Local recurrence of sporadic mesenteric fibromatosis following radical surgery attacking the proximal jejunum

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Gastroenterology Rev 2017; 12 (3): 229–234
DOI: https://doi.org/10.5114/pg.2017.70478

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The term "desmoid" was first coined by Müller in 1838, having derived it from the Greek word "desmos," meaning ligament or tendon [1]. Desmoid-type fibromatosis, also known as aggressive fibromatosis, is a rare mesenchymal tumour characterised by the over-multiplication of fibroblasts and myofibroblasts originating from the deep muscular fascia, aponeurosis, tendon, and scar tissue [2]. It accounts for about 0.03% of all tumours, while its rate is about 3% in all soft tissue tumours. Its annual incidence is 2–4 per million. Desmoid-type fibromatosis is seen more often in female patients aged between 10 and 40 years [3].

It histologically has a benign morphology, but it has been classified as "intermediate malign" due to its high rate of local recurrence because of the infiltration of neighbouring structures following radical surgery [4]. Although desmoid tumours have been characterised as aggressive with these characteristics, most of them grow slowly and do not metastasise [5].

A 48-year-old female patient presented with complaints of intermittent epigastric pain, nausea, and rarely vomiting. The patient, who had no previous history of abdominal surgery, had menstrual irregularities. Her family history revealed no malignity cases. There were no pathologies in her laboratory parameters other than iron deficiency anaemia. Her tumour markers were within normal values. The patient's preoperative gastroscopy and colonoscopy results were normal. The abdominal computed tomography (CT) showed a heterogeneous solid mass of 9.5 × 8 × 7 cm in the upper abdomen middle part with smooth borders localised in the mesenteric bowel, closely neighbouring the transverse colon and intestinal loops, displacing them, but whose origin could not be clearly differentiated (Figure 1 A). Intraoperative findings included a mass invading the neighbouring omentum majus by surrounding the jejunal serosa originating from the jejunal mesentery at 10 cm distal from the Treitz (Figure 1 B). No additional intraabdominal pathologies and metastases were found. The 25 cm jejunum and the invaded omentum were resected in a block alongside the mass (Figure 1 C). End-to-end jejunojejunostomy was performed for intestinal continuity. The macroscopic analysis of the surgical piece revealed a circular, partly lobulated mass of 9.5 × 8 × 7 cm with smooth borders localised in the jejunal mesentery attacking the jejunal serosa, which had elastic consistency and a cross-section coloured pink-white; it was accompanied by omental fat tissue 8 × 7 × 0.5 cm in size. The histopathological analysis showed a neoplastic lesion with irregular borders and infiltrative progress among striated muscles, which was formed by fusiform cells that were sporadically parallel or cross with one another on the hyalinised fibrotic stroma. Table I summarises the histopathological and immunohistochemical analyses of the mass. The pathological diagnosis was reported to be "mesenteric fibromatosis". The patient was discharged a week after the surgery and was taken into the follow-up program without any adjuvant therapy. There were no problems in her first-year check. The patient's second year abdominal CT check, however, revealed a mass of 5 × 6 × 6 cm in the previous operation site concordant with local recurrence (Figures 2 A, B). The patient was taken into surgery and the exploration showed a mass in the first operation site's inferior area neighbouring the aorta and the vena cava which had invaded the duodenal

