

Cancer mortality in relatives of desmoid sarcoma patients

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Summary

Desmoid sarcoma patients from the U.S. and Canada, diagnosed under the age of 16 years and referred to the University of Texas, M.D. Anderson Hospital - MDAH - between 1944 and 1975 were surveyed. Family information was collected for grandparents, parents, parental siblings, proband offspring and siblings.

Expected mortality was calculated by applying age-race-sex specific U.S. mortality rates to the person-years at risk. Standardized mortality ratio's - SMR- were calculated. Among 429 relatives of 26 desmoid sarcoma probands no overall cancer excess was found, observed/expected = 13/24.7. The risk among parents, the ones more informative for genetic analysis were also not significant, observed/expected = 2/1.83. An updated follow-up of incidence data of the study population and of the general population is suggested in the years to come, and in doing so, the inclusion of all family members history should pull the results to a number closer to reality.

Key Words: *desmoid sarcoma; relatives mortality in desmoid sarcoma*

Introduction

The term desmoid tumor is used to describe a curious neoplastic proliferation of a fibroblastic tissue with some features of both a benign fibroma and a malignant fibrosarcoma [2, 9, 11, 13, 16, 17, 23, 29, 39]. The presenting sign is a rapidly growing swelling. It does not arise from the muscle but rather from the musculoaponeurotic structure of the body [31]. Metastasis, if it ever occurs, is a rare event [10, 22, 28, 35, 36, 42, 44, 45] however, it is locally invasive and death may result from pressure on, or invasion of vital structures as in the neck or mediastinum [45, 55] where complete surgical excision, the recommended treatment [20, 21, 47], is impossible.

The two most common anatomic sites of DTs referred in the literature are the abdominal DTs, which can be internal or external but, in the abdomen area, and the extra-abdominal that is located in other parts of the body with some predilection to the shoulder, arm, thigh and buttocks [4, 7, 12, 24, 25, 33, 53, 54].

Trauma and endocrine imbalance have been reported as possible etiologic factors contributing to

the development of DT [27]. There is only one report suggesting that an inherited defect in growth regulation of the connective tissue is the underlying cause of DT [18]. References of histologically similar tumors or aggressive fibromatosis however, support the concept of a hereditary inherited tendency to fibroblast proliferation [3, 5, 14, 15, 19, 37, 51, 57-59]. Furthermore, studies of soft tissue sarcomas, a category which includes DT, have given reason to suspect such a relation [1, 8, 26, 30, 38, 40, 41, 43, 46, 48, 52, 56, 59]. If an inherited or mutant gene is involved in the etiology of malignant neoplasm and particularly of soft tissue sarcomas, a clustering pattern should be observed within families. We wished to test the association between DT and cancer mortality among family members of DT cases.

Materials and methods

All DT cases referred to the MDAH from 1944 to 1975 under 16 years of age at the time of onset were compiled. Patients from outside the United States and

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Canada, and adopted patients were not included. Twenty-six eligible cases were identified.

All parents of eligible patients were contacted by letter and asked to participate in an interview and provide information on the current health status of the patient family members. The questionnaire included date of birth, death and occurrence of tumors for the proband and his/her parents, siblings, half-siblings, aunts, uncles, grandparents and offspring. Cousins and other relatives were excluded due to the difficulty in ascertaining this information on all the families involved in this study. Relatives whose country of origin and permanent residence were outside the U.S. and Canada were excluded from the analysis.

The underlying cause of death was coded according to the Eighth Revision of the International Classification of Diseases - ICD-8- [34]. When a cancer death was reported in any of the relatives, death certificates along with existing medical records were obtained. Failure to verify the cause of death caused the reported cancer to be dropped from the analysis.

Person-years at risk were determined from the entry date - 1944 - to the date of death or date of study termination - 1980. Age-sex-year-specific U.S. cancer mortality rates for the period 1925-1979 were applied to generate the expected cancer death rates for each DT relative. Mortality rates from 1925 were used to compute the expected deaths for those entering the study prior to 1925. Those rates were considered the best available cancer data for that period. The SMR then, is the ratio of the observed number of deaths to the expected number of deaths. The 95% confidence intervals - CI - for the risk were determined by the assumption of a Poisson distribution for the numerator - observed number of deaths - and a constant denominator - expected number of deaths [6, 32]. We computed the attained significance levels - P-values - for the risks by taking the expected number of deaths as the Poisson parameter and assessing the probability of the Poisson distribution tail area defined by the observed number of deaths [32]. We computed tests of significance between risks by using normal distribution approximations considering the relative risk as a Poisson variate divided by a constant.

Results

A significant deficit of overall cancer mortality was observed, O/E = 13/24.7. Other studies have reported similar deficits of deaths in the overall run [41]. No deficit of cancer deaths among parents of the cases however, was observed, O/E = 2/1/83 95% CI = 0.12 - 3.92.

We had a total number of 53 reported cancers among DT relatives of which 19 were non-confirmed cancers. Fourteen referred to cancer deaths and 5

referred to cases of cancer. Of the 14 non-confirmed cancer deaths 10 referred to cancers occurring in cousins and other relatives.

