

Familial ovarian cancer: report of ovarian carcinoma in three sisters

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SUMMARY

This is a report of ovarian carcinoma occurring in two sisters diagnosed almost at the same time, prompting prophylactic oophorectomy in a third sister. Histology of the overtly normal ovary in the third sister showed a focus of ovarian cancer. Discussion and a review of the literature suggest that any program designed to reduce the incidence of late-stage ovarian carcinoma should include the surveillance of family members of the index case, including the performance of prophylactic oophorectomy in the unaffected members of the family after they have completed their families.

Introduction

Evidence consistent with a prominent role for genetics in cancer aetiology has rapidly accrued in the past two decades. This has led to the identification of an increasing number of hereditary cancer syndromes including those involving the ovaries (1,2). The time lag between recognition of genetic involvement and the clinical application of this knowledge is of particular concern, especially for ovarian carcinoma because of the usual advanced stage at diagnosis and the dismal therapeutic outcome.

In recent years, carcinoma of the ovary has been increasing in frequency, particularly in the western world, making it one of the most lethal malignant diseases of women. At the Port Moresby General Hospital (PMGH), ovarian cancers form 30% of all gynaecological cancers and they are almost always diagnosed very late resulting in a very low 5-year survival rate.

In several large families breast and ovarian cancers appear as a dominant hereditary trait. It has been estimated that in women who report ovarian cancer in one or more sisters or in their mothers, the risk of developing ovarian cancer

by the age of 65 years is 4.4% and the life-time risk is 9.4%. This is in comparison with the risk in the total population of 0.8% (3).

We report on two sisters who were admitted with advanced ovarian carcinoma almost simultaneously and a third sister who underwent prophylactic oophorectomy which revealed a focus of cancer at histology.

Case 1

The patient was a 53-year-old para 6 (three daughters) who presented with a three-month history of abdominal swelling and discomfort. Examination showed a markedly tense and distended abdomen which on ultrasound examination revealed massive ascites associated with a multiloculated cystic mass with solid areas suggestive of ovarian carcinoma. At laparotomy, bilateral oophorectomy, omentumectomy and debulking of the tumour was performed. Hysterectomy could not be performed because of dense adhesions in the pelvis. The histological diagnosis was high-grade papillary serous ovarian carcinoma with vascular invasion. She was started on combination chemotherapy consisting of cisplatin and chlorambucil.

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Case 2

This patient was the second sister. She was a 50-year-old para 4 (two daughters). She presented with a two-week history of vaginal bleeding associated with lower abdominal pain. Examination revealed a large abdominal mass which on ultrasound examination showed a complex multiloculated cystic mass suggestive of ovarian malignancy. Exploratory laparotomy was performed but the growth was so extensive that no operation could be performed. Histology also showed high-grade papillary serous carcinoma of the ovary with metastasis in the omentum. She was started on combination chemotherapy. She died a year later.

Case 3

This patient was the third sister. She was a 43-year-old para 4 (one daughter). She was advised to undergo prophylactic oophorectomy. The ovaries looked normal clinically but at histology they were reported on as follows. "The left ovary is normal but there appears to be a focal tumour in the right ovary. The cells are round to oval with amphophilic cytoplasm and prominent nuclei. There is no breach of the ovarian parenchyma but the tumour cells almost reach the surface. The exact histogenesis is not clear. The pattern does not conform to that of a metastatic tumour. In view of the history it appears to be an early primary tumour. Sex cord stromal tumour of indeterminate type is a possibility." She is currently on long-term follow-up.

Family history

Extensive questioning of our patients and other members of the family did not reveal any relatives with breast or ovarian cancer. It has to be said, however, that eliciting such history is very difficult in our population. This is basically due to limited education, the incomplete recording of cause of death and the almost universal absence of autopsies to help establish cause of death.

