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Metachronous Dermatofibrosarcoma Protuberans (DFSP) and Gastrointestinal Stromal Tumour (GIST): Case Series with Review of Literature

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Abstract

Introduction: The occurrence of metachronous Dermatofibrosarcoma protuberans (DFSP) and Gastrointestinal stromal tumour (GIST) in the same individual is very rare, with few cases reported in the literature. Individually, (DFSP) and (GIST) are slow-growing tumours which are notorious for recurrence, especially if incompletely excised. They are both related to a mutation in the function of platelet-derived growth factor Receptor (PDGFR). We present two cases of metachronous DFSP and GIST, and review the literature. A 60-year-old male presented with a recurrent anterior abdominal wall mass of 2 years' duration. He had 4 excisions, in 6 years. Histopathologically, the last lesions was diagnosed as DFSP. Five (5) years later, the patient presented with an abdominal mass that was excised and histopathologically reported as Extra Gastrointestinal Stromal Tumour (eGIST). The second patient was a 35-year-old male who had had recurrent excision of a mass at the lower right back, which was histopathologically diagnosed as DFSP. The area was treated with radiotherapy after the surgery. Five (5) years later, he presented with haematemesis and weight loss. A CT scan of the abdomen revealed a large mass closely associated with the stomach. Though initially deemed unresectable, it was later resected because of poor response to targeted therapy with imatinib, with the patient continuing to have

persistent severe anaemia and fever. Confirmatory immunohistochemistry (CD117 and DOG-1) was performed in both cases to confirm the diagnosis. Patient number 2, the 35-year-old, only received adjuvant targeted therapy without response. Informed written consent was obtained from the patients, and medical records were obtained from the electronic medical records of the Korle Bu Teaching Hospital. One patient died within 21 days of follow-up, while the other is living without disease 7 months after surgery. CONCLUSION: These two cases highlight the possibility of metachronous occurrence of DFSP and GIST and underscore the need for attending clinicians to maintain a high index of suspicion for this occurrence in patients managed for DFSP.

Keywords

Gastrointestinal Stromal Tumour (GIST), Dermatofibrosarcoma Protuberans (DFSP), Imatinib, Metachronous, eGIST, Platelet-Derived Growth Factor (PDGF)

1. Introduction

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the gastrointestinal (GI) tract, accounting for 80% of all such GI tumours, and 0.1 to 3% of all gastrointestinal malignancies [1]-[3]. About 60% are found in the stomach, 20% - 30% in the small intestine and may rarely occur outside the GI tract (eGIST) in locations such as the omentum (80%), mesentery and retroperitoneum (20%) [4]. They can occur at any age but are most commonly diagnosed in the seventh decade. GISTs occur at a fairly equal rate among males and females [3].

GISTs arise from the interstitial cells of Cajal [4]. Mutations of the KIT (CD117) or platelet-derived growth factor receptor alpha (PDGFRA) have been shown to be associated with approximately 85% of sporadic GISTs [5] [6]. Forty-one per cent of GISTS are benign, 42% are malignant, and the rest have intermediate features. They most commonly spread haematogenously to the liver and peritoneum. Histologically, they could be of the spindle cell type (70%), the epithelioid cell type (20%), or a mixed type (10%). The most common markers in IHC analysis are KIT, anoctamin I / Discovered On GIST-1 (DOG1), and CD34 [5] [6].

Some common presentations of GIST are GI bleeding, abdominal discomfort/pain, early satiety, abdominal distension and a palpable mass [3]-[6]. They may also be asymptomatic and incidentally found on imaging, during surgery, or at autopsy [3].

Contrast-enhanced CT or MRI may show a solid, contrast-enhancing mass with smooth margins. Endoscopically, GIST may appear as a sub-epithelial lesion (SEL) with a smooth bulge covered with normal-appearing mucosa [7]. An Endoscopic USG may help differentiate GISTs from other SELs appearing as a hypoechoic solid mass originating from the muscularis mucosa or muscularis pro-

pria [8]-[10]. Definitive diagnosis is based on its histologic characteristics.

