Case Report
Étude de cas

Chemotherapy for desmoid tumours in association with familial adenomatous polyposis: a report of three cases

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Objective: To determine the efficacy of chemotherapy for inoperable desmoid tumours associated with familial adenomatous polyposis.

Design: A review of three cases of unresectable desmoid tumours and of the literature on the subject.

Setting: The Steven Atanas Stavro Polyposis Registry at Mount Sinai Hospital in Toronto.

Patients: Three patients with symptomatic, unresectable desmoid tumours associated with familial adenomatous polyposis and unresponsive to conventional hormone therapy.

Intervention: A chemotherapy regimen of seven cycles of doxorubicin (dose ranging from 60 to 90 mg/m^2) and dacarbazine (1000 mg/m^2), followed by carboplatin (400 mg/m^2) and dacarbazine.

Outcome Measures: Clinical improvement and tumour regression demonstrated by computed tomography.

Results: In each of the three cases significant tumour regression was seen clinically and radiologically.

Conclusions: Cytotoxic chemotherapy is an effective treatment for desmoid tumours associated with familial adenomatous polyposis. The chemotherapy should be started early in cases of symptomatic desmoid tumour unresponsive to conventional medical therapy.

Objectif : Déterminer l'efficacité de la chimiothérapie dans le cas des tumeurs desmoïdes inopérables liées à la polypose adénomateuse familiale.

Conception : Étude de trois cas de tumeurs desmoïdes irrésécables et de la littérature scientifique sur la question.

Contexte : Le Steven Atanas Stavro Polyposis Registry du Mount Sinai Hospital de Toronto.

Patients : Trois patients présentant des tumeurs desmoïdes irrésécables symptomatiques liées à une polypose adénomateuse familiale et qui n'ont pas réagi à l'hormonothérapie classique.

Intervention : Chimiothérapie constituée de sept cycles de doxorubicine (dose variant de 60 à 90 mg/m^2) et de dacarbazine (1000 mg/m^2), et ensuite de carboplatine (400 mg/m^2) et de dacarbazine.

Mesures des résultats : Amélioration clinique et régression de la tumeur révélée par scanographie.

Résultats : Dans chacun des trois cas, on a pu constater à l'examen clinique et radiologique une régression importante de la tumeur.

Conclusions : La chimiothérapie cytotoxique est un moyen efficace de traiter les tumeurs desmoïdes liées à la polypose adénomateuse familiale. Il faut commencer la chimiothérapie tôt dans les cas de tumeurs desmoïdes symptomatiques qui ne réagissent pas au traitement médical classique.

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Desmoid tumours (DTs) are defined histologically as benign fibrous tumours consisting of mature fibroblasts within a collagen matrix. They rarely occur in the general population and constitute less than 0.1% of all tumours.[1,2] However, they develop in a relatively high percentage (4% to 13%) of patients with familial adenomatous polyposis (FAP).[3–7]

In patients with FAP, DTs usually occur in the mesentery, retroperitoneum or abdominal wall and tend to progress and enlarge postoperatively. These DTs are a major cause of morbidity and mortality. They have a propensity to infiltrate surrounding viscera and surround major blood vessels, causing pain, intestinal and ureteral obstruction, and fistulas. They are rarely small enough or sufficiently localized to allow complete surgical resection without sacrifice of vital structures. Therefore the objective of surgery is usually to provide relief by bypassing the obstruction.

The role of nonoperative therapy remains controversial. Radiotherapy is limited by the radiosensitivity of the normal intra-abdominal structures. Medical therapies such as nonsteroidal anti-inflammatory drugs (NSAIDs), antiestrogens such as tamoxifen and toremifene, colchicine and steroids have produced inconsistent results.

The purpose of this report is to present our experience with cytotoxic chemotherapy (doxorubicin and dacarbazine followed by carboplatin and dacarbazine) in the management of three patients with aggressive, inoperable DTs unresponsive to conventional medical therapies.

Case reports

Case 1

In February 1991, a 31-year-old man underwent total proctocolectomy and ileostomy for FAP. Intraoperatively, a mass, measuring 6 × 6 × 6 cm and compatible with a DT was found in the mesentery of the jejunum. A total of 90 cm of small bowel was resected along with the mesenteric DT. There were no complications postoperatively.

