

A nation-wide study comparing sporadic and familial adenomatous polyposis (FAP) related desmoid-type fibromatoses

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Abstract

Desmoid-type fibromatoses are neoplasms of fibroblastic origin, occurring sporadically or associated with familial adenomatous polyposis coli (FAP). By comparing sporadic and FAP-associated desmoid-type fibromatoses, we tried to identify clinical characteristics which may indicate FAP. Histopathology data of all Dutch patients with desmoid-type fibromatoses diagnosed between 1999 and 2009 were retrieved from PALGA, the nation-wide network and registry of histopathology in the Netherlands. For calculation of incidence rates, person years from the general matched population were used. Based on polyp counts in pathological records, the cohort was divided into a FAP group and a non-FAP group. Patient- and tumor characteristics were compared between the two groups. A total number of 519 patients older than 10 years with a confirmed diagnosis of desmoid-type fibromatoses were included. Thirty-nine (7.5%) desmoid patients were documented of having FAP. The incidences of sporadic and FAP-related desmoid-type fibromatoses were 3.42 and 2784 per million person-years, respectively. The majority of FAP patients developed desmoid-type fibromatoses after the diagnosis of FAP. Having FAP was associated with male gender (OR 2.0, $p=0.034$), desmoid diagnosis at an earlier age (mean 36 vs. 42 years, $p=0.031$), and desmoid localization intra-abdominally (OR 18.9, $p<0.001$) or in the abdominal wall (OR 4.8, $p<0.001$), compared to extra-abdominal desmoid localization.

In conclusion, patients with desmoid-type fibromatoses are at risk of underlying FAP.

Especially cases with desmoid localization intra-abdominal or in the abdominal wall, and all patients younger than 60 years, have a substantial increased risk and should be referred for colonoscopy.

Introduction

Desmoid-type fibromatoses, previously known as aggressive fibromatoses, musculoaponeurotic fibromatoses or desmoid tumors, is a rare neoplastic disorder with an unpredictable disease course. Histologically, these neoplasms are benign fibroblastic tumors consisting of spindle cells and fibroblasts with a low mitotic rate. Differentiation from other soft tissue tumors, for example low grade fibromyxoid sarcomas, can be difficult (1). Clinically, desmoid-type fibromatoses either presents as a solid tumor, located in muscles, or as diffuse fibromatoses in the mesentery. Despite the histological bland morphology, desmoid-type fibromatoses show locally aggressive features such as infiltration in surrounding tissue, and a tendency to recur after resection. Desmoids lack metastatic potential. The etiology of desmoid-type fibromatoses is thought to be multifactorial (1). Supposed risk factors are exposure to estrogens, trauma (associated with surgery or pregnancy), and a positive family history of desmoid-type fibromatoses (2,3,4,5).

Desmoid-type fibromatoses are rare in the general population with estimated incidence rates of two to four per million individuals per year (6). However, in patients with familial adenomatous polyposis (FAP), desmoid-type fibromatoses are reported in 10-30% (2-4,7,8-10), whereas about 10-20% of all patients with desmoids have FAP (12). FAP is a dominantly inherited colon cancer predisposition syndrome, caused by a germline mutation in the *APC* gene (13). FAP patients develop hundreds to thousands of colonic adenomas from a young age of onset. Without treatment, virtually all patients develop colorectal carcinoma by the age of 40-50 years (1,11).

Given their risk to develop colonic cancer, it is important to identify patients at high risk for FAP, and refer them for colonic examination. By this strategy, development of colorectal cancer can be prevented in patients and in their family members, by including them in screening programs.

The aims of this study were 1) to calculate incidence rates of sporadic and FAP-related desmoid-type fibromatoses and 2) to compare clinical characteristics of sporadic and FAP-related desmoid-type fibromatoses, to identify specific clinical features which are associated with FAP.

