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Multifocal occurrence of extra-abdominal desmoid type fibromatosis – A rare manifestation. A clinicopathological study of 6 sporadic cases and 1 hereditary case☆

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ABSTRACT

Desmoid-type fibromatosis, also called desmoid tumor, is a locally aggressive myofibroblastic neoplasm that usually arises in deep soft tissue with significant potential for local recurrence. It displays an unpredictable clinical course.

β-Catenin, the genetic key player of desmoid tumors shows nuclear accumulation due to mutations that prevent its degradation leading to activation of Wnt signaling and myofibroblastic cell proliferation. The corresponding hot spot mutations are located in exon 3 of the *CTNNB1* gene or alternatively, in the *APC* tumor suppressor gene, most often as a germline mutation.

Multifocal desmoid tumors are very rare and clinical characteristics are poorly understood. Here we present six sporadic and one familial case of multifocal desmoid tumors.

Four female and three male patients, aged between 7 and 30 years (mean 18.4 years) were identified in a cohort of 1392 cases. Tumors were located in (distal) extremities, thorax, breast, abdominal wall, shoulder, and neck. Four cases showed a *CTNNB1* mutation and one an *APC* germline mutation. In two sporadic cases no *CTNNB1* mutation was identified. Four patients showed (multiple) recurrences and one patient was lost to follow-up.

In conclusion, multifocal desmoid tumors are a very rare disease and may occur in sporadic cases that are characterized by recurrent *CTNNB1* mutations. However, the underlying pathogenesis of multifocal desmoid tumors remains poorly understood with often aggressive clinical behavior and challenging therapeutical management.

1. Introduction

Desmoid-type fibromatosis, or desmoid tumor, is a locally aggressive, infiltrative growing myofibroblastic lesion with unpredictable clinical behavior. It may originate at any part of the body with extremities, abdominal wall and mesentery being the most common sites [1]. The peak incidence is in the third decade [1].

Desmoid tumors arise sporadically in approximately 90% of the cases with the remaining 10% being familial [1]. Dysregulation of the Wnt signaling pathway is characteristic in both settings with β-catenin

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Table 1
Clinical data and mutation status.

Case nr.	Sex (m/f)	Age of first presentation (y)	Tumor localizations	Therapy	*CTNNB1* Mutation status	Recurrence (after n months)
1	m	13	Knee and gluteus	Resection, RT	c.121A > G[a] p.Thr41Ala	No
2	f	24	Breasts (left + right)	Resection	No mutation found	No
3	m	17	Upper leg and hallux	Resection	c.134C > T; p.Ser45Phe	Upper leg (10) and hallux (63)
4	f	27	Upper leg and lower leg	Resection	c.121A > G p.Thr41Ala	Lost to follow-up
5	m	11	Upper leg and hallux	Resection	c.121A > G[a] p.Thr41Ala	Hallux (36)
6	f	30	Abdominal wall, thorax, back, shoulder, neck	Resection, Lucrin, LHRH antagonist, Tamoxifen, RT	No mutation found	Multiple, in all locations (6)
7	f	7	Ankle, back and lower leg	Resection	*APC* mutation[a] (Gardner)	Ankle (7, 18 and 28), back (10)

M, male; f, female.
[a] Mutation in two lesions tested.

