Short reports

A novel case of a sporadic desmoid tumour with mutation of the β catenin gene

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Abstract

A 42 year old man without familial adenomatous polyposis had recurrent desmoid tumours in the left subclavicular site. Histological examination showed a typical desmoid tumour. Molecular analysis was performed in genomic DNA from this tumour, using polymerase chain reaction–single strand conformation polymorphism (PCR-SSCP) and direct sequencing methods. No mutation could be detected in the entire coding sequence of the APC gene, nor in H-ras, K-ras, N-ras, or p53 genes. On seeking a mutation of the β catenin gene (CTNNB1), an activating mutation from ACC (Thr) to GCC (Ala) at codon 41 was found. Immunohistochemical staining showed that accumulated β catenin protein was predominantly localised in the nuclei of desmoid cells. This is the first example of a sporadic desmoid tumour in which a mutation of the β catenin gene was revealed.

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Keywords: sporadic desmoid tumour; β catenin mutation; β catenin expression

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Desmoid tumours (aggressive fibromatosis) are generally considered to have locally infiltrative features, and they do not metastasise. Although they are recognised as common tumours in a variety of extracolonic lesions in familial adenomatous polyposis, sporadic desmoid tumours are very rare. We have previously reported that inactivation of the APC gene through germ line and somatic mutations contributes to the development of desmoid tumours in patients with familial adenomatous polyposis.[1] In sporadic desmoid tumours, somatic mutations of the APC gene have been detected in several cases.[2] However, it has been supposed that some sporadic desmoid tumours may lack somatic mutation of the APC gene, and be associated with other genes.[3] Recently, activating mutation of the β catenin gene has been suggested to have oncogenic activity resulting in tumour development, similar to the inactivating mutation of the APC gene.[4] Based on this assumption, we looked for a mutation of the β catenin gene and found a somatic mutation of this gene in a sporadic desmoid tumour which had no somatic mutation of the APC gene.

Methods

MUTATION ANALYSIS

DNA samples from the desmoid tumour and the corresponding normal tissue were amplified for single strand conformation polymorphism (SSCP) analyses of β catenin, APC, H-ras, K-ras, N-ras, and p53 genes, using polymerase chain reaction (PCR) under the same conditions as previously described.[1] Primers used to amplify exon 3 of the β catenin gene were the same as those reported.[5] Abnormal single stranded DNA fragments in the SSCP analysis were extracted and amplified by asymmetrical PCR, and then subjected to direct sequencing by dideoxy chain termination reaction.[1]

IMMUNOHISTOCHEMISTRY

Standard immunohistochemistry was performed on formalin fixed, paraffin embedded material by the ABC method. Sections (4 μm) were mounted on Superfrost Plus glass slides and dried overnight at 37°C. Slides were deparaffinised in xylene, rehydrated in graded alcohols, and washed in water. The desmoid tumour tissue was stained using mouse antihuman β catenin monoclonal antibody (clone 14, 250 μg/ml; Transduction Laboratories) which was diluted to 1:50. Colorectal carcinoma tissues with β catenin mutation (with strong staining in nuclei), which were obtained from the department of pathology of Tokyo Metropolitan Komagome Hospital, were used as positive controls. White blood cells and normal colonic mucosa (with staining on cell membrane) were used as negative controls.

Results

CASE REPORT

A 42 year old man was admitted to the department of surgery of Jichi Medical School for treatment of the left subclavicular mass. He had had desmoid tumours removed twice at 30 and 36 years of age, and a tumour had recurred again. In histological studies, both of the previously removed tumours had been identified as desmoid. He had no family history of colorectal carcinoma or familial adenomatous polypo-

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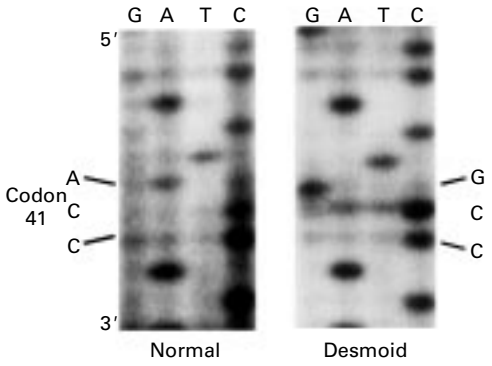

Figure 1 Nucleotide sequences of the β catenin gene in DNAs from desmoid PLK177D and corresponding normal tissue. Mutation from A to G at codon 41 is present in the desmoid.

