Desmoids are rare in the general population but occurs in between 10 to 20% of patients with familial adenomatous polyposis (FAP). This risk is about 852 times the risk for the population at large. Desmoids are benign neoplasms that are capable of infiltrating locally with a high risk of recurrence (25-65%) even after extirpating surgery. Desmoids in FAP may occur extra-abdominally, or within the abdominal wall or most commonly intra-abdominally within the mesentery or retroperitoneal. Desmoids are a major problem in patients with FAP. Mortality from desmoids is high in such patients and ranges from 18 to 31%, compared to peri-ampullary carcinomas at about 22% and cancer in the retained rectum at only about 8%.

SUSCEPTIBILITY TO DESMOIDS

Desmoids tend to be clustered in susceptible individuals, irrespective of the germline APC mutation. However germline mutation distal to codon 1399 is strongly associated with the formation of desmoids. A strong family history of desmoids is therefore strongly predictive of the possibility of the development of desmoids in members. Strangely the French registry found that belonging to a family affected by desmoids did not increase the individual’s risk in their study population. Most studies including the St Mark’s group however agree that a family history of multiple desmoids increased an individual’s own risk of multiplicity.

They showed that females had twice the odds of developing desmoids compared with males. Desmoids tend to cluster in susceptible individuals, irrespective of the germline APC mutation. Independent predictors of increased desmoid risk were: germline mutation distal to codon 1399; any family history of disease; and a strong family history of desmoids.

A family history of multiple desmoids increased an individual’s own risk of multiplicity. The French polyposis registry looked at 442 FAP patients with desmoids from 1983 to 2004. A total of 124 desmoids were found
in 50 patients, half of whom were females. Although their study did not find a female preponderance, females developed desmoids earlier than males. However, they found that an identified point mutation in the adenomatous polyposis coli (APC) gene after codon 1444 was a significant risk factor (hazard ratio 3.3 (95% confidence interval 1.5 to 7.3)).

The National Cancer Institute in Milan, Italy evaluated the occurrence of desmoids, colorectal cancer and other extra-colonic manifestations in 897 FAP patients, 653 of whom were also investigated for APC mutations. Desmoids developed in 107 patients (11.9%), with a cumulative risk of 20.6%. Females had a significantly higher risk than males.

A family history of desmoids, osteomas and epidermoid cysts were also significantly associated with the occurrence of disease. Subjects with APC mutations beyond codon 1444 had a 12-fold increased risk, compared with patients with mutations located upstream. Mutations beyond codon 1309 conferred a 17-fold higher risk, compared with mutations upstream codon 452. Multivariate analysis identified as independent predictors mutation beyond codon 1444, family history of desmoids, female gender and the presence of osteomas.

The Singapore polyposis registry examined genetic mutation in the APC gene in relation to the development of desmoid tumors in FAP. Two hundred five patients from 75 families with FAP were reviewed. Genetic mutations were identified in 107 patients. Out of these patients with FAP, 23 (11.2%) developed desmoids. The male-to-female ratio was 1:1.3. Of 92 patients with mutations 5’ to codon 1444, 11 patients (12 percent) developed desmoids compared with 6 of 15 (40 percent) patients with mutations 3’ to codon 1444 (P). There are no reliable genetic markers available for prognostication of the severity of the desmoids.

The Dutch identified desmoid tumors in 66 of their 735 patients (9%) with a cumulative risk of developing desmoids was 14%. No correlation was found between specific adenomatous polyposis coli mutation sites and desmoid development. They found family history for desmoids to be a significant risk factor for desmoids (30% vs 6.7%, P .0001). Female sex or pregnancy however was not positively related to desmoid development.

The Toronto registry found that the prevalence of desmoids in the 5’ and 3’ groups was 13% and 38%, respectively (P = .0005). Patients with a mutation after codon 1399 were found to have 4 times greater chance of developing a desmoid.

COMPLICATIONS OF DESMOIDS

Data from the Singapore Polyposis registry showed the clinical course of their 23 patients with desmoid tumors to be divided into stable (n=11), variable (n=3), progressive (n=6), or aggressive growth (n=3)\(^6\). Only 3 (13 percent) patients with aggressive tumor growth required chemotherapy. The most common complications related to the mesenteric desmoids were intestinal obstruction (21.7 percent), ureteric obstruction (17.4 percent), and encasement of superior mesenteric vessels (13 percent). The clinical course of desmoids in an individual familial adenomatous polyposis patient remains unpredictable. Two cases from this Registry who developed desmoids 0.7 and 2.5 yrs after ileal-pouch anal anastomosis and went on to have ureteric obstruction were also described\(^7\). Both had been on tamoxifen and sulindac but developed progressive ureteric obstruction nonetheless. Both patients required per-cutaneous urinary drainage with good results at 10 and 18 months respectively. Difficult cases may be successfully treated by renal auto-transplantation.