Methods

Patients and data collection

Pathology records of patients who were diagnosed with a desmoid-type fibromatoses between January 1, 1999 and January 1, 2009 were retrieved from the PALGA, the nationwide network and registry of histopathology and cytopathology in the Netherlands, which has nationwide coverage since 1991 (14). In this database, summaries of all histopathology and cytopathology reports of Dutch patients are collected and coded similar to the Systematized Nomenclature of Medicine Classification of the College of American Pathologists (SNOMED) (15). This database offers unique possibilities for studying true-pathology based incidence rates (16) or associations between biopsy-proven disease types (17). Handling of samples and data retrieval was according to the ethical guidelines “Code for proper secondary use of human tissue in The Netherlands” established by the Dutch Federation of Medical Sciences.

In order to obtain information on all Dutch patients with desmoid-type fibromatoses, a search was performed with the search terms “desmoid” and “aggressive fibromatoses”. The retrieved data included information on sex and age, place of birth, year of desmoid discovery, and additional pathological diagnoses. The retrieved pathologic reports also included the indication for the examination, i.e., information on the endoscopic findings. Inclusion criteria were 1) a diagnosis of desmoid-type fibromatoses between January 1, 1999 and January 1, 2009, and 2) age above 10 years. Cases suffering from superficial fibromatoses of the hands or feet (Dupuytren’s disease), and juvenile fibromatoses were excluded. The database was corrected manually for obvious miscoding. Records with a doubtful diagnosis of desmoid-type fibromatoses were discussed by the authors, one of which is an experienced soft tissue pathologist, and included if the diagnosis was revised to desmoid-type fibromatoses. Based on the information on colorectal polyps in pathology records of any date, and clinical background information given by the request to the pathologists, patients were divided into a “confirmed FAP” or a “non FAP” group. “Confirmed FAP” was defined as more than 10 colonic adenomas and/or duodenal polyps detected under the age of 60 years.

Desmoid localizations were categorized into three groups, defined as 1) at least mesenterial 2) abdominal wall and 3) extra-abdominal sites, including head, neck, trunk, back, gluteal region, arms and legs. Further variables were retrieved from the database, including sex, age at primary desmoid-type fibromatoses, desmoid size, and recurrence of desmoids. It was impossible to distinguish between recurrent and new primary desmoid-type fibromatoses by pathological records only. All other pathology records were categorized into one of the following groups of comorbidity: colorectal cancer, inflammatory bowel diseases (Crohn’s disease and ulcerative colitis), benign diseases of the skin (lipomas, epidermoid cysts, and

fibroadenomas), malignant diseases of the skin (melanoma, basal cell carcinoma, and squamous cell carcinoma), benign diseases of the genitourinary tract (prostate hypertrophy, uterine fibroids), malignant diseases of the genitourinary tract (cancer of the bladder and prostate, cancer of female reproductive organs), breast cancer, and hematological cancers.

Statistics

Incidence rates were calculated using data of the Dutch National Statistics Service (CBS) to estimate Dutch population numbers. In this database, population numbers are reported stratified per decade, sex, and different age groups. To calculate incidence rates, the time period 1999 - 2009 was used to calculate the denominator. Based on previous reports, the prevalence of FAP was set at one per ten thousand persons per year (18). This FAP prevalence was used to estimate incidence rates of desmoid-type fibromatoses in FAP patients. Clinical and tumor related characteristics were compared in patients with and without FAP by univariate analysis using chi-square and Fisher's Exact Test for categorical variables, and the unpaired t-test for numerical variables. Logistic regression was used for multivariate analysis. Statistical significance was set at a p-value of less than 0.05. Statistical analysis was performed using SPSS version 16.0.0 (SPSS Inc, Chicago, IL, U.S.).

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Results

Incidence of desmoid-type fibromatoses

A total of 519 patients met the inclusion criteria of this study. The Dutch population above 10 years of age comprised on average 14,015,356 persons between 1999 and 2009. Four hundred and eighty patients had sporadic desmoid-type fibromatoses, leading to an incidence of 3.42 per million person-years and a mean of 48 newly diagnosed patients per year in The Netherlands.

Assuming the FAP prevalence being 1/10.000, the FAP population comprised 1400 patients older than 10 years between 1999 and 2009. Thirty-nine patients developed desmoid-type fibromatoses, leading to an incidence of 2784 per million person-years and 4 diagnoses per year in The Netherlands FAP-population.