In December 1992 the patient presented with an increase in abdominal girth. On physical examination a periumbilical mass was palpable. Computed tomography (CT) demonstrated a large intra-abdominal DT extending into the pelvis, displacing major vessels and small bowel, producing hydronephrosis of the left kidney and proximal dilatation of the left ureter. Despite the size of the mass, the patient was relatively asymptomatic, so the only treatment was insertion of a ureteral stent.

Over the next 3 months the DT continued to increase in size, so in March 1993 the patient was started on NSAID therapy with a combination of sulindac (150 mg twice daily) and tamoxifen (10 mg twice daily). Renal function deteriorated because of bilateral involvement of the ureters by the DT, and he required restenting on several occasions (Fig. 1). Over the next 8 months the tumour continued to progress, causing several episodes of small-bowel obstruction, which resolved with conservative management. However, in November 1993 he presented with complete obstruction of the proximal bowel at the level of the duodenum (Fig. 2). Because of the extent of the tumour, surgery was not undertaken. Instead a gastrostomy tube was inserted. Because the DT continued to be unresponsive to sulindac and tamoxifen, alternative therapies were considered. Toremifene was unsuitable because only an oral form was available. It was decided, with

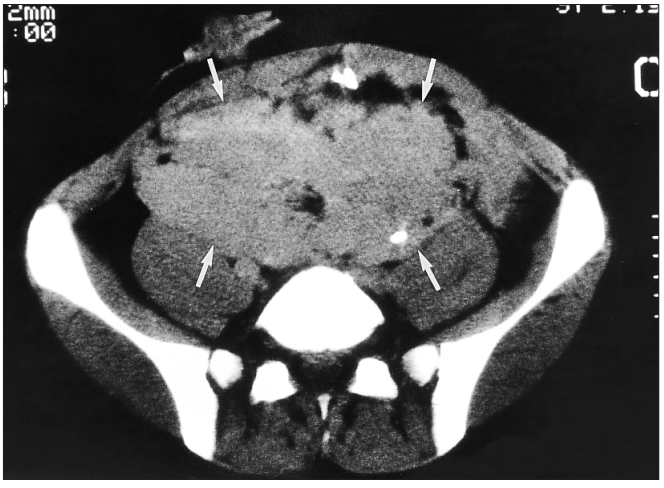

FIG. 1. Case 1: Pelvic computed tomography (CT) scan demonstrating pelvic extension of large desmoid tumour (DT) (arrows). Left ureteric stent is seen.

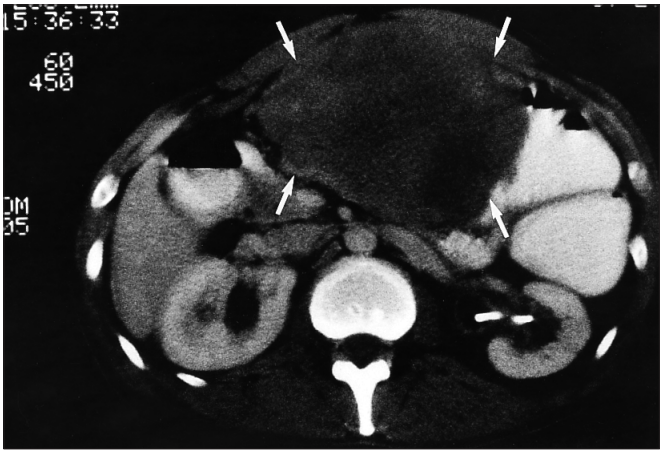

FIG. 2. Case 1: Abdominal CT scan shows proximal small-bowel obstruction by large intra-abdominal DT (arrows). Gross dilatation of small-bowel loops is clearly seen.

some hesitation because of his poor physical condition, to institute cytotoxic chemotherapy, consisting of doxorubicin and dacarbazine as a continuous infusion for 4 days, repeated approximately every 28 days for a total of seven cycles. For the first four cycles he received doxorubicin (80 mg/m^2) and dacarbazine (1000 mg/m^2), but after several episodes of febrile neutropenia, the dose of doxorubicin was reduced to 60 mg/m^2 for the remaining three cycles. After seven cycles, doxorubicin was discontinued to prevent cardiotoxicity and was replaced by carboplatin (400 mg/m^2). At the time of writing the patient was still receiving carboplatin and dacarbazine.