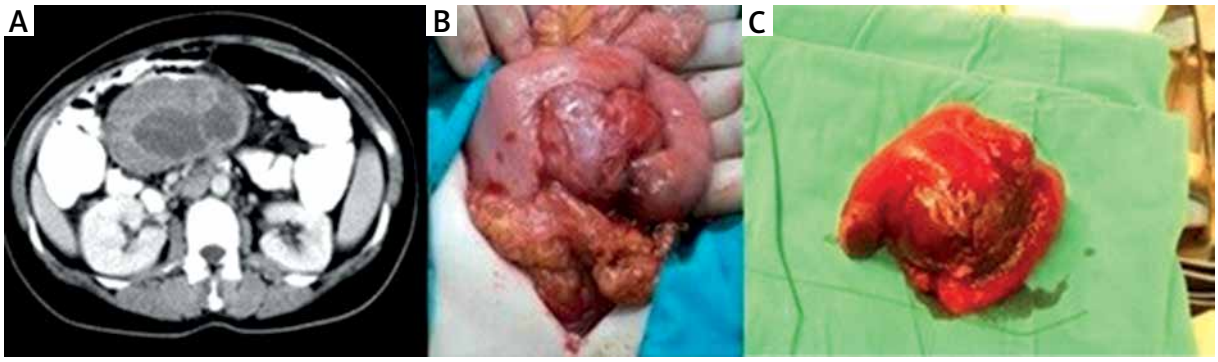

Figure 1. First operation. **A** – CT findings; hypodense lesion 9.5 × 8 × 7 cm in size with smooth borders, localised in the prox. small intestine's mesenteric root, attacking the neighbouring loop. **B** – Intraoperative findings; tumorous mass originating from the proximal jejunal meso surrounding the jejunal serosa and invading the omentum. **C** – The mass after resection. Deformations related to jejunum invasion explaining the subileus picture (the omentum was removed from the piece for the photograph)

fourth part from the lateral and the superior from one, the jejunum from two, and the transverse colon from one point millimetrically. The mass was extirpated from the base towards the intestinal loop with negative margins (Figure 2 C). All the millimetric invasion sites were removed tangentially instead of large wedge resections because of the possible morbidity, and the defects were primarily repaired in a single layer. The histological diagnosis was concordant with local recurrence (Figure 2 D), and the closest surgical border was 2 mm. The patient was discharged on the fifth post-operative day. No adjuvant therapy was planned following recurrence because the patient refused. The patient's latest control magnetic resonance imaging (MRI) done 18 months after the second operation showed no local recurrence.

Desmoid tumours can be divided into three main subgroups according to their localisation as: abdominal wall, intra-abdominal, and extra-abdominal fibromatosis. Abdominal fibromatosis frequently springs from the abdominal wall of female patients during or after pregnancy. Intra-abdominal fibromatosis, on the other hand, frequently originates from the small intestinal mesentery, as was the case with our patient, and from inside the pelvis and the retroperitoneum to a lesser extent. Extra-abdominal fibromatosis, however, mostly takes its origins from an extremity or body [6, 7].

The sporadic form, which includes most of the cases including our own, is generally characterised by the somatic mutation of the third exon of β-catenin's (CTNNB1) 41st or 45th codon [8]. The intra-abdominal form coexists at a rate of 10–20% with Gardner's syndrome [9] (a variant of familial adenomatous polyposis coli (FAP)) and demonstrates APC gene mutation [8]. The mutation of CTNNB1 and APC enables the stabilisation of β-catenin protein and this, in turn, allows the resulting nuclear translocation of target genes and binding with the T cell factor/lymphoid enhancer factor (TCF/Lef), which is a member of the transcription family. This action may form the basis of the biological and clinical behaviour of the desmoid tumour [8]. Individuals with FAP or history of desmoid tumour in their families pose a 25% risk of developing desmoid tumours [10]. Only about 5% of sporadic tumours have intra-abdominal localisation, while 80% of desmoid tumours related to

Table I. The histopathological and immunohistochemical analyses of the first piece

Histopathology		Immunohistology	
Dominant cell	Fusiform	CD 117	(–)
Cytological type	Slight	CD 34	(–)
Coagulative tumour cell necrosis	None	Desmine	(–)
Mitotic index (MI)	< 5 mf/10 hpf	S-100	(–)
Hyaline degeneration	Yes	Dog-1	(–)
Haemorrhage	None	Smooth muscle actin	(+)
Microcalcification	None	Vimentin	(+)
		Ki-67 index	< 1%