Of the 35 cancer deaths reported, 25 occurred in first or second degree relatives, those relatives for which information was collected systematically for every kindred. Of those 4, not confirmed deaths and one cancer death of a mother half-sibling were excluded from the analysis making 20 eligible deaths. From those 20 eligible cancer deaths, only 13 were considered in this study and refer to the cancer deaths that had death certificates stating cancer as cause of the death. The decisions taken here might seem unreasonable for that we perpetuate the inaccuracies in the report of cause of death in death certificates, despite the fact that we have available the pathology reports of the seven cases left out. Those inaccuracies however, are thought to be also present in the general population rates used to generate our expected rates.

The most frequent cancer site among DT relatives was cancer of the lung, five cases or deaths, followed by three cases or deaths of stomach cancer, three of cancer of the prostate, two of the bladder, one of cancer of the sigmoid, one the rectum, one of the cecum, one of the pancreas among other sites. Six families had no cancer history and 18 first line relatives have had benign fibromatosis reported.

Discussion

Since there was no excess cancer mortality we did not pursue the analysis any further and could say that there is no indication in this data set of a genetic causation for the desmoid tumors.

The sample size - 26 kindreds - may be too small to have included the *congenital* form of DT, which is, genetically very interesting. The extreme rarity of desmoid tumor mostly contributed for this, given that only 26 cases were accumulated in a fairly large period of time, 31 years. Genetic mutations on the other hand, are rarely detected even in established known hereditary tumors. An excess of cancer risk would then be expected only in a few kindreds. Therefore, to increase the chance of detecting a cancer risk, additional kindreds is needed and highly recommended. The fact that not all reported deaths could be verified plus the exclusion of deaths of cousins and other distant relatives, added with the above comments, may have influenced the deflated results seen here. Finally, the need for a more detailed family history such as information about polyposis coli, palmar and plantar fibromatosis and thickening of the tendons among family members of DT cases and the frequency of those neoplastic processes in the general population, appear to be first priority in future research.

Table 1. Cancer mortality in relatives of DT patients

Relation	N	Obs.	Exp.	O/E	LL	UL	Support	Person-years	P-value
Sib	63	0	.1795	.0000	.0000	20.4319	-.1795	1697.9	***
Father	26	1	1.0264	.9742	.0127	5.4206	-.0003	691.9	***
Mother	26	1	.8131	1.2299	.0161	6.8431	-.0200	724.3	***
Father-sib	86	3	4.5295	.6623	.1331	1.9352	-.2935	4736.4	***
Mother-sib	75	5	3.4397	1.4536	.4684	3.3922	-.3100	3894.1	***
P G-father	26	1	3.4502	.2898	.0038	1.6126	-1.2118	994.6	***
P G-mother	26	0	3.6405	.0000	.0000	1.0076	-3.6405	1206.3	***
M G-father	26	2	4.3062	.4644	.0522	1.6769	-.7724	956.5	***
M G-mother	25	0	3.3748	.0000	.0000	1.0869	1136.6	***	***
P half-sib	3	0	.0289	.0000	.0000	127.0796	-.0289	105.4	***
M half-sib	8	0	.0135	.0000	.0000	270.9450	-.0135	181.2	***
Offspring	17	0	.0048	.0000	.0000	766.6413	-.0048	84.2	***
All others	10	6	.7808	7.6844	2.8060	16.7263	-7.0160	497.9	.00016
Total	29	20	25.9909	.7695	.4698	1.1885	-.7506	17537.6	00016

Relation	N	Obs.	Exp.	O/E	L	UL	Support	Person-years	P-value
Sib	63	0	.1795	.0000	.0000	20.4319	-.1795	1697.9	***
Parents	52	2	1.8395	1.0873	.1221	3.9255	-.0068	1416.2	***
Parent-sib	161	8	7.9692	1.0039	.4322	1.9781	-.0001	8630.4	***
G-parents	103	3	14.7717	.2031	.0408	.5934	-6.9894	4293.9	.00025
Offspring	17	0	.0048	.0000	.0000	766.6413	-.0048	84.2	***
Total	396	13	24.7647	.5249	.2792	.8977	-3.3866	16122.7	.00730

Resumo

Pacientes menores de 16 anos, com diagnóstico de sarcoma do tipo desmóide atendidos no Hospital M.D. Anderson da Universidade do Texas pelo período de 1944 e 1975, foram revistos.

A mortalidade esperada foi calculada aplicando-se as taxas de mortalidade específicas por idade, raça e sexo dos Estados Unidos sobre a mortalidade pessoa/ano de risco observado. A razão da mortalidade padronizada - SMR - foi computada.

Para o conjunto dos 429 parentes dos 26 casos de sarcoma do tipo desmóide aqui analisados, não foi encontrado excesso de mortes, observado/esperado = 13/24.7. O risco dos pais terem câncer também não foi significativo, observado/esperado = 2/1.83. Esses resultados são indicativos de que as taxas de mortalidade por este tipo de tumor, tanto para este grupo particular de famílias como para a população em geral, não são os parâmetros adequados para estudar fatores hereditários e ocorrência de tumores desmóides. Sugere-se a comparação de taxas de incidência de tumores benignos em tecidos moles entre os membros da família dos casos com as taxas destes mesmos tumores na população em geral.

Unitermos: sarcoma desmóide; mortalidade de parentes no sarcoma desmóide

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