

Mifepristone (RU486), a pure antiprogesterone drug, in combination with vinblastine for the treatment of progesterone receptor-positive desmoid tumor

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Abstract We report the case of a patient who developed a desmoid tumor following total proctocolectomy and J-pouch reconstruction that was unresponsive to any medical treatment. Based on estrogen receptor alpha (ER α) and progesterone receptor (PR) evaluation (ER α -negative, but PR-positive), treatment with mifepristone, a pure antiprogesterone drug, was initiated, and partial tumor regression was achieved.

Keywords Desmoid tumor · Hormonal receptor · Mifepristone

Introduction

Desmoid tumors develop in 4–13% of all patients suffering from familial adenomatous polyposis [1–5], with a cumulative lifetime risk of 21% [6]. Some of these tumors are inoperable at the time of diagnosis, some will recur following resection and some will remain stable or decrease in volume following medical therapy.

Different treatment modalities summarized in a review article by Knudsen et al. [2] have been suggested, including surgery; hormonal manipulation by tamoxifen; progesterone and LHRH analogues; the use of nonsteroidal anti-inflammatory drugs; steroids; various chemotherapeutic regimens (single drug or combined); radiotherapy; and interferon alfa-2b combined with toremifene [7].

Mifepristone (RU486) is an 11 beta-dimethyl-amino-phenyl derivative of norethindrone with a high affinity for the progesterone and glucocorticoid receptors [8]. In clinical practice, it is widely used to provoke pregnancy termination at the earliest stage of pregnancy.

We used mifepristone in combination with vinblastine to treat an inoperable intraabdominal desmoid tumor unresponsive to conventional treatment modalities (long-term treatment with tamoxifen and nonsteroidal anti-inflammatory drugs (NSAIDs)), with a very good response and partial tumor regression.

Case report

A 40-year-old man known to have familial adenomatous polyposis underwent total proctocolectomy and J-pouch ileoanal anastomosis.

During a regular follow-up, which included computed tomography (CT), pouchoscopy and gastroduodenoscopy, he presented with an episode of pulmonary embolism (PE) 3 years after surgery. The patient was treated successfully with anticoagulant therapy.

An abdominal CT scan performed immediately following the PE showed a huge retroperitoneal mass involving the mesenteric root (Figs. 1, 2). Tru-Cut biopsy confirmed the diagnosis of a desmoid tumor.

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Fig. 1 Axial CT image at presentation. A huge retroperitoneal mass involving the mesenteric root is observed. The tumor extends from the level of the duodenum to the level of the urinary bladder. Two small bowel loops are enclosed inside the tumor (*arrows*). Mixed enhancement of the mass is observed

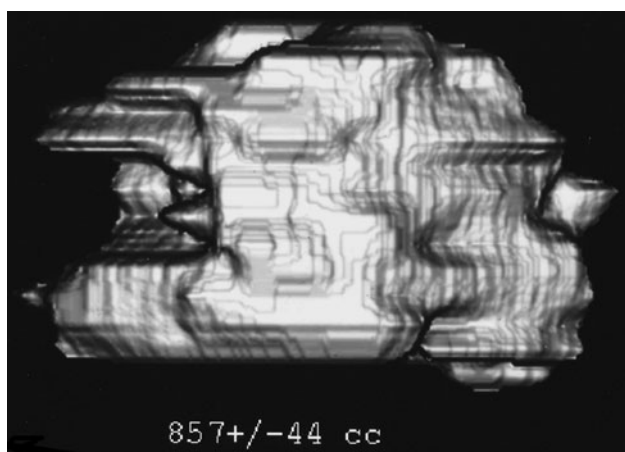


Fig. 2 Three-dimensional volumetric reconstruction of the tumor. The tumor volume is 857 cc

Treatment with indomethacin (100 mg twice a day) was initiated and administered for 4 months. Following recurrent episodes of partial small bowel obstruction, an exploratory laparotomy was performed with the intent to resect the desmoid tumor. However, this was not possible without leaving the patient with a very short segment of small bowel necessitating lifelong home total parenteral nutrition (TPN). A feeding jejunostomy was created.