Discussion

One of the clinically useful hallmarks of hereditary cancer is its predictability, particularly of specific targeted organs, a factor

which can be used by the physician to identify relatives who are at increased risk for cancer (1,4-6). However, there are many difficulties in documenting genetic mechanisms and delineating hereditary cancer syndromes in humans. The absence of premonitory physical stigmata, absence of biomarkers of sufficient sensitivity and specificity to the cancer-prone genotype, non-paternity, limited family size, differences in sex ratios (predominance of the male sex would obfuscate identifying the genetic significance of female cancers) and reluctance of patients to partake in studies all contribute to the difficulties.

Cancer of the ovary is a major public health problem. Any progress in its control would require identification of its aetiology and effective surveillance and diagnostic measures for its early detection. The hereditary role for breast and ovarian cancer is now well recognized and in some countries this recognition has led to the creation of registries of familial ovarian cancer (4,7,8).

Hereditary ovarian neoplasms have an association with several familial precancer disorders. Examples are mixed gonadal dysgenesis (with XO/XY mosaicism) associated with gonadal germ-cell tumours in general; and Peutz-Jeghers syndrome associated with granulosa cell tumours and papillary adenocarcinoma. Ovarian carcinoma is also an integral lesion of the Lynch syndrome II (ovarian, breast, colorectal and endometrial cancers) (9,10).

The majority of familial ovarian cancers are high-grade, serous, papillary carcinomas which are usually detected when they are already at an advanced stage, as was found in our first two patients. Moreover, it has been shown that the age of onset is earlier than in patients with no family history of ovarian cancer (11). The nature of the gross lesions in ovaries removed for prophylaxis do not necessarily show specific characteristics for identification of malignant potential.

Detailed questioning of our patients concerning history of other cancers in the family did not indicate any. However, many workers have suggested that the breast-ovarian cancer syndrome is transmitted as an autosomal dominant trait with both father and

mother capable of transmitting the gene. These cancers have been linked to chromosome 17(17q12-q23) and the gene identified as BRCA 1 (2,12). On the other hand, hereditary site-specific ovarian cancer is rare, accounting for 5% of all malignancies (13). The inheritance is not fully understood but presumably it is heterogenous. It has been estimated that in families with two first-degree relatives (ie, mother, sister or daughter) with documented epithelial ovarian cancer the risk that a female first-degree relative will have an affected gene could be as high as 50% and, as mentioned earlier, the life-time risk of developing ovarian cancer is about ten times more than in the general population (3,14).

In view of the fact that this aggressive cancer may be genetically transmitted, women members of ovarian-cancer-prone families, particularly those who have one or more affected first-degree relatives, should be under strict surveillance and thoroughly educated about the natural history, genetics, surveillance and management of the condition. Annual pelvic examinations and ovarian ultrasound form the basis of this surveillance. Vaginal ultrasound has a higher positive predictive value than abdominal ultrasound. These methods, in combination with serum assays of CA-125 and other tumour markers, merit investigation. The patients need to be cautioned, however, about the limitations of this exercise.

Considering the fact that there is a strong correlation in the ages at death from ovarian cancer among sisters (15), prophylactic oophorectomy combined with hysterectomy for these women at high risk for ovarian cancer should be seriously considered in the overall management of this malignancy, especially in our community. We are aware that the benefits of this operation have not been fully evaluated; however, the facilities for adequate follow-up of patients in our practice are limited. We are not able to perform many biochemical tests and we do not have vaginal ultrasound facilities to mount an effective surveillance for ovarian neoplasia. These limitations equally apply to other gynaecological cancers. We believe therefore that the policy of hysterectomy and oophorectomy in these patients at high risk is reasonable. But when making this recommendation, it is mandatory that we make

patients aware of the possibility that adenocarcinoma of ovarian origin may arise directly from extraovarian pelvic mesothelium in the face of histologically normal ovaries excised at prophylactic oophorectomy. In addition, the timing of such an operation should be carefully considered in view of the well-known complications of surgically induced early menopause such as osteoporosis and cardiovascular disease. We have asked the six daughters of these patients to come for a discussion on this matter.

Above all, the main purpose of this presentation is to draw the attention of medical workers to the fact that part of the management of some cancers, and particularly ovarian cancers, is to seek information on the family members and to take appropriate measures to minimize the impact of the burden of this cancer on families and on society in general.

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