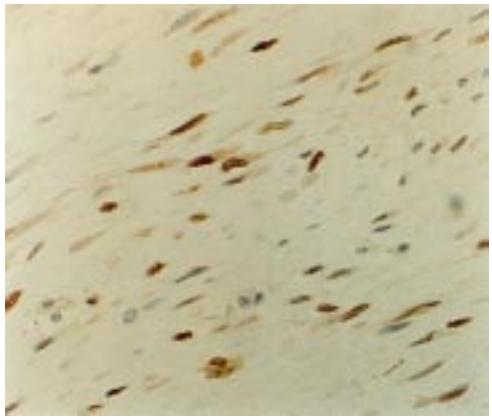

Figure 2 Immunohistochemical staining of β catenin protein in PLK177D desmoid tissue, using anti human β catenin monoclonal antibody. Nuclei of desmoid cells are positively stained.

sis. Computed tomography showed a mixed dense tumour which occupied from the left subclavicular site to the left axillary site surrounding the thoracic wall. The tumour was resected and has not recurred.

PATHOLOGICAL FEATURES

The resected specimen was poorly circumscribed and measured 13 × 13 × 5 cm. On macroscopic examination, the tumour was seen to be invading the striated muscle. Microscopic examination showed that it consisted of many fibroblasts with high cellularity forming collagenous tissues. This pathological feature was consistent with a desmoid tumour.

MOLECULAR FEATURES

A section of the recurrent desmoid tumour was frozen immediately after surgery and stored at −80°C until use. Genomic DNA was extracted from this tumour and screened for mutation in the entire coding sequence of the APC gene by the PCR-SSCP method. However, we detected no mutation in this gene. Moreover, mutation was not detected in H-ras, K-ras, N-ras, and p53 genes. We then looked for a mutation in the β catenin gene (CTNNB1). After evaluating by PCR-SSCP, DNA fragments in the mutant bands were analysed by direct sequencing. A missense mutation from ACC (Thr) to GCC (Ala) at codon 41 was detected, as indicated in fig 1. The same mutation has also been detected frequently in colorectal cancer.[6] Immunohistochemical staining of β catenin protein in this tumour showed strong staining in nuclei (fig 2).

Discussion

In patients with familial adenomatous polyposis , desmoid tumours are caused by a constitutional defect in the APC gene and additional somatic mutation in the other allele of the same gene.[1] However, in patients without familial adenomatous polyposis, the extent of contribution of the APC gene mutation to desmoid tumours is still uncertain. Giarola *et al* have reported that mutation of the APC gene is uncommon in sporadic desmoid tumours[3], although they did not mention other candidate genes that contribute to the formation of sporadic desmoid tumours. On the other hand, Alman *et al* have found possibly biallelic truncation mutations of the APC gene in three of six sporadic desmoid tumours.[2] It has previously been shown that intact APC forms a complex with β catenin and other proteins, facilitating degradation of β catenin,[7] and mutant APC lacks the ability of complex formation, resulting in an increased level of β catenin.[8] Accumulation of β catenin has recently been demonstrated in colorectal tumours that have no APC mutations, through dominant activating mutations in the regulatory domain of the β catenin gene (codons 29 to 45).[4 9] Such a loss of control of the β catenin level by mutation in either APC or β catenin gene has been assumed to contribute to colorectal tumorigenesis. In our desmoid tumour, a β catenin mutation was present instead of an APC mutation, which may bring about the same effect as that observed in colorectal tumours. Moreover, β catenin protein was found to be predominantly localised in nuclei of desmoid cells, which suggests that mutant β catenin functions in the nucleus. In the absence of mutation of other genes, including p53, H-ras, K-ras, and N-ras, β catenin mutation may be the main contributor to the development of this desmoid tumour.

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