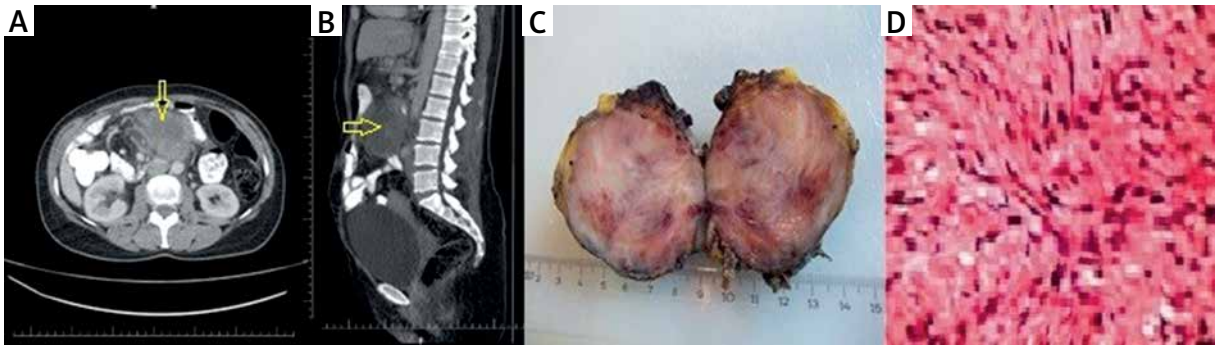

Figure 2. Second operation. **A, B** – Local recurrence by abdominal CT (arrow). The close neighbouring of the mass recurring in the first operation site with the aorta, v. cava, colon, and the jejunum stands out. **C** – The macroscopic image of the locally recurring mass. **D** – The microscopic image of the recurrent mass (H + E, 40×). Fusiform cells with irregular borders in sections, sporadically parallel or cross with one another on the hyalinised fibrotic stroma

FAP are intra-abdominal [6]. Patients who have total colectomy because of mesenteric fibromatosis FAP are generally diagnosed within the first 4 years [11].

Abdominal pain, nausea, vomiting, epigastric palpable mass, weight loss, and fever are prominent in the clinical picture of such patients. The tumour may cause such complications as the obstruction of the small intestine and the urethra, intestinal haemorrhage and perforation, and enterocutaneous fistula [1].

Other solid tumours of the area are the first to note in differential diagnosis. Lipoma, leiomyoma, xanthogranuloma, neurofibroma, and the malign forms of these alongside gastrointestinal stromal tumour (GIST), lymphoma, lymphangioma, carcinoid tumours, and metastatic disease can be listed among these [1, 11]. As mesenteric fibromatosis is often confused with GIST, the clinicopathological characteristics utilised for the differential diagnosis of these two have been summarised in Table II. The definitive diagnosis of the desmoid tumour is based on microscopic and immunohistochemical analyses [7].

The treatment of mesenteric fibromatosis generally necessitates a multimodal approach, and to ascertain a single treatment principle is challenging [12]. The treatment options for the desmoid tumour include follow-up, early surgery, and neoadjuvant and adjuvant therapy [13]. While the goal of neoadjuvant therapy is to render primary unresectable tumours resectable by surgery, the goal of adjuvant therapy is to prevent recurrences by enabling local control. Radiotherapy (RT), antioestrogen treatment (tamoxifen, toremifene, raloxifene), non-steroid anti-inflammatory drugs (NSAID), treatment of the target cell, biological agents like interferon, and cytotoxic chemotherapy agents can be listed among the treatment modalities that can be utilised to this end [14].

Koh *et al.* classified mesenteric fibromatosis according to its clinical progress into five categories in order to ascertain appropriate treatment: (1) spontaneous regression, (2) stable, (3) variable growth, (4) progressive growth, and (5) aggressive growth. According to Koh *et al.*, 75% of the patients had a "progressive growth" pattern and necessitated early surgery [15]. The algorithm devised by the Collaborative Group of the Americas on Inherited Colorectal Cancer takes the growth rates of the tumour into consideration as well. Moreover, the group also stated that those smaller than 10 cm, asymptomatic, and with a stable growth pattern could be followed-up by taking the size of the tumour and whether the patients were symptomatic or not into consideration [16] (Table III). Salas *et al.*, in their retrospective study covering 426 patients, reported that 20% of a total of 27 patients with desmoid tumours in the follow-up program had spontaneous regression during an average of 52 months of follow-up, while 60% remained stable, and only 20% had progressive growth, but the number of subjects followed-up within the scope of this study was not adequate to reach a conclusion [13].

