurrent, sporadic and familial desmoid tumors, especially in asymptomatic individuals and with tumors found in non-critical locations[1,2,6]. Large cohort studies comparing initial surgery to observation showed no significant difference in 2-year event free survival[1]. This was the consensus to avoid potential harm and overtreatment of tumors that may spontaneously regress or stabilize, which occurs in 20% of desmoid tumors[2]. The surveillance modality must be tailored to the site of the tumor[4]. Hence, to reduce radiation exposure[6] and for proper visualization of intra-abdominal structures, an abdominal MRI at 1-2 months since diagnosis, then at 3–6-month intervals for two years is recommended for intraabdominal desmoid tumors[13].

In 20% of cases, patients with intraabdominal desmoids, especially as small tumors, remain asymptomatic or minimally symptomatic[4,6,13]. When rapidly enlarging, however, these tumors are found to have the worst prognosis due to complications such as bowel or renal obstruction, bowel ischemia or bleeding and perforation[6,1]. In case of progression, management should be site specific and via a stepwise approach[1]. Therapeutic toxicities should be carefully weighed before choosing treatment[1,2,5]. In general, surgical excision is considered if complete resection is possible and if post-surgical morbidities are limited[4,6]. This is the accepted second-line management for abdominal wall tumors that have failed observation[1]. The effect of surgical margin status, whether microscopically positive (R1) or not (R0), on recurrence rates is still controversial[14]. On the other hand, surgery for intra-abdominal desmoid tumors is more hazardous due to hemorrhagic complications and extensive enterectomy especially when there is involvement of the small bowel or mesenteric blood supply[3,4,6]. These features were seen in our patient intraoperatively, hence only a biopsy was obtained. However, if there is clinical obstruction, a bypass procedure rather than excision or debulking is the primary therapeutic measure[2,6].

Medical or systemic treatment is the second-line option for sporadic tumors not found on the abdominal wall and all familial tumors that progress after observation[1]. Treatment options with limited evidence include the use of imatinib, pegylated doxorubicin, non-steroidal anti-inflammatory agents, alone or in combination with high dose tamoxifen or other hormonal therapies[1,2,7,13]. Treatments assessed through randomized trials include sorafenib, pazopanib as well as methotrexate and vinblastine[1,2,13].

A decision towards more active treatment should be postponed until the occurrence of subsequent progression or an increase of symptom burden, assessed with at least two further surveillance imaging[1,13]. Our patient had two documented progressions already. Furthermore, her tumor originates at the root of the jejunal mesentery, a critical conduit for neurovascular structures that supply the small intestine. Further increases in the tumor's size may cause worrisome complications, such as bowel obstruction, ischemia, bleeding or perforation. Minimally toxic agents such as anti-estrogen therapy and sulindac may be the best initial strategy in minimally symptomatic patients[2,6]. Apart from two phase II trials that showed limited response rates (only 8%), a large retrospective cohort study evaluating high dose tamoxifen with sulindac yielded response rates of 25% and stable disease control in up to 90% of patients[1,13]. Furthermore, a small prospective study showed favorable results after treating FAP-associated desmoid tumors with 120mg tamoxifen or 120mg raloxifene, and 300mg of sulindac daily for 6 months, with 10 of their 13 participants (77%) showing stable disease, partial or complete response during the 30 months follow-up[1,15]. The development of ovarian cysts was the most common adverse event reported[15]. Our team decided to forego giving sulindac due to the patient's previous experience of epigastric pain and nausea upon intake of other NSAIDs (mefenamic acid and ibuprofen).

Ideally, tyrosine kinase inhibitors, such as sorafenib and pazopanib or vinorelbine monotherapy or the combination of methotrexate and vinblastine would have been the preferred regimens for our patient[1,13], given her tumor's unresectability and critical location[13]. These options would have offered impressive progression free survivals (not reached for sorafenib on 400mg daily at 11.3 months, 88% for oral vinorelbine at 12 months, 84% for pazopanib at 6 months, 45% for methotrexate and vinblastine at 6 months)[1,13]. After presenting the available options to our patient and taking her family's financial situation into account, the least toxic and least expensive regimen of high dose Tamoxifen, at 120mg per day, was chosen as our initial treatment regimen. It is also possible to discontinue treatment and resume watchful waiting for patients not progressing for two years[1].

Conclusion

Desmoid fibromatosis represents a benign histology with a malignant and unpredictable course that warrants a multidisciplinary team approach upfront[1,13]. The location of the tumor and general symptomatology directs appropriate surveillance and stepwise management. Watchful waiting is the first line approach in all types of desmoid tumors[1]. A decision towards more active treatment should be postponed until the occurrence of subsequent progression or an increase of symptom burden[1,2,7,13]. For those arising from the mesentery and failing initial observation, medical therapy, instead of surgical excision, has become the second-line option[1,2]. Most studies and efficacious regimens include sorafenib, pazopanib, vinorelbine and methotrexate with vinblastine. Less established options include imatinib, anti-estrogen therapy and NSAIDs[1,2,13]. It is possible to stop active therapy and resume watchful waiting in patients with stable disease for two years[1].

Patient Perspective

I honestly do not feel anything. I eat well and am even gaining weight. I think I will get more anxious if I just wait. They said that it is not really cancer but it behaves like one. So I agreed with the doctors when they started me on the oral medication. At least, we are doing something to prevent my tumor from growing. It is also inexpensive, so I can continue taking it in the next few months.

LEARNING POINTS

- **The rarity and unpredictability of desmoid fibromatoses warrants a multidisciplinary team approach to achieve appropriate management**
- **Watchful waiting is the first line strategy for all types of desmoid fibromatoses**
- **For unresectable, intra-abdominal desmoid tumors failing observation, systemic medical therapy is second-line**
- **A stepwise escalation of therapy from less to more toxic agents are a reasonable approach**

Declarations

Ethics Approval and Consent to Participate

A written informed consent was obtained from the patient for this case report and any accompanying images. Exemption from ethics review was granted by the institutional ethics review committee of St. Luke's Medical Center – Quezon City

Consent for publication

A written consent for publication and presentation was obtained from the patient. All images are entirely unidentifiable. The patient understands that details ang images pertaining to the case will be freely available on the internet and may be seen by the general public.

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

PF contributed to the conception of the article, review of patient records, active management of the patient's case, acquisition of images and reports, drafted the work and substantially revised the manuscript. AG was the consultant co-author and contributed substantially in the conception, manuscript writing and revisions. Both authors read and approved the final manuscript. Both authors have agreed to both be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of a pat of the work are appropriately investigated, resolved and the resolution documented in the literature.

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