Compared to the general population, FAP patients have a more than 800-fold risk of developing desmoid-type fibromatoses.

Variables associated with FAP-related desmoid-type fibromatoses

Among the 519 desmoid patients, 39 (7.5%) FAP patients were identified. Thirty-three of these patients were diagnosed with FAP before the diagnosis of desmoid-type fibromatoses, whereas six patients developed FAP after a diagnosis of desmoid-type fibromatoses.

The comparison of patient characteristics between the FAP and non-FAP group is shown in table 1. Overall, more female than men were affected by desmoid-type fibromatoses. In the group with sporadic desmoids, 70% were female, and in the group with FAP-related desmoids 54% were female. An evaluation of the available pathology reports per patient showed FAP patients more often having colorectal cancer, compared to non-FAP patients. No statistical association was found between desmoid-type fibromatoses and other comorbid conditions.

Patients with FAP were significantly younger at the diagnosis of primary desmoid-type fibromatoses (mean age 36 vs. 42 years, $p=0.031$). Figures of age distribution of primary diagnosis of FAP-related and sporadic desmoids follow the same pattern, as shown in figure 1. FAP-related desmoids were found most often intra-abdominally (51%), whereas 50% of sporadic desmoids was located extra-abdominally. The odds ratio for a localization in the abdominal wall compared to extra-abdominal localizations was 4.76, whereas the odds ratio was 18.87 for intra-abdominal desmoid-type fibromatoses. In both the FAP and non-FAP groups, 38% and 37% of desmoid-type fibromatoses was located in the abdominal wall, respectively. In figure 2, the proportion of patients per desmoid localization is shown.

As desmoid localization, sex, and age showed statistical significance at univariate analysis, these variables were put into a logistic regression model (table 2). After adjustment, the odds for FAP was still statistically increased in male (odds ratio 3.25). Importantly, after adjustment for age and sex, the odds for FAP in abdominal desmoid-type fibromatoses was much higher than for extra-abdominal desmoids, with an odds ratio of even 23 for intra-abdominal desmoid-type fibromatoses.

Discussion

Desmoid-type fibromatoses are rare neoplasms, occurring either sporadically or in the context of FAP. In the present study, at least 7.5% of desmoid-type fibromatoses were associated with FAP. The calculated incidence of sporadic desmoids was 3.42 per million person years, whereas for the FAP population, the incidence was 2784 per million person-years. This shows that the risk to develop desmoid-type fibromatoses for a FAP patient is more than 800-fold increased. However, most of these neoplasms seen by surgeons and pathologists are sporadic ones, due to the relative low incidence of FAP. Factors which we found to be associated with FAP-related desmoids were male sex, age of desmoid development younger than 60 years, and desmoid localization intra-abdominally.

The incidence rates of sporadic and FAP-related desmoid-type fibromatoses, calculated in our cohort, resemble that of previous reports (9,6).

One previous study compared characteristics of sporadic and FAP-related desmoid-type fibromatoses (12), reporting 70 of 447 (16%) desmoid patients having FAP. In our study, a lower percentage (7.5%) of desmoid patients were found to have FAP. This difference may be explained by different ways of data collection. We used data from all Dutch hospitals, collected in a national pathology registry. Fallen et al. retrieved data from the Mayo Clinic, which is a tertiary care institution, to which generally the more complicated cases (mesenterial desmoids) are referred (12). Moreover, we may have under-estimated the incidence of FAP-related desmoid-type fibromatoses. First, there might be patients with an as yet undiagnosed FAP, presenting with sporadically-appearing desmoid-type fibromatoses. Furthermore, we might have missed FAP patients who have had colectomy before 1991, whose pathological records on colonic polyps were recorded incompletely.

Both in Fallens' study as in our study, women were more often affected by desmoid-type fibromatoses than men. This might be attributed to the influence of estrogens (4). However, as the sex difference in FAP patients was considerably smaller than in non-FAP patients, hormonal influences may be less important in FAP-related desmoids.