Desmoid tumours with intra-abdominal localisation prove to be riskier in surgery in comparison to those with abdominal wall localisation and are closely related to increased morbidity and mortality. This picture may be related to haemorrhagic complications, large enterectomy procedures performed because of the involvement of the mesenteric root or the main artery feeding the small bowel (short bowel syndrome), and the patients may be exposed to long-term parenteral feeding [17]. The primary treatment of local, resectable desmoid tumours with smooth and good borders is surgery [18, 19]. The rate of postoperative recurrence has been reported to vary between 30% and 40% in many published studies with

Table II. The clinicopathological characteristics utilised in the differential diagnosis of mesenteric fibromatosis and gastrointestinal stromal tumour (GIST)

Parameter	Mesenteric fibromatosis	GIST
Demographic	25–35 years of age, F > M	50–60 years of age, F = M
Clinical	Asymptomatic Intestinal infiltration, symptoms related to urethral and vascular compression Frequent abdominal pain Rare gastrointestinal haemorrhage, perforation	Frequent abdominal pain, gastrointestinal haemorrhage Rare perforation, obstruction
Localisation	Mesentery of the small bowel	At any place along the GIST but frequently in the stomach and the small bowel
USG	Smooth environmental borders, homogenous or heterogeneous tumour with varying echogenicity	Extraluminal hypoechoic mass, small tumours homogenous and large tumours heterogeneous. More than one anechoic area or wide central area with low echogenicity
Computed tomography	Homogenous mass with smooth environmental borders, isodense or hyperdense compared to the muscular tissue, infiltration of the mass borders at a rate of 1/3, rare cystic degeneration	Heterogeneous mass with smooth environmental borders and solid characterisation of the peripheral part with contrast, fluid image at the centre of the mass (necrosis, haemorrhage, cystic degeneration), small tumours can be homogenous
Magnetic resonance imaging	T1-weighted images containing lesser signal density compared to the muscular tissue (hypointense), varying signal density in T2-weighted images	T1-weighted images containing lesser signal density compared to the muscular tissue (hypointense), higher signal density in T2-weighted images (hyperintense)
Macroscopy	Hard and sound mass, sections white-grey in colour, quite bright	Soft tumour with haemorrhage, necrosis, and cystic degeneration in sections
Microscopy	Fusiform cells with homogenous distribution without atypia, arteries with thick walls and dilated veins with thin walls, mild cellularity, infiltrative growth pattern	Fusiform or epithelioid cells generally forming fascicule and palisade and characterised by atypia and atypical mitosis, medium or rich cellularity, general presence of necrosis, widening growth pattern
Immunostaining profile	β-catenin (+) CD117 (+) 75% CD34 (–) Vimentin (+) Smooth muscle actin (+) 75% Desmin (+) 50%	β-catenin (–) CD117 (+) 90% CD34 (+) 42% Vimentin (+) Smooth muscle actin (+) 63% Desmin (+) 8%

Table III. Clinical staging of intra-abdominal desmoids

Stage	Size [cm]	Symptoms	Growth	Treatment recommendation
I	< 10	Asymptomatic	Stable	Observation ± NSAIDs
II	< 10	Mild	Stable	NSAIDs ± anti-estrogen drugs, resection
III	10–20	Moderate	Slow growing	NSAIDs + anti-estrogen drugs, cytotoxic therapy
IV	> 20	Severe/complications	Rapid growing	Resection

Mildly symptomatic – sensation of mass, pain, but no restrictions; moderately symptomatic – sensation of mass, pain; restrictive but not hospitalized; severely symptomatic – sensation of mass, pain; restrictive and hospitalized.

a large population [20]. The anatomical localisation of intra-abdominal desmoid tumours may pose challenges against treatment modalities. Wheeler *et al.* reported that simultaneous intestinal transplantation could be useful in selected cases with advanced stage intra-abdominal desmoid tumours having a remaining small bowel segment of shorter than 60 cm [12], but it is clear that more studies on the subject should be conducted. Resection is not possible because intraabdominal fibromatosis frequently has a close relationship with vital structures. In such cases, systemic treatment can be considered without any surgical procedures or it can be combined with surgical treatment [18]. Radiotherapy can raise the rates of local control to about 75–80% in large tumours in order to make inoperable lesions operable by shrinking them before the surgery of recurrence cases or microscopically after incomplete resections [19, 21]. The use of RT in intraabdominal desmoid tumours, however, is still

limited because of actinic enteritis, which is a potential complication [7, 22].

Non-steroid anti-inflammatory drug treatment is the first treatment option in patients with unresectable, advanced-stage tumours with no clinical symptoms [18], and the success rate of NSAID has been reported to be 57% [14].