The treatment of GIST is mainly surgical if the tumour can be completely resected with clear margins of normal tissue [7]-[9]. In advanced disease, neoadjuvant, adjuvant, or palliative immunotherapy may be employed, using imatinib 400mg daily or adjusted to suit disease response [2] [5]. Multiple studies have shown improved recurrence-free survival (RFS)/overall survival (OS) in advanced or metastatic disease [2]. A multidisciplinary approach is employed to manage such patients.

Dermatofibrosarcoma protuberans (DFSP) is an uncommon slow growing firm soft tissue neoplasm primarily found on the trunk and proximal extremities [11]-[13]. DFSPs are associated with a t (17;22) (q22;q13) translocation, generating the fusion protein COL1A1-PDGFB [11] [14].

Extensive local infiltration characterises DSFP, with distant metastasis being rare unless fibrosarcomatous transformation occurs [15] [16]. Both males and females are equally afflicted, although some studies suggest a slight male preponderance [11]. It is commonly diagnosed in the third and fifth decades of life; DFSPs typically start as asymptomatic, poorly circumscribed, firm plaques involving the dermis and subcutaneous tissue and later progress to multiple raised nodules [11]. Histologically, DFSP shows spindle cell morphology with or without myxoid change [11]. Surgical excision with clear margins is often preferred [16]. Radiation therapy helps to decrease local recurrence, particularly in cases where wide margins are impractical [14].

McCarthy et. al. reported the occurrence of DFSP and GIST in a 61-year-old in 2010 [10]. They postulated that their patient might have a previously undescribed genetic mutation in the PDGF signalling pathway, resulting in these two very rare tumours [10]. eGIST usually has a very aggressive, persistent, and malignant course [4] [17]. To the best of our knowledge, no cases of GIST and DFSP occurring in the same individual have been reported in Africa. We report two cases of metachronous DFSP and GIST/eGIST managed at Korle Bu Teaching Hospital (KBTH).

2. Case 1

A 60-year-old male presented to KBTH with a huge anterior abdominal wall protrusion with a mass, about 20 x 15 cm, well defined, irreducible, but not tender, had no visible or palpable cough impulse and originated in a previous surgical scar (**Figure 1(A)-(B)**). The lesion had been growing progressively over 3 years, associated with weight loss. The patient had a previous history of three anterior abdominal wall mass excisions with the last histopathological diagnosis of DFSP. first excision in 2014, (15 × 10 cm), second excision in 2016, (17 × 17 cm), third excision in 2019, (20 × 17 cm), after first three excisions the tissue samples were discarded. However, last excision in 2020 was 5 years prior to this current presentation. Histopathological examination of the 2020 specimen showed grossly a multilobulated 29 × 24 × 13 cm mass weighing 4.2 kg, with an overlying ellipse of skin measuring 42 × 24.5 cm and a scar measuring 7 cm long. It further described a variegated cut surface with necrotic areas. Microscopically, a spindle cell tumour

was seen with storiform and cartwheel arrangement of lesional cells that trapped fat at the deep margin which was involved by tumour signifying incomplete excision. The features were consistent with DFSP. It was CD34-positive. Over the past 5 years he has noticed a gradual increase in size of the mass and heaviness and has decided to come again for assessment. He does not drink alcohol nor smoke.