Following surgery, treatment with a combination of tamoxifen 40 mg/day, prednisone 40 mg/day and indomethacin 200 mg/day was initiated. Shortly after surgery, an enterocutaneous fistula developed, and the patient's physical condition deteriorated rapidly. Chemotherapy consisting of vinblastine (8–10 mg/day) was added. The dosage interval was one to four weeks depending on the



Fig. 3 CT examination at the end of treatment, 15 months after diagnosis: an axial CT image demonstrates 65% shrinkage of the tumor to 300 cc

patient's performance status. Following 5 courses of vinblastine, the tumor still showed no response.

As the patient did not respond to this treatment regimen and continued to deteriorate, an unconventional approach was used. Based on the hormonal status of the tumor, which was estrogen receptor alpha (ER α) negative, but strongly progesterone receptor (PR) positive, and after obtaining the consent of the Helsinki Committee from the Ministry of Health, a daily treatment with 200 mg mifepristone (RU486) twice a day was initiated for the first 4 months. This amount was increased to 300 mg twice a day for a further 22 months.

Mifepristone was administered in combination with 17 courses of vinblastine during the first 10 months of the regimen. Under this treatment protocol, CT volumetric studies indicated a reduction of 65% in the volume of the tumor [from 875 cc at admission (Fig. 2) to 300 cc 15 months later (Fig. 3)].

A further surgical attempt was made to treat the enterocutaneous fistula. A segment of small bowel containing the fistula was resected, the ileal J pouch disconnected and an end ileostomy constructed. However, shortly after this procedure, multiple new enterocutaneous fistulas developed.

For a period of 20 months, the patient was hospitalized and treated with TPN. Slowly, but gradually, all vascular access options failed and the only option left was that of intestinal transplantation.

The patient was referred for intestinal transplantation, but died after the procedure.

Discussion

Mesenteric desmoid tumors are difficult to treat, especially if they are inoperable. In patients with such tumors, total

small bowel resection and transplantation have been attempted [9, 10]. However, the more common treatment modalities combine surgery, hormonal manipulation, steroids, nonsteroidal anti-inflammatory drugs, chemotherapy and in rare cases even radiotherapy.

Hormonal manipulation of desmoid tumors is most commonly performed with tamoxifen. The question as to why some desmoid tumors regress following hormonal manipulation, while others do not, has not been clarified and may be related partly to the hormonal status of the tumor. The desmoid tumor in our patient was found to be ER α negative, but strongly PR positive, which may explain the unresponsiveness to tamoxifen treatment. Based on the hormonal profile of the tumor in our patient, we decided to stop the noneffective treatment with tamoxifen and treat him with mifepristone in combination with vinblastine, as the patient's condition was desperate. The response was dramatic, with a 65% reduction in tumor volume within 15 months.

The decision to treat the patient with mifepristone, as well as the dosage, was empiric since, to the best of our knowledge, there are no previous reports regarding the in vivo hormonal profile of desmoid tumors, although in vitro studies have shown estrogen expression in desmoid tumor tissue [11] and in desmoid tumor-derived cells in culture [12]. In their extensive review on selective estrogen receptor modulators (SERMs) in desmoid tumors, Picariello et al. [13] raise the question of whether estrogen status in desmoid tumor biopsies should be evaluated before embarking on treatment with SERMs. A literature search was performed, and reports were found on the use of mifepristone in a patient with an unresectable meningioma [14], in cases of advanced breast, ovarian and prostate cancers, and in the treatment of endometriosis and leiomyomas [15, 16].

Although a significant volume reduction was observed using this treatment modality, some questions are still to be answered. The first question is whether mifepristone on its own is effective or whether its effect is enhanced by the combination with vinblastine? It is important to stress that the patient was treated with a low dose of vinblastine with no effect, but that once mifepristone was added to the treatment regimen, a dramatic reduction in tumor volume ensued. The second question, which remains open, refers to the dosage of mifepristone and treatment duration.

No adverse effects of the drug were noticed during treatment, and the hormonal profile of the patient remained within normal limits, as proved by blood tests.

Based on this case report, we suggest that desmoid tumors should be evaluated for hormonal status. In the case

of ER α -positive desmoid tumors (any of the SERMs), tamoxifen or raloxifene treatment should be administered [13]. For ER α -negative/PR-positive desmoid tumors, treatment with mifepristone should be considered, either as a single drug or in combination with other drugs.

To the best of our knowledge, this is the first reported case of the use of a pure antiprogesterone drug in a patient with an intraabdominal desmoid tumor based on the hormonal profile of the desmoid tumor itself, with an objective response proven by CT.

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