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Fibromatosis, desmoids, fibroblasts, and tamoxifen

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SUMMARY. **A review of recent developments in the treatment of desmoid tumours (musculoaponeurotic fibromatoses) by tamoxifen and other drugs is presented.**

Fibromatoses are either superficial, fascial, fibromatoses such as Dupuytren's disease or deep, musculoaponeurotic, fibromatoses also known as desmoid tumours (desmos meaning "band" in Greek).[1]

Musculoaponeurotic fibromatosis (plural: fibromatoses), which for brevity will be called desmoid tumour in this review, is a rare tumour of spindle-shaped fibroblasts and collagen which infiltrates muscle and can become densely adherent to major vessels and nerves. Desmoid tumours are more common in females than males and about 50% occur in the anterior abdominal wall. They occur at all ages; in the young and old they are mainly extra-abdominal while between about the ages 15–59 years most are abdominal.[2] By local spread, extra-abdominal desmoids can cause compression of nerves, major vessels and the trachea, while intra-abdominal desmoids can cause compression of intestines, ureters, the bladder, the vagina, nerves and major vessels. Because of compression of vital structures, the spread of desmoid tumours has in rare cases been fatal.[1,3] In view of this aggressive potential, these fibromatoses are also called "aggressive fibromatoses"[4] but since the clinical course of individual cases varies some question the value of this term.[1] Desmoid tumours do not metastasise but may be multicentric.[1,5,6] The differential diagnosis includes fibrosarcoma and reactive fibrosis.

The early literature on desmoid tumours has already been summarised in this journal.[5] Until recently, treatment has been surgery with or without radiotherapy or chemotherapy.[1,5,7] Surgery can give high cure rates for abdominal desmoid tumours,[1] and in some cases is successful for extra-abdominal tumours.[3,7] Surgery for extra-abdominal desmoid tumours is complex if structures such as the brachial plexus are involved and to achieve complete local excision would in some cases require forequarter or hindquarter amputation. Surgery can also be difficult to plan in young children. Radiotherapy and cytotoxic drug therapy may be beneficial but may cause significant side effects.[8–10] Overall, treatment of extra-abdominal tumours is associated with high recurrence and complication rates.

The search for alternative treatments took a new direction in 1983 when Kinzbrunner *et al.* reported one case in whom painful recurrent desmoid tumours of the back partially regressed with tamoxifen treatment[11] and Waddell *et al.* reported apparent complete regression of one intra-abdominal desmoid treated with tamoxifen and sulindac (a drug related to indomethacin).[12]

Tamoxifen and toremifene

Tamoxifen has become the main adjuvant drug in the treatment of breast cancer. It improves survival in post-menopausal women and reduces the risk of a second, contralateral, primary breast cancer by 39%.[13] In some elderly patients with breast cancer, treatment with tamoxifen alone causes complete tumour regression.[14] Toremifene is a similar compound with differences in toxicity and antitumour activity and has been used for breast cancer failing to respond to tamoxifen.[15]

Since 1983, there have been several more case reports on the treatment of desmoid tumours with tamoxifen. In some cases, there has been complete clinical regression of tumour. In one case, for example, a 30-year-old woman had wide excision of a desmoid in the left upper arm and scapular region; the tumour recurred but with tamoxifen treatment it then completely regressed.[16] In another case, an abdominal wall desmoid in a 26-year-old woman completely regressed with tamoxifen treatment.[6]

A series of 20 adult patients, 15 females and 5 males, with desmoid tumours treated with triphenylethylenes (tamoxifen and toremifene) gives a clearer picture of the effectiveness of these drugs.[15] 15 of the 20 patients had abdominal desmoid tumours, either alone or with desmoids elsewhere. Tumour response was assessed clinically and/or by CT scans. 8 patients had tamoxifen as the first-line treatment: there was complete tumour response in 2, partial tumour response in 1 and progression of tumour growth in 5. 12 patients had toremifene as the first-line treatment: there was complete tumour response in 1, partial tumour response in 5, no response or progression in 5, and progression of tumour growth in 1. The overall "cure" rate was low but the majority of patients in this selected series had responses ranging from stabilisation to complete remission of their disease.