Complications of chemotherapy included several episodes of fever and sepsis requiring hospitalization. The DT showed significant regression and the duodenal obstruction resolved. At the most recent follow-up the patient was well, able to eat a normal diet and had returned to work.

CT before the start of chemotherapy showed that the DT occupied a volume of 3000 cm^3. After four cycles of chemotherapy, regression was noted both clinically and radiologically. By February 1995 the volume of the DT had decreased 47-fold to 64 cm^3 (Figs. 3 and 4).

Case 2

In July 1984, a 19-year-old girl underwent subtotal colectomy and ileorectal anastomosis for FAP. She remained well until January 1989, when she presented with a large, firm mass below the umbilicus, extending over the right side of the abdomen. Abdominal ultrasonography showed a mass measuring $9 \times 3 \times 9$ cm obstructing the right ureter and causing right hydronephrosis, compatible with a DT. She was relatively asymptomatic for 2 months. Then she was admitted to hospital with partial small-bowel obstruction. Laparotomy confirmed a DT in the mesentery of the ileum that was responsible for this obstruction. Because of the size of the DT and its encasement of the superior mesenteric vessels, only a defunctioning jejunostomy was performed. Her postoperative recovery was complicated by a ureterocutaneous fistula, which required a nephrostomy. The bowel obstruction resolved over the next 8 weeks, and the jejunostomy was closed.

In July 1990 she was found to have masses in the area of the nephrostomy scar and right rectus muscle (Fig. 5), both compatible with DT. A combination of regimen of sulindac (150 mg twice daily) and tamoxifen (10 mg twice daily) was started, but the DTs progressed, and in February 1992 she was started on a trial of toremifene (200 mg every morning). No progression of the DTs was seen until April 1993, when the toremifene was stopped for 3 weeks because of the possibility of pregnancy. Once pregnancy had been ruled out the toremifene was restarted, but the DT seemed to have been affected by the cessation of toremifene and progression of the disease was seen radiologically. In January 1994, because of the increasing size of the DTs and bilateral hydronephrosis seen on CT, cytotoxic chemotherapy was begun.

Doxorubicin and dacarbazine were given as a continuous infusion over 4 days, repeated approximately every 28 days for a total of seven cycles. For the first two cycles she received doxorubicin (90 mg/m^2) and dacarbazine (1000 mg/m^2), but after an episode of febrile neutropenia the dose of doxorubicin was reduced to 60 mg/m^2 for the remaining five cycles. After seven cycles, the doxorubicin was discontinued to prevent cardiotoxicity and replaced with carboplatin (400 mg/m^2). She tolerated the chemotherapy relatively well. At the time of writing she was still receiving carboplatin and dacarbazine.

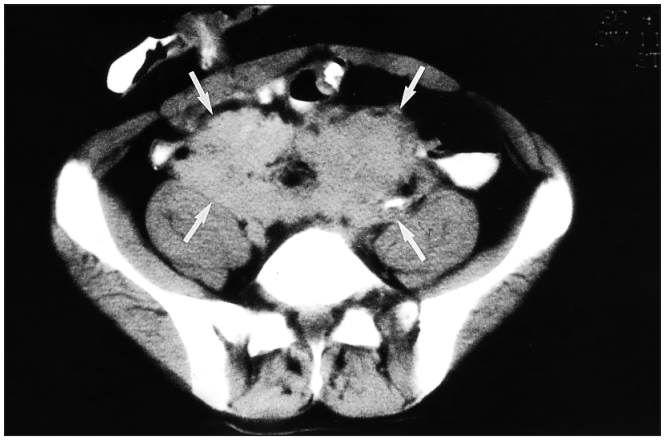

FIG. 3. Case 1: Marked regression of pelvic component of DT (arrows) seen after 14 months of chemotherapy.