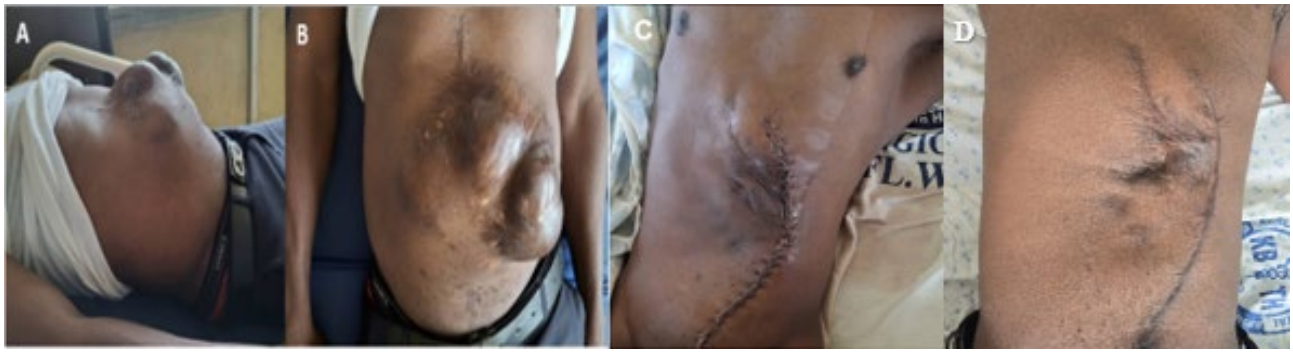

Figure 1. Frontal and side view of patient showing the mass protruding through the anterior abdominal wall (A,B): C shows the anterior abdominal wall after excision of the mass. D 7months post-surgery.

Abdominopelvic CT scan (10/03/25) at the current presentation showed a large, ill-defined, approximately (22.6CC × 22.2TR × 19.4AP) cm heterogeneously enhancing intra-abdominal soft tissue density mass, which showed cystic/necrotic areas as well as intralesional calcifications. Part of the lesion had protruded through a 10 cm defect in the anterior abdominal wall (**Figure 2**).

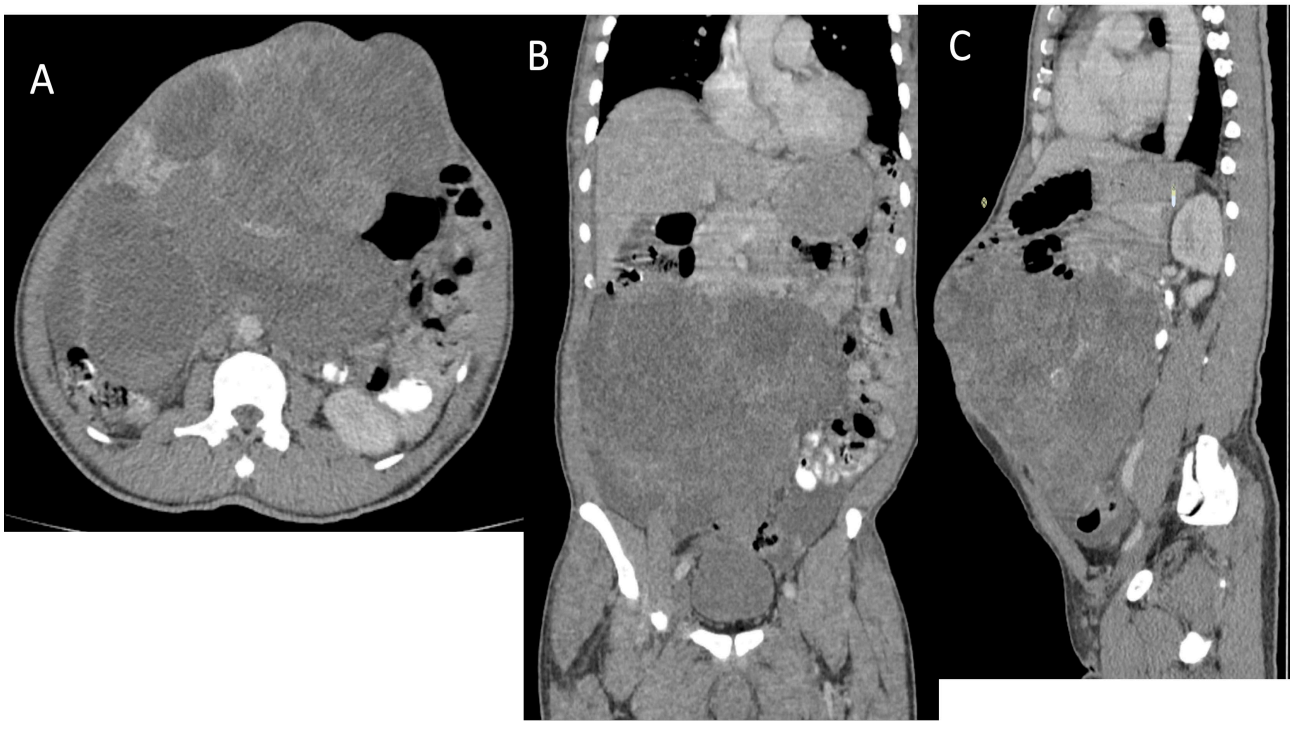

Figure 2. Large heterogeneously enhancing lobulated abdominal mass which protrudes through the anterior abdominal wall, displacing bowel laterally and posteriorly.

