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Desmoid tumours of the extremities and trunk: a review of the literature

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Abstract Desmoid tumours are rare neoplasms that display local aggressiveness but no propensity to metastasise. They are mainly localized in the abdominal wall, the bowel, and the mesentery or in extra-abdominal sites such as the trunk and the extremities. Surgical resection is the main treatment modality in extremities and trunk, with the optional combination of radiotherapy and/or chemotherapy. However, these tumours have a high propensity for recurrent growth.

Résumé Les tumeurs desmoides sont des néoplasmes rares qui ont un caractère agressif local, mais aucune propension à métastaser. Elles sont principalement localisées dans la paroi abdominale, l'intestin et le mésentère et dans des sites extra-abdominaux tels que le tronc et les extrémités. La résection chirurgicale est la principale modalité du traitement pour les extrémités et le tronc avec la combinaison facultative de radiothérapie et/ou chimiothérapie. Cependant, ils ont une haute tendance à la récurrence.

Introduction

Desmoid tumours (DTs) are rare neoplasms arising from fascial or deep musculo-aponeurotic structures. McFarlane first described them in 1832 while Muller, in 1838, used the

term desmoid, deriving from the Greek “desmos” (meaning tendon-like) [20]. They are localized in the abdominal wall, the bowel, and the mesentery (associated with familial adenomatous polyposis) or in extra-abdominal sites, such as the trunk and the extremities. The incidence of DTs ranges from 2% to 4% per million; almost half of them occur in the extremities and trunk [18]. Extremities and trunk DTs (ETDTs) are mainly seen in young adults, with a peak incidence between the ages of 25 and 35 years [19]. Rare cases occurring in patients younger than 10 years have been reported [6]. They have a female preponderance with a female/male ratio of 2:1 [19, 20]. The most common localization is at the shoulder girdle followed by the chest wall, back, thigh, and head and neck [19]. Most patients appear with an asymptomatic mass. Symptoms such as pain, deformity and organ dysfunction are seen after the infiltration of tissue structures. Death is extremely rare when vital organs are invaded [7].

Several factors have been implicated in the pathogenesis of DTs. Among them, genetic abnormalities, steroid sex hormones, and trauma are most commonly reported. Genetic abnormalities include defects in growth regulation of connective tissue, chromosomal abnormalities, and increased expression of cytokines associated with angiogenesis [4, 15]. DTs seem to have a close relationship with steroid sex hormones since they are more common in women; particularly those in the reproductive age and those receiving contraceptive pills. In support of this relationship are the high incidences of oestrogen and anti-oestrogen binding sites in DTs and the production of collagen by tissue cultures of DT cells in response to oestrogen [22].

Imaging

Several imaging techniques are useful in establishing the diagnosis of ETDTs. Radiographs show either a non-specific soft tissue mass or a soft tissue swelling or no evidence of abnormality although positive findings are seen in the presence of bone involvement due to local infiltration

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causing bone erosion, periosteal reaction, deformation, or bowing of bone. Invasion of the medullary canal is rarely seen [8]. Computer tomography (CT) provides evidence of the extent and anatomical relationships of the tumour although findings are non-specific. The density of most tumours is similar to that of muscles or, on non-contrast scans, slightly more dense. After the administration of contrast material, the density of the lesion is enhanced. Contrast scans contribute to the evaluation of the anatomical relations of the tumour with major vessels. In such cases, angiography can be helpful [8].

Magnetic resonance imaging (MRI) is considered the best imaging modality in the diagnosis and staging of the disease. MRI has the advantage over CT of the greater ability to delineate extension of the tumour and greater appreciation of infiltration of adjacent structures [8]. Lesions are usually iso-intense in T1-weighted images with respect to muscle signal [3, 9] although cases of hypo- or hyper-intense lesions can be seen. On T2-weighted images, lesions are hyper-intense and intermediate between muscles and fat [3, 9]. On both images (T1, T2), zones of low-signal intensity that reflect hypo-cellularity and abundant collagen can be seen [8]. After the intravenous administration of contrast material, ETDTs enhance on MRI. Other imaging methods for ETDTs, such as scintigraphy, are still under investigation.

Histology

Macroscopically, ETDTs are generally uni-centric, firm, non encapsulated, and poorly defined masses of grey-white tissue. The average size of the tumour ranges between 1 cm and 10 cm in diameter. Microscopically, the lesion is poorly circumscribed and infiltrates the surrounding tissues. It consists of interlacing bundles of elongated, spindle-shaped cells separated by amounts of collagen. Reticulin preparation and the Mason trichrome stain bring out the collagen between the individual tumour cells. Typically, the cells have vesicular nuclei, one to three minute nucleoli, and rather indistinct cytoplasm. In some cases, at the peripheral portion of the tumour where the lesion has infiltrated muscle tissue, the tumour cells entrap remnants of striated muscle fibres. As a result, the muscle fibres can form multinucleated giant cells that may be interpreted as a malignant neoplasm.