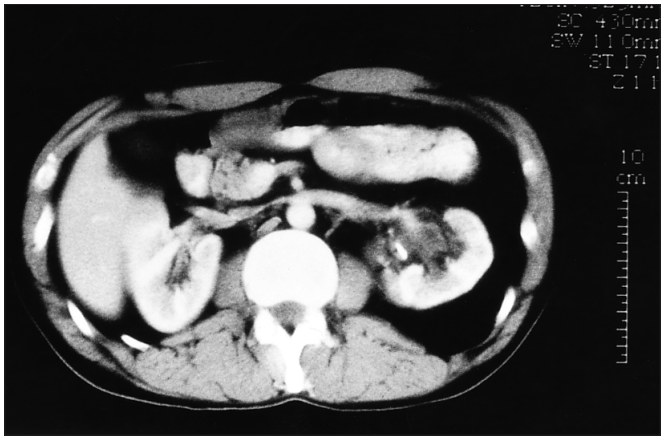

FIG. 4. Case 1: Apparent complete regression at 14 months of DT at same level as in Fig. 2.

At the start of chemotherapy in January 1994 the mesenteric DT occupied a volume of 480 cm^3; 13 months later the tumour volume was reduced threefold to 160 cm^3. The DT situated within the right rectus muscle showed a similar reduction in volume (Fig. 6). At the last follow-up she was asymptomatic.

Case 3

In 1986, a 19-year-old man underwent total colectomy with mucosal proctectomy and ileal reservoir formation for FAP. Biopsy of a nodule found intraoperatively in the colonic mesentery was compatible with a DT. He remained well until June 1993, when he had symptoms of small-bowel obstruction. CT showed a DT in the pelvis, surrounding the right iliac vessels. The tumour invaded the right ileopsoas muscle and sacrum and obstructed the right ureter, producing hydronephrosis. At laparotomy the tumour was deemed unresectable so only a loop ileostomy was performed and a ureteral stent inserted.

In September 1993 combination NSAID medical therapy with sulindac (150 mg twice daily) and tamoxifen (10 mg twice daily) was begun. The DT showed no response and continued to progress, resulting in deteriorating renal function because of bilateral ureteric involvement. In January 1994 he experienced swelling of the right leg, and duplex ultrasonography showed extensive clot in the iliac veins due to compression by the DT. An inferior vena caval filter was inserted prophylactically.

Because of the aggressive nature of his DT, cytotoxic chemotherapy was begun with the same regimen as in the other cases. He received doxorubicin (60 mg/m^2) and dacarbazine (1000 mg/m^2) for each of the seven cycles. The doxorubicin was then replaced by carboplatin (400 mg/m^2) to prevent cardiotoxicity. At the time of writing he continued to receive carboplatin and dacarbazine. He tolerated the chemotherapy well.

At the start of chemotherapy in January 1994 the DT occupied a volume of 3944 cm^3 (Fig. 7). Over the next 10 months there was a 4.7-fold decrease in the volume occupied by the DT to 841.5 cm^3 (Fig. 8). At the last follow-up he was well and asymptomatic.

Discussion

DT in association with FAP occurs in the abdominal wall, mesentery or retroperitoneum. The management of the disease in patients with FAP is extremely difficult, and no treatment protocol has given consistent results. Surgery to reduce or bypass intestinal obstruction may benefit some symptomatic patients. However, most of these tumours, particularly those in the retroperitoneum, are unresectable. In asymptomatic FAP patients with intra-abdominal DT, surgery should not be undertaken,[8] because serious morbidity and mortality are associated with attempts to resect mesenteric and retroperitoneal DTs. Tumour resection should be avoided unless obstruction occurs. At that point it may be preferable to bypass areas of obstruction and follow up with medical therapy. Not only is attempted resection usually incomplete but recurrence rates are high, ranging from 69% to 85%.[7,9]

There are conflicting reports of the role of radiotherapy in the management of DT. Because large doses and wide fields of radiation are required, recognizable complications are frequent.[10] Tsukada and colleagues[11] found intra-abdominal DT unresponsive to radiotherapy. Pack and Ehrlich[1] suggested that the favourable response of DT to irradiation in female patients may be due to a radiation effect on the ovaries, producing an artificial menopause with secondary antiestrogen effects. Radiotherapy has a defined role for extremity DTs, but these are rarely seen in patients with FAP.