A diagnosis of a primary peritoneal or retroperitoneal neoplasm was suggested, and a biopsy was recommended. At surgery, a huge multilobulated intrabdominal mass with cystic, haemorrhagic and solid components was seen attached to the infra-colic part of the transverse mesocolon. The tumour was not attached to the overlying anterior abdominal wall, other viscera or the retroperitoneum. There was significant atrophy of the liver, stomach and small bowel, but no ascites. He was discharged on post-operative day 4 and made an eventful recovery (**Figure 1(C)**).

Histopathology revealed a high-grade spindle and epithelioid cell tumour with features consistent with a high-grade GIST, and positive confirmatory immunohistochemical staining for CD117 and DOG-1 negative for CD 34.

3. Case 2

A 35-year-old male who had 4 excisions of a flank mass over 2 years presented with a recurrent, gradually increasing mass in the lower back of 4 years' duration. A CT scan showed a right lumbar region cutaneous/subcutaneous soft tissue mass with features consistent with DFSP without liver metastasis. Histopathology and immunohistochemistry confirmed DFSP, and the patient received 66Gy of radiotherapy to the back (**Figure 3(A)**). Post radiation, a discussion on starting imatinib by the clinical oncologist on account of several recurrent disease was initiated; however, patient was lost to follow-up by all teams.

Five years after the last excision, he presented again with haematemesis to a private facility. Was admitted and transfused with 2 units of blood. He was referred to us and had an upper GI endoscopy, which did not show any area of bleeding, but some mucosal oedema at the greater curvature.

An MRI study of the abdomen was requested because of the haematemesis, which showed a heterogeneously enhancing lobulated left upper quadrant mass which involved the body and tail of the pancreas. Patient, however, got lost to follow up and then returned after 3 months with a CT scan showing a 14.7 × 18.4 cm left upper quadrant mass (**Figure 4(A)**), which projected into the gastric lumen and infiltrated the pancreatic body and tail and the spleen. He had apparently undergone a laparotomy at a peripheral facility on account of a suspicion of GIST on imaging. Intraoperatively, an extraluminal firm mass was found in the lesser sac measuring approximately 12 cm in its greater diameter. Its stalk was attached to the posterior aspect of the lesser sac. It was abutting the medial aspect of the spleen and the posterior wall of the stomach but not attached to any of these organs. But for its stalk, it was loosely adherent to surrounding tissue and was easily bluntly dissected from them. The stalk, after skeletonization, was doubly ligated and submitted for histopathological analysis. Histology showed an intrabdominal tumour spindle cell neoplasm with features suggestive of spindle cell type Gastrointestinal stromal tumour (GIST). To confirm, histological diagnosis, immunohistology analysis showed positive CD 34 but negative S-100, SMA, Desmin, CD117, DOG1, STAT6, CD99, BCL2, SOX10, TLE1, PanCK and EMA.