Although Fallen detected no significant differences in ages between development of desmoids in FAP and non-FAP settings, we found desmoid development on average six years earlier in FAP patients, compared to non-FAP patients. However, the age distributions of FAP-related and non-FAP-related desmoids show great similarity, making age as a discriminating factor to identify FAP unreliable for individual patients.

Although we categorized desmoid localizations slightly different than Fallen, in both studies the majority of FAP-related desmoid-type fibromatoses were located intra-abdominally, whereas the majority of sporadic desmoids were located extra-abdominally.

We also assessed tumor size and desmoid recurrence, both showing no significant differences between FAP and non-FAP groups. As expected, colorectal cancer was more common among the FAP patients. Despite the spectrum of extracolonic manifestations in FAP, including multiple benign skin lesions, comparable numbers of such lesions were observed in both groups.

Strengths of this study were the large number of cases with complete data, which were retrieved from the nation-wide PALGA database. This nation-wide coverage enhances the generalizability of the study results (19). A limitation of using this database was that only pathology reports and no colonoscopy reports were available. Information on *APC* mutation status and family history of desmoid-type fibromatoses and of colorectal cancer would have lead to a more exact estimation of the number of FAP patients (2,13,20,21). Various other potential predictive factors were not taken into account since these could not be extracted from pathology reports and tracing of these data was not compatible with ethical considerations. For example, previous pregnancy, exposure to estrogens, and surgical trauma are considered to be important risk factors for developing abdominal wall desmoids (5). In addition, we may have underestimated the number of FAP related desmoid-type fibromatoses, as biopsies are not always taken in these cases.

Identifying FAP patients has obvious clinical implications, not for the patient only but also for family members, who may be affected by FAP too. Due to hereditary cancer registrations, FAP is generally diagnosed early in life, and as shown in our study population, FAP is often diagnosed earlier than desmoid-type fibromatoses. However, about one-third of FAP patients has *de novo* mutations of the *APC* gene, being the first person in the family that is diagnosed with FAP. Furthermore, several previously published case reports show that there are still patients with apparently sporadic desmoid-type fibromatoses who were found to have FAP at further examination (22,23,24).

In conclusion, as at least 7.5% of desmoid-type fibromatoses are associated with FAP, the possibility of FAP should be considered in each patient presenting with desmoid-type fibromatoses. Based on our results, colonic examination is highly recommended in patients younger than age 60 years and patients with intra-abdominal or abdominal wall desmoid localizations. Of course, all patients should be asked for clues pointing to FAP, including abdominal complaints, rectal blood loss, and details of gastrointestinal disorders in the family. In the case of any suspicion of FAP, referral to a gastroenterologist is essential.

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Table 1 Patient characteristics compared for FAP and non-FAP groups, respectively.

	FAP yes N (%)	FAP no N (%)	Odds ratio	95% CI- interval	p- value
Total	39	480			
Sex					
Male	18 (46)	143 (30)	2.0	1.05-3.91	0.034
Female	21 (54)	337 (70)	1 (ref)		
Age at diagnosis of 1st DT (yrs)					
Mean (SD)	36.0 (12.9)	41.6 (15.8)		0.52-10.70	0.031
Age 1st DT, 10yrs categories (yrs)					
11-20	4 (10)	23 (5)	1 (ref)		
21-30	10 (26)	94 (20)	0.61	0.18-2.13	0.436
31-40	13 (33)	156 (32)	0.48	0.14-1.60	0.222
41-50	5 (13)	85 (18)	0.34	0.08-1.36	0.113
51-60	6 (15)	58 (12)	0.60	0.15-2.30	0.448
61-70	1 (3)	33 (7)	0.17	0.02-1.66	0.161*
71-80	0	22 (4)	N.E.	0.73-0.997	0.117*
81-90	0	9 (2)	N.E.	0.73-0.997	0.553*
Localization 1st DT					
At least intra-abdominal	19 (51)	61 (13)	18.87	6.17-58.82	<0.001
Abdominal wall	14 (38)	175 (37)	4.76	1.54-14.71	0.003
Extra-abdominal	4 (11)	238 (50)	1 (ref)		
Size of first desmoid (cm)					
Median (min-max)	7.0 (5-16)	7.0 (1-35)		-5.36-5.64	0.950
Mean (SD)	9.0 (4.5)	9.1 (6.6)		-5.84-6.12	0.963
Recurrent /new primary DT					
No	36 (92)	424 (88)	1.59	0.47-5.32	0.604*
Yes	3 (8)	56 (12)	1 (ref)		
Age of recurrent/new primary DT					
Mean (SD)	42.7 (10.7)	41.0 (14.0)		-18.2-14.8	0.837
Comorbidity					
Colorectal carcinoma	7 (18)	14 (3)			<0.001
IBD	2 (5)	42 (9)			0.763*
Benign skin disease	11 (28)	99 (21)			0.265
Malignant skin disease	0	28 (6)			0.256*
Benign GU-tract disease	2 (5)	59 (12)			0.297*
Malignant GU-tract disease	0	10 (2)			1.00*
Breast cancer	0	15 (3)			0.618*
Hematological cancer	0	4 (0.8)			1.00*