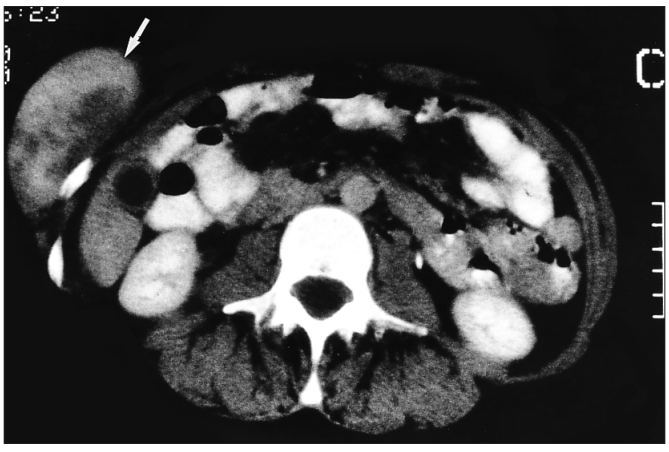

FIG. 5. Case 2: CT scan demonstrates DT (arrow) within right rectus muscle.

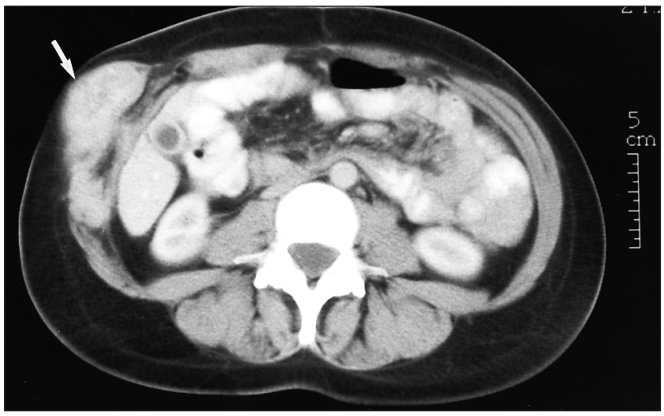

FIG. 6. Case 2: After 13 months of chemotherapy, DT (arrow) is much smaller.

Because surgery is often unsuccessful and radiotherapy is unsuitable for the intra-abdominal DT commonly seen in patients with FAP, it is not surprising that many different medical therapies have been tried. NSAIDs, especially sulindac, have been used in FAP with mixed results, producing regression of rectal adenomas and variable regression of duodenal adenomas or DTs. It has been proposed that NSAIDs may inhibit tumour growth by interfering with prostaglandin suppression of the immune system and by blocking the induction of ornithine decarboxylase, thereby restricting cell growth and proliferation. Klein and associates[12] reported on seven patients with intra-abdominal DTs, treated with high-dose NSAIDs and tamoxifen. Only one patient, on indomethacin, had resolution of a minimally sized anterior abdominal-wall DT. Lofti and associates[7] described eight patients with previously resected recurrent DT on sulindac and tamoxifen. Of three patients on sulindac alone, the mass was no longer clinically palpable in one and was decreased on CT in the others, although the amount was not specified. Tsukada and colleagues[11] discussed their results with NSAIDs in 16 patients with DT, 14 of whom were treated with sulindac alone. Despite a response in eight patients, the significance and duration of the decrease in tumour mass were not reported. Of further interest was that the long interval of 24 months for response, was preceded in five patients by progression of the disease.

The role of antiestrogens such as tamoxifen and toremifene in the treatment of DT is based on the hypothesis that these neoplasms may be stimulated by estrogens. They appear to have good effects in some patients.[13] Testolactone, medroxyprogesterone and prednisolone,[14] colchicine and theophylline[15] have all been tried, with no consensus as to the tumour response. It can therefore be seen from the number of different medical alternatives that there is no ideal medical therapy for DT. The advantage of medical therapy is that it is relatively non-toxic and therefore may be considered, at least on a trial basis, for the treatment of asymptomatic DT.

The role of cytotoxic chemotherapy in the treatment of DT is not clear, and there is a relative paucity of literature on the effect of chemotherapy on DT associated with FAP. Because chemotherapy is often considered as a last resort in the management of DT, the patients selected often have advanced disease, with severe complications.