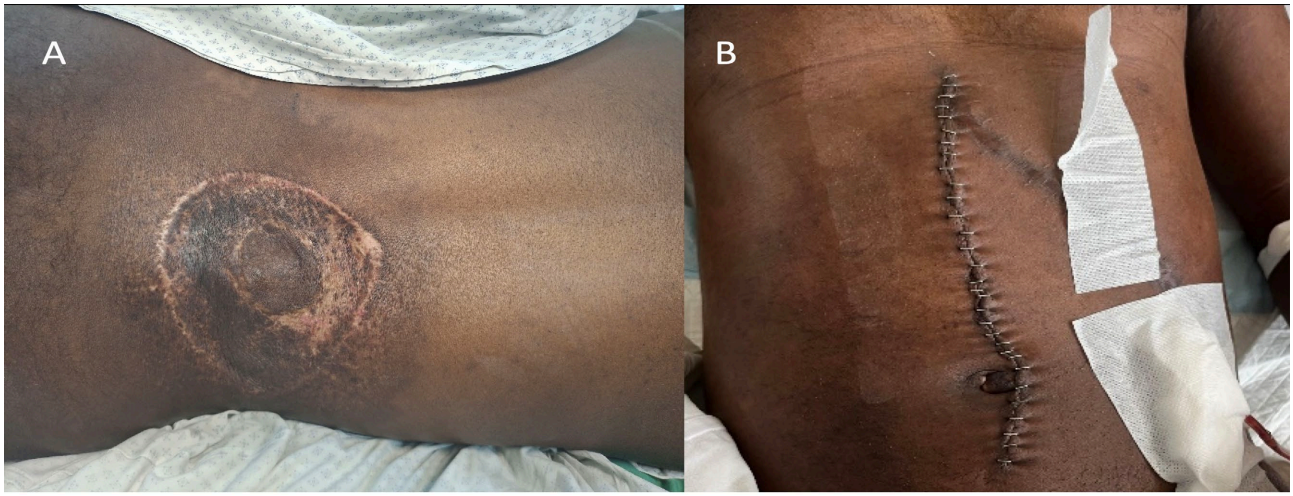

Figure 3. Patient's abdomen showing A. the appearance of the skin due to the lesion and previous treatment (surgery and radiotherapy). B. postsurgical wound from recent surgery.

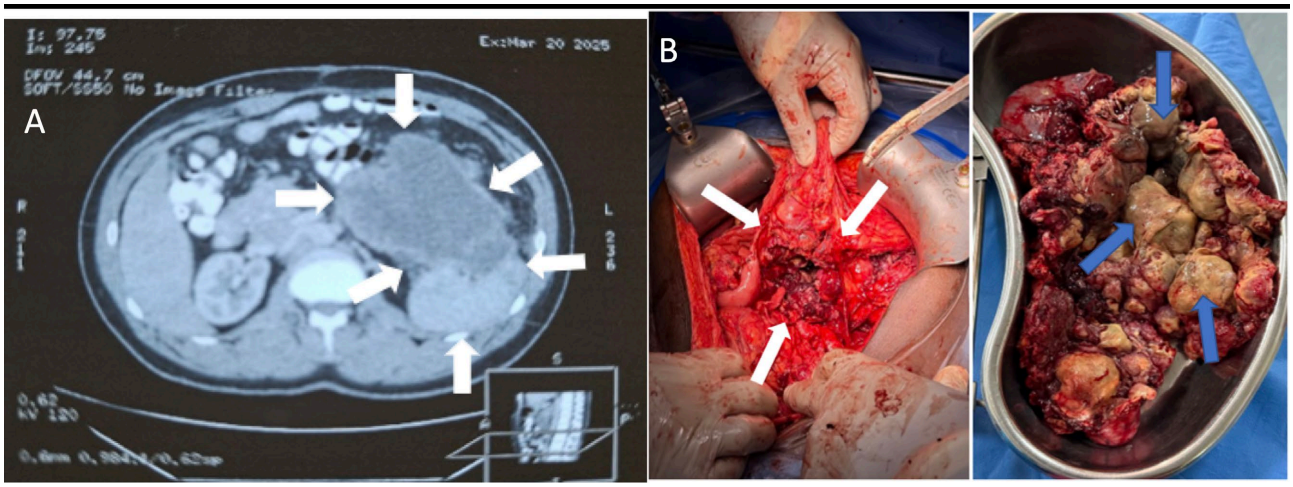

Figure 4. Left upper quadrant lesion; A CT scan of the abdomen showing a heterogeneously enhancing left upper quadrant mass in the region of the pancreatic body and tail, and infiltration of the spleen. B. intraoperative lesion (white arrow) and post-excision abscess cavity blue arrows.

Based on this new information, the MDT decided to treat as GIST. The case was discussed at MDT with the new findings and decision was to treat for GIST. Patient was started on imatinib at 800 mg daily. Unfortunately, he had another episode of haematemesis and a repeat upper GI Endoscopy to evaluate the cause of the bleeding revealed an oedematous and erythematous mucosa, but no evidence of bleeding.

He was deemed inoperable at further MDT discussion and continued the imatinib. He completed 2 more weeks uneventfully. However, during the third week of administration of imatinib, the patient developed haemorrhagic shock from massive haematemesis requiring multiple transfusions.