The Parisian registry\(^1\) had three patients with abdominal pain, short bowel syndrome in four, six with altered bowel function, six with ureteric obstruction, and two died from desmoids. Desmoids causing fistula into the rectum and resulting in massive rectal bleeding or multiple fistulation were seen in two cases. In another study from Paris\(^10\), with 96 patients who were followed up for at least 11 years, seven have died, three from metastatic adenocarcinoma and two from mesenteric desmoids. Thirteen patients in all have symptomatic desmoids (13.5%).

The Danish registry\(^1\) had 486 patients with FAP, of whom 27 had desmoids(6%). Mesenteric desmoids were found in 42%, abdominal wall desmoids in 40%, retroperitoneal desmoids in 8%, and the last 10% had desmoids in the extremities.

Fifty percent of the patients had complications (intestinal obstruction, hydrenephrosis or fistulas), and two of nine deaths were caused by desmoids. Ninety-three percent were treated with surgery, NSAIDs, antioestrogenic drugs, chemotherapy or radiotherapy, but all modalities proved disappointing, except for treatment with a combination of the NSAID sulindac and tamoxifen. Five patients treated with this combination showed extensive and long lasting response.

The British North West Region FAP registry records 363 patients with FAP, of whom 47 had desmoids\(^12\). Of 22 patients who had surgery, 16 developed desmoids, and of these 12 had mesenteric desmoid disease. Complications from mesenteric desmoids were death (two patients), enterectomy (three), local resection (three), fistula (one), cholangitis and local resection (one), bowel obstruction (one) and bowel and ureteric obstruction (one). They noted that patients with 3’ APC mutation undergoing abdominal surgery had a 65% risk of mesenteric desmoids.

SURGERY AS A PREDISPOSING FACTOR FOR THE DEVELOPMENT OF DESMOIDS

Early colectomy had been said to result in an increased risk for the development of desmoids. The Singapore Polyposis Registry found that seventy-four percent of desmoids (17/23) developed at a mean interval of 2.98 years after restorative proctocolectomy, while only 30 percent (7/23) were diagnosed preoperatively or discovered during the initial surgery\(^6\). The Dutch found that most desmoid patients (95%) had undergone previous abdominal surgery\(^7\). The French found that desmoids appeared only after surgery in 34 out of 50 patients regardless of the type
The management of desmoids in patients with familial adenomatous polyposis

of operation. They were recognized before surgery in five and during operation in 11 patients.

The Toronto FAP registry found 121 (14%) desmoids in 930 patients with FAP. Female (17%) patients were more likely to develop desmoids than male patients (11%). Female patients who had a colectomy at 18 years of age or earlier were more than 2 times more likely to develop a desmoid, compared with women who had a colectomy after this age. Early colectomy did not increase risk of developing a desmoid in male patients. Female patients who had a colectomy at or before 18 years of age were 2.5 times more likely to develop desmoids, compared with male patients who had a late colectomy after 18 years of age (P = .05). They suggested that delayed colectomy might be considered in young female patients with FAP to decrease the chances of developing desmoids.

In an interesting case report a 17 year old patient had a complete response to therapy with doxorubicin and dacarbazine. This patient had a prophylactic colectomy at 14 and developed desmoids three years later unresponsive to radiation, surgery, sulindac or tamoxifen. A laparoscopic confirmation of complete response resulted in a massive recurrence of desmoids tumours within a few months. The patient recurred with tumour at every port site and died from massive desmoids.

SURGERY IN THE MANAGEMENT OF DESMIDS

St Marks’ Polyposis Registry reported on 20 patients who had surgery to remove 32 desmoid tumours (16 intra-abdominal, 12 abdominal wall, four extra-abdominal). They managed to obtain complete clearance in 19 tumours, however, clinically significant recurrence occurred in eight and this was not related to site. Small intestinal resection length ranged from 10 cm to 200 cm. There was no mortality from desmoid disease at a median follow-up of 5 (range 0.6-10) years. They concluded that surgery for intra-abdominal desmoids in selected patients is less hazardous than previously reported but recurrence remains a major problem.

The Heidelberg registry identified 29 patients (17%) with desmoid tumors. In that series R0-resection with a wide margin was obtained in 12 cases, three of which developed a recurrence and eight are free of desmoids and one refused a radiological re-evaluation. Tumor debulking was performed in six patients but this led to aggressive desmoid progression in four patients despite tamoxifen and sulindac. Fifty per cent (11/22) of their desmoids were diagnosed within the first two years after surgery, and 72% (18/22) of their desmoids developed within the first four years after colectomy.