All three of our patients achieved a good response and tolerated chemotherapy reasonably well. We used the regimen of doxorubicin and dacarbazine, followed by carboplatin and dacarbazine because Lynch and associates[16] reported that this regimen induced complete remission in two patients with DT associated with FAP. The rationale for using these chemotherapeutic agents is that DTs arise from similar tissue as fibrosarcomas; thus, agents active against sarcomas may be useful in the treatment of DT. Most of the literature on the use of doxorubicin and dacarbazine to treat DT refers to extra-abdominal disease, but Patel, Evans and Benjamin[17] reported on the use of these two agents in four patients with FAP. Two complete remissions and two partial remissions were achieved.

Khorsand and Karakousis[18] described a patient with DT associated with FAP who achieved complete remission after receiving a combination of doxorubicin, actinomycin D and vincristine. Seiter and Kemeny[19] reported successful treatment of a DT associated with FAP using doxorubicin alone. However, several randomized clinical trials have shown a higher response rate with the addition of dacarbazine to doxorubicin in the treatment of sarcoma.[20,21]

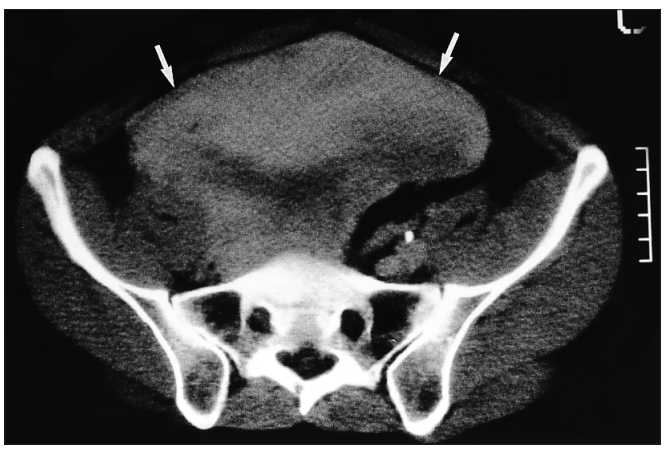

FIG. 7. Case 3: CT scan demonstrating extensive DT (arrows) within pelvis. Left ureteric stent is seen.

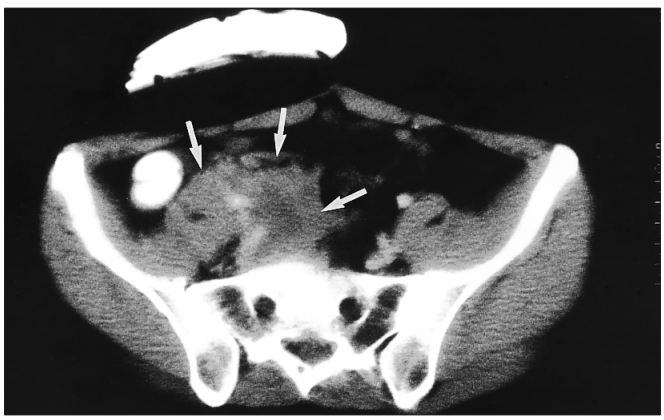

FIG. 8. Case 3: After 7 months DT has responded to chemotherapy. Areas of low attenuation at periphery and areas of higher attenuation within residual mass probably represent necrosis and fibrosis.

At the time of writing all our patients continued to receive chemotherapy and to have regression of their DTs. The end point of treatment will be when we are confident they have reached a stable phase of their disease as monitored by CT. Despite multiple conventional therapies (surgery, anti-inflammatory drugs and antiestrogens), our patients all had progressive disease causing severe complications. We have seen a significant response, both clinically and radiologically, to the chemotherapy used. Residual abnormalities seen on the most recent CT scans of these patients may in fact represent residual fibrosis after tumour regression, as described in the patients reported by Lynch and associates[16] who monitored the response to chemotherapy by second-look laparoscopy but did not recommend its routine use because of the potential for complications.

In summary, this small case series illustrates that chemotherapy is effective in the management of DTs and should be considered for patients who have FAP with a symptomatic, unresectable DT unresponsive to conventional hormonal therapy. Chemotherapy, if used at an early stage in the management of patients such as these, may diminish the need for surgery to alleviate functional consequences and complications due to the DT. Chemotherapy can cause substantial morbidity, but surgery in these complex cases has the potential for even greater morbidity and mortality. The durability of the remissions and the long-term outlook remain speculative.

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