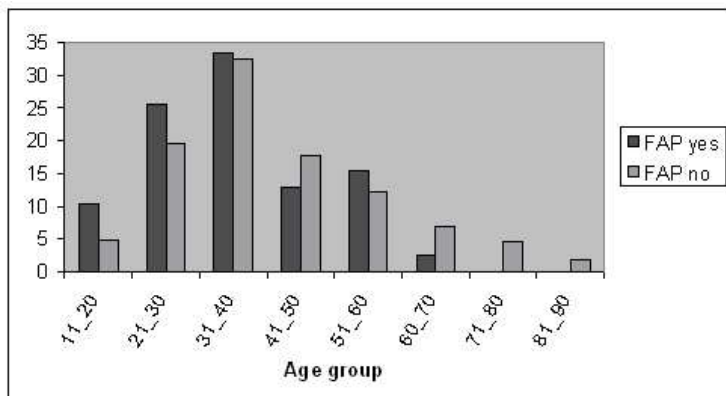
Abbreviations: FAP=familial adenomatous polyposis CRC=colorectal cancer DT=desmoid tumor IBD=inflammatory bowel disease GU-tract= genitourinal tract Ref=reference N.E.=not estimable

* Fisher's exact test

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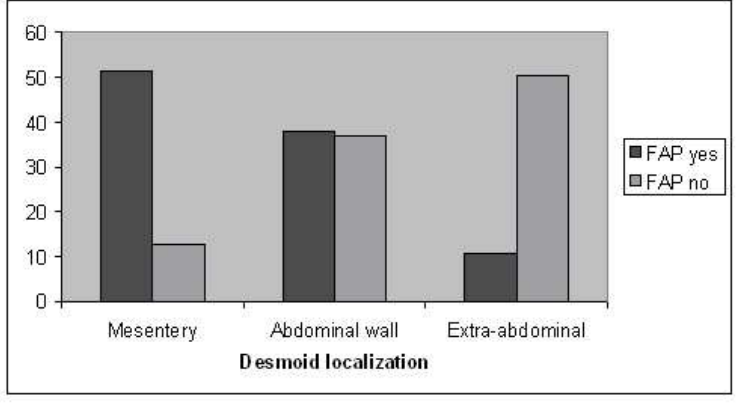
Table 2 Multivariate analysis with the risk of having FAP as dependant variable, and age of diagnosis of desmoid, localization of desmoid, and sex as covariates.

Variable	Odds ratio	p-value	95% confidence interval
Age (continuous)	0.95	0.002	0.92 – 0.98
Sex			
Male	3.25	0.007	1.38 – 7.67
Female	1 (ref)		
Localization desmoid			
At least intra-abdominal	23.22	0.000	7.21 – 74.75
Abdominal wall	6.70	0.002	2.00 – 22.43
Extra-abdominal	1 (ref)		



Proportion of patients per age group (10-year categories) having a primary diagnosis of desmoid-type fibromatoses, showing a mainly congruent age distribution between FAP and non-FAP patients.
175x161mm (96 x 96 DPI)

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Proportion of patients per desmoid localization, for FAP and non-FAP patients
175x161mm (96 x 96 DPI)