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Familial Ovarian Carcinoma

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ABSTRACT

Familial aggregation of patients with ovarian carcinoma is unusual. A family with four affected members in three consecutive generations is described. The tumors were all of the serous papillary adenocarcinoma type. The pattern of appearance of the malignant disorder in the present family may be explained as the result of transmission of a dominant mutant autosomal gene. The future long term management of such a family might include prophylactic oophorectomy in certain family members, and possibly selective terminations of pregnancies with female fetuses in high-risk women.

INTRODUCTION

Familial aggregation of patients with ovarian adenocarcinoma is unusual. Thus, only three cases with affected near relatives were observed in a study of 110 patients with ovarian cancer (5).

So far only seven families have been described, where ovarian adenocarcinoma has been present in two consecutive generations (1, 2, 3, 4, 6).

We here describe a family with serous papillary adenocarcinoma of the ovary present in four family members belonging to three consecutive generations, suggesting the transmission of a mutant dominant gene as a possible cause of this site-specific cancer.

METHODS

All affected members of the present family have been investigated and treated at the Department of Obstetrics & Gynaecology, University Hospital, Uppsala, where the first case appeared in 1925. Histopathological diagnosis were obtained by analyses of pathology specimens derived from operations and post mortem autopsies.

FAMILY HISTORY

Relevant family data and medical histories appear from the pedigree (Fig. 1) and Table I.

CASE REPORTS

I: 1. The patient was admitted after six months of symptoms including abdominal distension. A large pelvic mass was present. At operation, bilateral ovarian tumors with papillary projections were observed together with general engagement of adjacent tissues. She died at the age of 47.

II: 2. This patient was originally seen because of a large pelvic mass, subsequently found to consist of large bilateral cysts which were radically removed. Three years later and despite cytostatic treatment, the patient died from a recurrent tumor with ascites after a short course. She died at the age of 55.

III: 3. This patient was admitted after two weeks of abdominal distension with a large pelvic mass present. Laparotomy revealed wide-spread abdominal carcinosis of ovarian origin. Cytostatic therapy did not prevent her death six months later at the age of 45.

III: 6. Chest symptoms of nearly one year's duration brought this patient to attention, and she was found to have pleural effusion and metastatic lung tumors. By means of fineneedle biopsy a large pel-

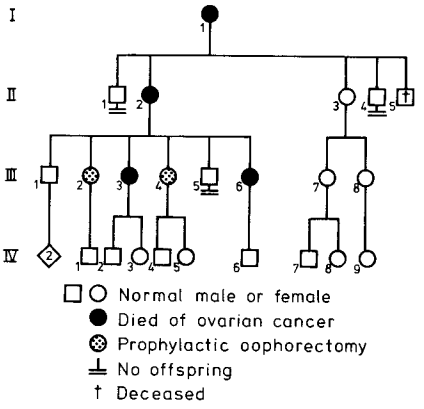

Fig. 1. Pedigree of a family with ovarian cancer.

Table I. *Clinical and histopathological data on six members of a family with ovarian adenocarcinoma*

	Age at first admission	Histopathologic diagnosis of the tumor	Type of therapy	Duration until fatal outcome
I: 1	47	Papillary serous adenocarcinoma	Operations and radiation therapy	<1 year
II: 2	51	Papillary serous adenocarcinoma	(1) Bilateral salpingo-oophorectomy+radiation therapy; (2) Cytostatic therapy	3½ year
III: 3	45	Papillary serous adenocarcinoma	Operation+cytostatic therapy	6 months
III: 6	38	Papillary serous adenocarcinoma	Cytostatic therapy	7 months
III: 2	46	Normal ovarian tissue	Prophylactic bilateral oophorectomy	–
III: 4	41	Normal ovarian tissue	Prophylactic bilateral oophorectomy	–

vic mass also present was found to consist of ovarian papillary adenocarcinoma. She died seven months later after several courses of cytostatic treatment at the age of 38.

III: 2&4. Due to the family history these two sisters demanded prophylactic oophorectomy to be performed, and their ovaries were found to be histologically normal.

II: 3. This 66 year old sister of II: 2 is still healthy, and no pathological findings have been demonstrated at repeated gynecological examinations.

III: 7&8. These two daughters of II: 3 are 45 and 41 years respectively. They are both in good general condition. Additionally IV: 8 has recently been found to be normal at gynecological examination.

DISCUSSION

In the present family all affected members suffered from papillary serous adenocarcinoma. This type of ovarian malignancy also seems to have been prevailing in the previously reported families (1, 2, 3, 4).

The probability of familial association of this site—specific malignancy by chance, has been regarded as extremely remote, and other explanations must therefore be considered. The appearance of the same type of rare disorder in consecutive generations suggests the possibility of transmission of a dominant autosomal gene according to the Mendelian laws of inheritance.

The family patterns reported by Liber (4), Lewis & Davison (2), Li et al. (3), Lynch & Krush (6) and Fraumein et al. (1) as well as in the present family are consistent with such an explanation. However, a polygenic mode of inheritance must also be considered.

In other families with aggregation of affected sibs as described by McCrann et al. (7) and Fraumein et al. (1), transmission of rare recessive genes might explain the findings, though genetic transmission of the disease could not be proven.

If mutant genes sometimes may be of importance in the etiology of malignant ovarian disease, they may of course differ with regard to mode of expression and transmission.

Li et al. (3) reported a large kindred, where a phenotypically normal male might possibly have transmitted a mutant gene, to his two daughters affected by abdominal carcinomatosis with unknown, primary site. So far there are no other reports on suggested male transmission of mutant genes for ovarian malignancy. Neither are there any reports on males affected with gonadal carcinoma as a result of suggested inheritance of mutant genes.

The clinical management and counselling of families with several affected members must therefore be based on thorough considerations of all family data available for each specific family.

In the present kindred, the malignant ovarian disorder has been restricted in its appearance to descendants within one of the two "female" branches of the family, i.e. in II: 2 and her offspring, while II: 3 and her progeny have so far escaped the disease. This finding is consistent with an inheritance pattern of a dominant mutant gene, where

II: 3 may be a non-carrier of the mutant gene. Evidences in favor of such an interpretation are her present health condition together with her present age, which seems to be beyond the actual risk period within which the affected members of the family were taken ill. If II: 3 is a non-carrier, her two healthy daughters and their progeny may be considered not to be at risk. Regular clinical controls have been recommended for III: 7 and III: 8. Surgical intervention has for the moment not been considered necessary.

In the affected family branch, III: 2 and III: 4 had their ovaries removed prophylactically without histological signs of malignancy. There are two female descendants, IV: 3 and IV: 5, 8 and 17 years old respectively, who may be considered to be at considerable risk. These two females will require regular and thorough clinical controls until they have the number of children they want, when prophylactic oophorectomy may be indicated.

For the long term management of the present family it must be taken into consideration that only female members have been affected, and are likely transmittors, and that, so far, there is no evidence of male transmission of the alleged mutant gene. Prenatal sex determination and selective abortion of female fetuses in future pregnancies of IV: 3 and IV: 5 could therefore possibly reduce the rate of long term anguish for having in fact "affected" female offspring. Should it be, that male members of the present family do not transmit the genes for this disorder, then selective termination of pregnancies with female fetuses may in addition help to eventually eliminate the adverse gene from this family.

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