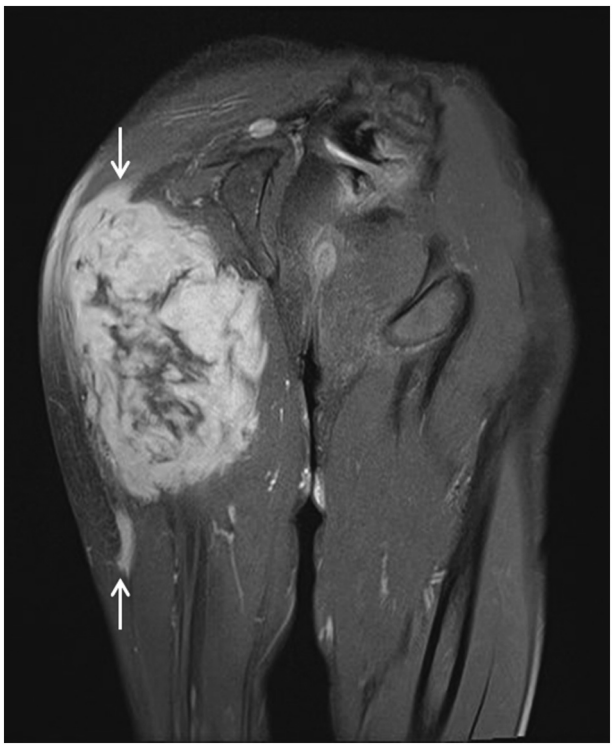

Fig. 1. Coronal contrast-enhanced spinecho T1-weighted MR-images with fat saturation of the buttock and proximal posterior side of the right lower leg showed an irregular lesion compatible with desmoid tumor. The extension of the lesion is displayed between the white arrows (Case 1).

being the key player. In sporadic cases, the most common activating mutations are located in exon 3 of the *CTNNB1* gene (chr 3p22.1) coding for β-catenin. Alternatively, in the remaining sporadic cases and the familial cases that occur in the context of Gardner syndrome (a form of familial adenomatous polyposis), there is a somatic or germline inactivating mutation or allelic deletion in the *APC* tumor suppressor gene (5q22.2) [1-4]. Both mechanisms lead to stabilization of β-catenin with cytoplasmatic and subsequently nuclear accumulation. Within the nucleus, β-catenin acts as a transcription factor regulating cell proliferation of myofibroblastic cells [1,5,6].

In the recent years, a paradigm shift in terms of treatment modalities has taken place for desmoids tumors and the overall management is increasingly complex. It has been shown that invasive treatment should be used with caution because of the potential of recurrence, irrespective of the margin status [5,7-9]. In this context, mutational analysis of *CTNNB1* can give prognostic information, where the hot spot mutation p.Ser45Phe (p.S45F), has been proposed as a possible marker for recurrence [10-12].

Single cases of multifocal desmoid tumors have been described [13-15], but their genetic and clinical characteristics are not well understood. We describe herein a series of multifocal desmoid tumors and their mutational status to pay attention on these rare cases.

2. Material and methods

The cases were collected from the authors' files and the nationwide network and registry of histopathology and cytopathology in the Netherlands. Clinical data and follow-up were obtained from the patient records. The study was performed in accordance with the Code of Conduct of the Federation of Medical Scientific Societies in the Netherlands.

In all cases the tissue was fixed in 4% buffered formalin and embedded in paraffin; 2–4 μm thick sections were stained with hematoxylin and eosin and immunohistochemically by the labelled Streptavidin Biotin technique using a commercially available antibody against β-catenin (BD Biosciences, clone 14, dilution 1:100). Appropriate positive and negative controls were used throughout.

DNA was isolated from formalin-fixed, paraffin-embedded material (without decalcification) by proteinase K digestion and the crude DNA extract was used in a standard PCR. The hot spot region for *CTNNB1* was amplified using primers: 5′-ATGGCCATGGAACCAGACAGA-3′ and 5′-GCTACTTGTTCTTGAGTGAAGGACTG-3′. The region most frequently mutated in *APC* (NM_000038.5: amino acids 1200–1580) was amplified using the following primer pairs: 1) 5′-CAGATATTCCTTCATCACAGAAAC-3′ and 5′-GGAGTATCTTCTACACAATAAGTCTG-3′, 2) 5′-GCCACTTGCAAAGTTTCTTC-3′ and 5′-TCACAGGATCTTCAGCTGACCT-3′, 3) 5′-TCAGACGACACAGGAAGCAGAT-3′ and 5′-TTTTGGGTGTCTGAGCACCACT-3′, 4) 5′-AGCCAGGCACAAAGCTGTTGAA-3′ and 5′-TGTCCAGGGCTATCTGGAAGATCA-3′, 5) 5′-ACCATGCAGTGGAATGGTAAGTGG-3′ and 5′-TGGAAGAACCTGGACCCTCTGAA-3′, 6) 5′-TGGACCTAAGCAAGCTGCAGTA-3′ and 5′-CTGCTCTGATTCTGTTTCATTCCCATTGT-3′, 7) 5′-TCTGAGCCTCGATGAGCCATTT-3′ and 5′-ACGTGATGACTTTGTTGGCATGG-3′. All PCR products were analyzed by fluorescent di-deoxysequencing.