The patient had a laparotomy in spite of an earlier decision not to operate because of the persistent bleeding and anaemia. Operative findings were: a large tumour involving the posterior aspect of the body and fundus of the stomach, infil-

trating the body and tail of the pancreas (**Figure 4(B)**) and the celiac vessels. It also had a necrotic cavity from which 50 mls of pus (**Figure 4(C)**) was aspirated. An R2 excision of the tumour with en bloc splenectomy was only achievable, considering the morbid adherence to the pancreatic body and tail. No liver metastasis or ascites was noted.

Histology showed an irregular nodular pale brown mass measuring 24 × 13 × 7 with a gastric wall attached to one side 15.5 × 5 cm, attached to the opposite end is spleen 11.6 cm together weighing 927 g. The cut surface on the tumour is pale brown with large areas of necrosis. The overlying gastric mucosa appears normal. Microscopically, a hypercellular spindle cell tumour with mild to moderate nuclear pleomorphism. There are cohesive clusters of cells; epithelioid with minimal pleomorphism IHC was not done.

Postoperatively, the patient received 7 days of intravenous meropenem, 6 units of concentrated red cells, and 6 units of fresh frozen plasma. He was discharged on postoperative day 10 with an HB 9.3 g/dL. The patient unfortunately passed away on postoperative day 21 following another episode of massive haematemesis at a peripheral hospital.

4. Discussion

The first patient is 60 years old, while the second is 35 years old. The documented age range of DFSP is 20 to 60 years [13], while that of GIST is often in the 7th decade [2]. While both of them were within the age range of DSFP, the second patient seems to have developed GIST earlier than expected. He also had more recurrent disease and required radiotherapy to achieve remission of the DFSP. He also had a more aggressive disease of GIST.

GIST and DFSP tend to have an aggressive course in younger patients [7] [9] [17]. This is consistent with the clinical course of the younger patient who presented with several recurrences even after adequate excisions and radiotherapy, and eventually died after developing GIST. It is also worth noting that the disease was at a locally advanced stage, unresponsive to immunotherapy and rapidly fatal. Studies suggest an equal male-to-female distribution, whereas our patients were all male. Although we are dealing with only two patients, the rarity of GIST and DFSP could make our findings in both males significant, suggesting male predominance in our environment.

Both patients had DSFP on the trunk, which is consistent with the 50% prevalence of the tumour in the trunk reported in the literature [11] [13]. In our two patients, both were diagnosed with DFSP about 5 years before the diagnosis of GIST, which is worthy of note, similar to what is recorded in the literature [10].

The term metachronous, as adopted from colorectal language, means that at the first diagnosis of DFSP, there was no sign of GIST within 6 to about 4 years of making the diagnosis. In both cases, a diagnosis of GIST was made after 5 years of prior excision. This term was first used by McCarthy et al., and our case may well conform to their case [10].

The first patient presented with abdominal pressure symptoms, including a mass sensation, early satiety, and protrusion of the anterior abdominal wall. The second patient presented with hematemesis and melaena with symptoms of severe anaemia, like easy fatigue, dizziness and palpitations. Both patients had weight loss, albeit insignificant. These clinical presentations are consistent with the literature [3] [8]. The second patient's repeated acute episodes of blood loss despite unremarkable endoscopic findings were particularly challenging, hence the decision to perform a laparotomy, though the tumour had initially been assessed to be inoperable.

GISTs generally present anywhere from the mouth to the anus [4] [6] [8] [9], are considered treatable, and their prognosis, in terms of disease-free and overall survival, is mild [2] [3] [5] [18]. Often, complete surgical excision affords patients a cure [2] [5]. However, our patients had a unique presentation, with DFSP developing before GIST. In addition, the older one developed eGIST, which is in the minority and the younger one, who by virtue of age was in the minority, developed a locally advanced disease which remained non-responsive to immunotherapy, although the tumour was CD 34 positive and KIT negative and was rapidly fatal. I must add that a differential diagnosis of metastatic DFSP could be entertained looking at how aggressive the tumour was. This may be similar to the findings in Deng *et al.* publication which also demonstrated the malignant DFSP in his patient.

Table 1. Table to compare our cases with the literature.