The success rate of antioestrogen hormonal treatment that can be utilised under systemic treatment (tamoxifen, toremifene, raloxifene) is around 50% [14, 18]. Likewise, 4 out of 9 patients receiving interferon treatment had a response, and two of these were reported to have full remission [18].

Cytotoxic chemotherapy may prove to be another treatment alternative for unresectable, rapidly growing, and/or symptomatic, and/or life-threatening desmoid tumours. Anti-neoplastic agents have an effect by inhibiting the growth and multiplication of tumour cells. It has been reported that about 40–50% response was achieved through the administration of doxorubicin, dacarbazine, and carboplatin among such agents that were tried on desmoid tumours, but the response time varies [21]. There is still no established chemotherapy agent specific to mesenteric fibromatosis. Bertagnolli *et al.* reported that they saw neither radiological nor clinical recurrence by a combined method bringing together follow-up, surgery, and chemotherapy in 96% of patients with mesenteric desmoid tumours, whom they followed-up for an average period of 50 months [23].

Successful results were reported for imatinib treatment used in desmoid tumour cases resistant to chemotherapeutic agents and in advanced stage GIST cases with imatinib being a tyrosine kinase inhibitor [24] but the RECIST (Response Evaluation Criteria in Solid Tumours) response of this treatment is < 10%, and this rate is rather low in comparison to classical chemotherapy or hormonal treatment [18]. Gounder *et al.* diagnosed intra-abdominal fibromatosis in 12 out of 26 patients with desmoid tumours, who received sorafenib treatment. The results of the study revealed no improvement in any of the patients with mesenteric fibromatosis. No shrinkage of tumour sizes, the fact that the greatest radiologically provable benefit covered cases with desmoid tumour, and the lack of statistically significant difference between the first and second sorafenib treatment regarding radiological benefit can be listed among the other notable results of the study [25].

The wide range of medical treatment options and the fact that physicians are still in search of an ideal treatment modality are signs demonstrating that there is no established and efficient treatment modality for desmoid tumours other than surgical treatment.

Cases with a surgical border that is microscopically positive (R1) are closely related to local recurrence [18]. Although wide resection is recommended to prevent such conditions [1], there are no controlled randomised studies on how wide the surgical borders should be. Salas *et al.* reported that < 37 years of age, > 7 cm tumour size, and extremity localisation were bad criteria in their study on the prognostic factors of desmoid tumours [13]. Fiore *et al.*, on the other hand, found that > 10 cm tumour size and body localisation predicted a high risk for recurrence [26]. Mullen *et al.*, however, argued that R0 resection was the sole determinative factor for local recurrence [27]. Moreover, Colombo *et al.* stated in their multi-centric study, which covered 179 patients with sporadic desmoid tumour, who had radical surgical resection, that those with S45F mutation had a higher rate of local recurrence in comparison with those who did not have the mutation [28].

Magnetic resonance imaging can be utilised in the follow-ups of desmoid tumour as an imaging method [3]. Although there is no specific follow-up schedule for desmoid tumours, the following follow-up protocol was recommended at the 2015 European consensus meeting: first imaging after 4 to 8 weeks to prevent delayed diagnosis of a rapidly growing tumour, especially in the presence of a tumour that is hard to palpate or localised in a critical area; every three months in the following first year if the MRI results are normal; every 6 months from 1 to 5 years; and annual MRI in the following years. Imaging should be done once every 3 to 6 months depending on the localisation of the disease and the symptoms in cases under medical treatment [29].

Positron emission tomography (PET-CT) is not a routine practice, but it has been argued that it is a prognostic marker to determine whether patients under tyrosine kinase treatment are responding to the treatment or not [3].

The existing treatment modalities are experimental, with variable results, and the lack of an established treatment modality are signs showing that further multi-centric studies are needed. Nowadays the best treatment choice of resectable intra-abdominal desmoid tumours is surgical resection with wide negative margins. Its insufficiency to prevent surgical recurrences on its own and the need for a more efficient adjuvant therapy underline the necessity that the genetic and molecular mechanism of desmoid tumours should be better understood.

Conflict of interest

The authors declare no conflict of interest.

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Received: 28.04.2017
Accepted: 7.06.2017