The natural history of the disease must be remembered. Tumour progress varies; in general, tu-

mour growth is slow in males and in juvenile and elderly females but rapid in females from about 15–59 years old.[17] Occasionally spontaneous regression can occur.[1,17] It is not known how long tumour remission persists after drug therapy nor how long tamoxifen or toremifene treatment should last. One case of a similar condition, retroperitoneal fibrosis, suggests long term treatment may be required.[18] Both desmoid tumours and retroperitoneal fibrosis show local fibroblast proliferation. Retroperitoneal fibrosis differs from desmoid tumours in that, for example, it occurs predominantly in males, it contains inflammatory cells in its early stages and then responds to steroids, and it does not seem to be affected by oestrogens. Nevertheless, in a 50-year-old man, the symptoms and signs of retroperitoneal fibrosis disappeared after 4 months of tamoxifen treatment.[18] He acted as his own longitudinal control; on two separate occasions he stopped therapy and within weeks his symptoms and his retroperitoneal mass reappeared, only to disappear when tamoxifen was recommenced.

The experience of an estimated 4.5 million women years of tamoxifen treatment shows that tamoxifen is a remarkably safe drug, so much so that it is now being used in breast cancer prevention trials.[19] However, there are reports of an increased incidence of endometrial cancer in humans[20] and the promotion of hepatic cancers in rats by tamoxifen.[19] The long term effects of tamoxifen in children, men and premenopausal women are not known.

Tamoxifen has oestrogen, antioestrogen and other actions and breast cancers with oestrogen receptors on their surface are more responsive to tamoxifen than breast cancers without these receptors.[13] Some desmoid tumours in men and women have both oestrogen receptors and anti-oestrogen binding sites[21] and this may be one reason for the effects of tamoxifen and toremifene on desmoid tumours. However, tamoxifen also improves survival for patients with breast cancers without oestrogen receptors and in such cases, as with desmoid tumours, this may be due to another action of tamoxifen on fibroblasts.

In both adults and foetuses, fibroblasts are subject to complex control mechanisms and have several functions, including the production of collagen.[22–25] Interactions between epithelia and their surrounding stroma are important for normal development and the notion that deranged stromal-epithelial interactions contribute to the development and spread of neoplasms, including breast cancer, has been proposed. There is evidence for aberrant fibroblasts in cancer patients.[26] Tamoxifen induces the secretion of active transforming growth factor beta in human foetal fibroblasts in vitro[27] and in human breast cancers in vivo.[28] Toremifene also reduces the size and number of gastrointestinal polyps in certain patients.[26] Benson and Baum have recently put forward a unifying hypothesis to explain the effect of tamoxifen on breast cancers, desmoid tumours and also familial adenomatous polyps and have linked it all to the effect of tamoxifen on fibroblasts.[26] Benson and Baum suggest that the transforming growth factor beta produced by fibroblasts in response to tamoxifen inhibits the malignant epithelial cells in breast cancers, while it inhibits the aberrant fibroblasts presumed to be present in desmoid tumours and gastrointestinal polyps. This has led to a lively debate about the originality and significance of the hypothesis and the debate will continue as more facts emerge; one point to be considered, for example, is that there are three different isoforms of human transforming growth factor beta with different effects, including stimulation of fibroblasts and thus collagen and scar formation.[29]

Conclusions

Desmoid tumours, otherwise known as musculoaponeurotic or aggressive fibromatoses, are fibroblast tumours which, in their development and their response to drug treatment, demonstrate the interrelationship between the biology of foetal and adult normal tissue development, wound healing and the development and progression of tumours.

Published case reports suggest that tamoxifen or related drugs are the first choice of treatment for desmoid tumours. Tamoxifen is a complex drug and in addition is not always effective. Patients with desmoid tumours will therefore be best managed by oncologists together with surgeons and radiotherapists. Desmoid tumours are rare and each case treated with tamoxifen or similar drugs requires detailed documentation.

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