Case	Age	Sex	Time of diagnosis of DFSP	Imatinib treatment	No. of excisions	Therapies	GIST diagnosis	Therapies
McCarthy et al. 2010	61	male	5 years earlier	did not state	2	Excision only	5 years after the last excision	Excision + imatinib
Deng et al. 2024	43	female	13 years earlier	10 years on 6 tablets of imatinib daily	9	Excisions only	Misdiagnosed as GIST	Excision + imatinib
Case 1 2026	60	male	5 years earlier	chemotherapy	4	Excision only	5 years after the last excision	Excision only
Case 2 2026	35	male	5 years earlier	800mg daily for 2 weeks	6	Excision + radiotherapy	5 years earlier	Excision only

The first case had the recurrent tumour on the anterior abdominal wall and re-excision was the only option he had for the DFSP because radiotherapy would have caused extensive collateral damage to other neighbouring organs. He did not pursue any form of systemic therapy because of a lack of funds. Therefore, whether the tumour would have responded to immunotherapy could not be determined. The question would then arise whether the previous diagnosis could have been GIST when it was actually diagnosed as DFSP or vice versa, similar to what was reported by Deng M et al., where a previous misdiagnosis of GIST was made because of response to imatinib for 10 years, only for the re-excision to be diagnosed as DFSP [19]. Indeed, both studies affirm the diagnostic challenges that

can arise in distinguishing GIST from DFSP. The FISH technique to detect the COLIAI-PDGFB fusion gene is currently not available at our hospital and is too expensive for the patient to have done in a private laboratory. The team continues to regularly monitor this patient's progress, as he is currently not on any immunotherapy. 7 months on patient remains stable with no evidence of tumour recurrence.

The presentation of these two cases, along with many unreported cases, makes the immunologic link between DFPS and GIST worth considering. Understanding the aetiology of these two conditions will improve the surveillance and treatment of patients who develop synchronous and/or metachronous lesions. Secondly, the realisation that the pathology is linked to mutations in the pathways of PDGFR alpha and beta synthesis and function will ignite research into the management of these two diseases, which, although rare, are notoriously recurrent and have malignant tendencies. McCarthy et. al. reported the occurrence of DFSP and GIST in a 61-year-old in 2010. At the time of his publication, he postulated that their patient might have a previously undescribed genetic mutation to the PDGF-signalling system, resulting in these two very rare malignancies [10]. Multiple studies continue to explore this link to afford adjuvant treatment of advanced and metastatic diseases [10] [14].

Surgical excision with clear margins remains the cornerstone of treatment for these two diseases, affording the potential for cure in early-stage disease [8] [9] [11] [13] [16]. Both DFSP and GIST are highly recurrent, so excision with clear margins is necessary [8] [16]. For the first patient, another nagging challenge was the ability to close the wound after excision of the recurrent lesion. Fortunately, it turned out to be associated only with the mesentery of the transverse colon, accompanied by redundant skin. However, due to the tumour's sheer size and mass effect, the intra-abdominal contents appear to have atrophied. Thus, closure with apposition of the recti and reinforcement with mesh was adequate. Patient was monitored for compartment syndrome post-op op but the recovery was uneventful. Our second patient was relatively younger and had an advanced disease such that an R_2 resection was an appropriate compromise for his treatment.

5. Conclusions

The metachronous existence of DFSP and GIST in the same patient is rare [10]. We have presented two cases managed at our hospital that initially presented with DFSP and later developed GIST within 5 years. We find it a very important clinical observation to report to add to the growing body of knowledge to help with the experience of such a presentation.

The systemic treatment of GIST with imatinib and its efficacy are evidence-based [5]. The use of systemic therapy for recurrent or metastatic DFSP is in its early stages, and the link between the two through the identification of an abnormal chromosome of PDGFB has postulated the effect of DFSP on immunotherapy [10] [15].

In low-resource countries like ours, access to genetic testing and molecular profiling is limited, making it financially challenging to distinguish between DFSP and GIST and therefore to manage them. Follow-ups of our patient has proven to be a challenge. However, with this addition to literature, we are encouraged to actively pursue our clients looking out for GIST in patients who continue to present with recurrent DFSP.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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