Treatment and prognosis

Surgery is the treatment of choice for ETDTs. However, local control remains difficult. The propensity for recurrence locally may be related to the lack of pseudocapsule and the non palpable diffusion along muscle bundles and fascial planes, making it difficult for the surgeon to identify the true extent of the disease. In cases where tumours infiltrate bone or neurovascular structures, the potential to achieve wide resection margins is compromised by the

equally important objective of maintaining a functionally intact extremity. Some believe that wide excision with clear margins should always be the goal, even when it has a significant impact on long-term function and morbidity. A large rim of normal-appearing tissue must also be removed since ETDTs usually infiltrate beyond margins recognized at surgery and defined at imaging [12]. On the other hand, others believe that marginal resection, with respect to the anatomy, should be performed, especially in lesions that would otherwise require amputation [5]. The often subtle, diffuse infiltration of muscle bundles renders intra-operative and histopathological assessments of surgical completeness inaccurate, leading to recommendations for amputation or radical resection of the tumour.

Radiation therapy (RT) is a viable alternative to surgery and a useful adjunct to incomplete resection of primary ETDTs for the control of residual disease [14]. RT alone can be used where surgery might lead to major morbidity and loss of function as well as for patients who have an inoperable tumour or gross residual disease after operative debulking [17]. In cases where surgery is not feasible, external RT with doses of 50–60 Gy has demonstrated high disease-free survival rates [24] and decreased recurrence rates [2] although unfavourable results have also been reported [19]. Generally, adjuvant RT, especially in cases with positive surgical margins, remains the main treatment approach in ETDTs and should be delivered with generous radiation fields, providing wide margins and high radiation doses, to achieve local control. Radiation-induced side effects that develop after high radiotherapeutic doses, such as oedema, fibrosis, ulcers, pathological fractures, secondary malignancies and others, should always be borne in mind [16].

The efficacy of chemotherapy in the treatment of ETDTs remains unclear. The non metastasising and indolent nature of the disease has limited the use of chemotherapy. Chemotherapeutic agents that have been used are doxorubicin, methotrexate, vincristine, dactinomycin, cyclophosphamide, vinblastine, and others, with contradictory results [1, 21]. Other agents that have been used for local control include hormonal therapy, nonsteroidal anti-inflammatory drugs, interferon-alpha, and drugs that inhibit the coagulation cascade [10, 13, 23].

Despite the improvement of therapeutic approaches, recurrences occur at high rates that vary between 15% and 77% in the reported series [5, 19]. Several prognostic factors have been reported to play an important role in the local control of the disease. Literature is dominated by a large number of trials investigating the role of margin status after surgical excision of ETDTs, with controversial results. Rock et al. studied 194 patients with ETDTs and found a greater tendency for local recurrence in lesions treated with intralesional or marginal excision [19]. Pritchard et al. analysed 50 previously untreated ETDTs [17]. Among patients treated with surgery alone, the local recurrence rates were statistically significantly higher for lesions that had undergone marginal or intralesional resection compared with those with wide resection. Finally, a retrospective

review of 189 patients found a statistically significant difference in the 10-year recurrence rate between patients with negative margins and those with positive margins (27% versus 54%) and a poorer prognosis in tumours of the extremities compared with those located in the trunk [2]. Conversely, Merchant et al. [14] prospectively analysed 189 patients with ETDTs. Twenty-two percent of patients with positive resection margins developed local recurrence compared with 24% in those with negative margins. The authors concluded that positive resection margins were not predictive of recurrence, and attempts to achieve a negative margin might result in unnecessary morbidity without preventing disease progression. A retrospective study of 203 consecutive patients with ETDTs reported that the presence of microscopic disease does not necessarily correlate with decreased disease-free survival in patients with primary tumours [7].

Most of the literature studies are inevitably underpowered to evaluate the impact of surgical margins in disease-free survival rates. This limitation is driven from the limited sample sizes of the reports, the mixed populations (intra-abdominal, abdominal, and extra-abdominal DT) and the inclusion of both primary and recurrent disease in the reported analyses. Moreover, the different therapeutic protocols that are used in the reported series preclude proper analysis for the evaluation of the role of margin status. Finally, the variety of terms regarding surgical margins among the reported studies rule out a rigorous comparison based on margin status.

Recently, Leithner et al. [11] conducted a comparative analysis in order to evaluate the prognostic significance of microscopic surgical margin status in ETDTs treated with surgery alone. The combined recurrence rate was extremely high (72%) after marginal or intralesional surgical procedures, in contrast to the rate after wide resection or radical surgery (27%). Based on this outcome, the authors suggested the strategy of wide resection or radical local excision as the main treatment option. Other factors that have been reported to play an important role in the prognoses of ETDTs are: primary or recurrent disease, tumour size, location (extremities or trunk), female gender, and age at diagnosis [7, 12].

Conclusion

ETDTs are rare neoplasms with aggressive local behaviour but no propensity to metastasise. Their infiltrative growth often results in local recurrences regardless of the choice of treatment. Surgical excision with clear margins seems to be the best option. In cases where wide resection would result in great loss of function or amputation, a more conservative surgical approach followed by radiotherapy should always be considered. Large randomised trials comparing the efficacy of the various methods of treatment and their prognostic significance should be the goal for the future.

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