CHEMOTHERAPY FOR DESMIDS

Non surgical treatment with tamoxifen and sulindac had been reported to be beneficial. The Heidelberg Registry reported these drugs to be beneficial in five of seven patients, with some showing a stagnation of tumor growth or a reduction in size. They also reported on the use of radiation therapy with remarkable tumor reduction in two of their patients.

Since 1992, 17 patients with FAP at Heinrich Heine University in Dusseldorf, Germany were treated with 120 mg of tamoxifen and 300 mg of sulindac daily. Every 6 months, the desmoid growth was measured by computed tomography and/or magnetic resonance imaging scans. Tumor responses were characterized as progressive disease, stable disease (SD), partial regression (PR), and complete regression (CR). Ten patients with FAP-associated desmoids achieved either a PR or CR. Patients with FAP-associated tumors, tamoxifen and sulindac was found to be less successful.

The Mayo Clinic used Pirfenidone or 5-methyl-1-phenyl-2-(1H)-pyridone, a broad-spectrum, noncytotoxic, oral antifibrotic agent that was able to inhibit or block the action of cytokine growth factors. They enrolled 10 women and four men with extensive desmoid in FAP in a 2-yr trial with oral pirfenidone. Seven patients dropped out (three because of progressive disease) but seven continued for at least 18 months. Of those that continued, two had partial but significant reduction in the size of their desmoids beginning in the first 6 months of treatment, and two others experienced relief of symptoms without change in desmoid size. Three patients experienced no change in tumor size or symptoms. Some patients with desmoid tumors treated with pirfenidone had regression of tumors, some had progression, and some had no response. Patients with rapidly growing tumors however did not respond to pirfenidone.

A Japanese study reported on seven of 11 individuals with symptomatic unreatsectable desmoid tumors that were unresponsive to conventional hormone therapy. These patients were started on a chemotherapy regimen comprising of a four or five cycles of DOX (20 mg/m² daily) plus DTIC (150 mg/m² daily) throughout 4 days of drip intravenous infusion (day 1 through 4) every 28 days, followed by the cyclooxigenase-2 inhibitor meloxicam (10 mg/m²).

They reported significant tumor regression both clinically and radiologically in all seven patients with three patients showing a complete response. The average progression-free survival period was 74.0 months (range, 32.5 to 107.5 months). They recommended that this regimen should be considered for use as first-line chemotherapy in symptomatic desmoid tumors.

The successful use of Dacarbazine-Doxorubicin therapy in a 30-year-old man with FAP who had prior prophylactic proctocolectomy and who grew large desmoids of between 10 to 25 cm in diameter thrice within 3 to 10 mths was recently reported.

During this period, the patient was given several drug regimens, including tamoxifen, non-steroidal anti-inflammatory drugs and imatinib mesylate (Gleevec), which had little or no effect. Finally, when the desmoid occupied the pelvic space, the patient was given dacarbazine and doxorubicin. After seven courses, the mesenteric tumor showed an almost complete response with no further recurrence desmoid for 4 years.
GENETIC TRANSFER

Liposomal transfection of APC genes resulted in a prolonged high-level expression of the transgene with no adverse effects recorded so far in mouse work. The APC gene was transferred into fibroblasts in tissue culture and then into peritoneum and small bowel mesentery in vivo. Transgene expression was recorded in vitro 7 days after transfection. High levels of transgene expression were also seen in samples of peritoneum, small bowel mesentery, liver and intestinal tissues following intraperitoneal treatment. Interestingly, transgene expression in gonadal tissues was occasionally noted as well.

Another basic molecular study from London looked at the constitutive activation of the Wnt signaling pathway. This is a hallmark of many cancers, including familial adenomatous polyposis (FAP)-related desmoid tumors. Endostatin is a well-known antiangiogenic protein that has been described recently as a potential inhibitor of this signaling pathway. They showed that endostatin directly induces cell death of primary FAP-related desmoid tumor cells in culture and postulated that endostatin gene therapy may represent an attractive new therapeutic approach for this disease.

CONCLUSION

Simple drug treatment with tamoxifen or NSAIDS like sulindac should be used as first line treatment as it carries a response in 30-50% of patients. Surgery should be reserved for extra-abdominal tumors alone and only when needed. Surgery for intra-abdominal desmoids should really only be attempted for intestinal obstruction or ureteric obstruction. Dacarbazine-Doxorubicin chemotherapy may have dramatic response in some cases. Genetic transfer may unlock this disease in future and this should give patients with FAP and desmoids hope for the future.

REFERENCES


