Familial cluster of ovarian small cell carcinoma: a new mendelian entity?

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Abstract

We report a pedigree in which three sisters had a particular type of ovarian cancer, small cell carcinoma of the hypercalcaemic type. This rare type of ovarian carcinoma is now well characterised by clinical and pathological findings and is well distinguished from other ovarian epithelial tumours and ovarian germ cell tumours. The occurrence of this rare type of cancer in several members of the same family and the existence of four other similar published observations raises the question of the genetic determination of this kind of tumour.

(J Med Genet 1996;33:333-335)

Key words: familial cluster; ovarian small cell carcinoma.

Ovarian small cell carcinoma of the hypercalcaemic type is rare and was first described in 1982.¹ Identification of this cancer is based on histological and clinical criteria; it is a tumour which occurs in young women, is almost always unilateral, and is associated in about 2/3 of cases with paraneoplastic hypercalcaemia in the genesis of which the secretion by the tumour cells of parathyroid hormone related protein has been suggested.² The most common microscopic pattern is a diffuse sheet of cells punctuated by a variable number of follicle-like spaces. The neoplastic cells are typically small and round with hyperchromatic nuclei and high mitotic activity, but 50% of

the tumours show a large cell component. Prognosis is very poor. In this paper, we report one such a tumour in three sisters in a family of 11 sibs (family pedigree shown in fig 1). This report raises the issue of specific genetic determination to account partially at least for this type of ovarian cancer.

Case reports

Patient III-25 was a young woman who, in February 1976 at the age of 19, became pregnant and presented with an abnormally increased abdominal girth for gestational age. Physical examination showed the presence of a large mass in the right iliac fossa and the hypochondrium. Laparotomy showed a tumour of the right ovary with apparently limited extension, since the liver, peritoneum, and left ovary were not involved. Simple salpingo-oophorectomy with omentectomy was performed to remove the tumour. Histological examination led to a diagnosis of "anaplastic carcinoma of the ovary". The tumour recurred three months after surgery and the patient died shortly thereafter. It was not possible to re-evaluate the histology slides. However, the description of the tumour given by the pathologist at the time was highly suggestive of small cell carcinoma of the ovary, hypercalcaemic type. The pathologist's report mentioned that, in places, the tumour cells "were spread out from each other, forming cavities congested with an albuminous coagulum", which corresponds to the follicle-like pattern usually observed in this

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Received 10 October 1995
Revised version accepted
for publication
30 November 1995

Figure 1 Pedigree of the family. Pul=pulmonary cancer, Br=breast carcinoma, Ov=small cell carcinoma of the ovary. Third line: age onset.

Figure 2 Patient III-30: proliferation of small cells with frequent mitoses (HES).

Figure 3 Patient III-31: large cell component with follicle-like pattern (HES).

type of tumour. We do not have data on this patient's serum calcium levels.

Patient III-30 was a 14 year old girl in whom, in November 1979, a palpable mass, confirmed by x rays of the abdomen, was discovered in the right iliac fossa following regressive episodes of abdominal pain of about three months' duration. Laparotomy showed a large isolated tumour of the right ovary, with no adhesions or abnormal peritoneal formations. Simple oophorectomy was performed to remove the tumour. Histological analysis led to a diagnosis of "undifferentiated carcinoma", but the precise histological type was not determined. Routine monitoring of this patient was initiated. Five months later, a massive abdominal relapse occurred which, despite chemotherapy, resulted in death two months later. Re-evaluation of the histology slides established the diagnosis of small cell carcinoma of the ovary, hypercalcaemic type (fig 2). Calcium levels during the relapse period remained normal.

Patient III-31 was a 28 year old woman in whom pelvic ultrasonography performed in May 1994 to evaluate a painful abdominal syndrome showed a right ovarian cystic formation, 88 mm in diameter. A previous ultrasound examination performed three months earlier had been normal. Simple right salpingo-oophorectomy was performed for diagnostic purposes. The diagnosis of small cell carcinoma of the ovary was established following histological analysis which showed a diffuse proliferation of small and large cells arranged in sheets, cords, and follicle-like structures. The large cells had an eosinophilic cytoplasm and a pale nucleus containing a prominent nucleolus (fig 3). Immunohistochemical stainings were partially positive for cytokeratin and vimentin and negative for alphafetoprotein, chromogranin, desmin, placental alkaline phosphatase, and smooth muscle actin. No initial hypercalcaemia was observed. Treatment consisted of another surgical procedure, extended total hysterectomy with omentectomy, followed by chemotherapy. This patient died within four months owing to a recurrence of the abdominal tumour.

Three other cases of malignant tumour had been reported in this family pedigree, all on the paternal side. Patients I-2 and II-3 were men known to have died from lung cancer at the ages of 73 and 55 years respectively; both

were smokers. Patients II-6, a woman, developed breast carcinoma at the age of 54 years.

Discussion

Familial forms of ovarian cancer, first reported in twin sisters in 1929,³ have frequently been reported since then and have been recorded since 1981 in the Gilda Radner registry of cases of familial ovarian cancer.⁴ Genetic determination of these familial clusters was fully confirmed by the demonstration of a genetic link between site specific familial clusters of ovarian cancer and the BRCA1 locus,⁵ which had just been implicated in a subset of familial forms of breast cancer⁶ and in the majority of breast-ovary syndromes.⁷ In our case, the presence of three cases of ovarian cancer and one case of breast cancer in a given family line is suggestive of a breast-ovary syndrome. However, the histological types observed in breast-ovary syndromes are represented almost solely by little or moderately differentiated serous cystadenocarcinomas⁸ and to the best of our knowledge no case of small cell carcinoma has been reported in these families. Furthermore, even though age at onset of ovarian cancer in breast-ovary syndromes is earlier than in sporadic forms (mean age 52.4 *v* 59 years),⁹ this type of tumour occurs at a much later age than small cell carcinoma, where mean age at onset is 24 years.¹⁰ A few cases of familial forms of ovarian tumours have been described in young girls and adolescents, but those tumours were germ cell tumours, such as mature teratoma^{11,12} or malignant germ cell tumour.¹³⁻¹⁵ Similarly, ovarian tumours occurring in the Peutz Jeghers syndrome¹⁶ or in gonadal dysgenesis^{17,18} are well characterised clinical entities.

It is only recently that ovarian small cell carcinoma of the hypercalcaemic type has been described. About 200 cases have been published¹⁰ since publication of the first series in 1982.¹ This tumour occurs in adolescents and young adults, between the ages of 9 and 43, and its symptoms usually include abdominal pain and abdominal swelling. The tumour presents as an adnexal mass, is unilateral in almost all cases, and is accompanied by paraneoplastic hypercalcaemia in 2/3 of cases, but not in our patients. The diagnosis is based on a histological pattern characterised by diffuse mul-

tiplication of small cells sometimes arranged in cords or nests or as isolated cells with a variable number of follicle-like spaces. Half of these tumours have a large cell component with an eosinophilic cytoplasm and a pale nucleus containing a prominent nucleolus. Prognosis is dismal, with almost inevitable progression to death within a few months for all stages beyond stage Ia. For stage Ia, survival has been reported to be 33% with an average 5.7 year survival rate.¹⁰ In the three cases we report here, age at onset, rapid fatal outcome, and microscopic pattern of the tumours are characteristic of a diagnosis of small cell carcinoma of the ovary, hypercalcaemic type. As far as we know, our case report is the fourth reported case of a familial form of this type of tumour. A case involving two first cousins, 10 and 22 years of age respectively, has been reported,¹⁹ but their exact degree of kinship and especially the sex of the parents belonging to the same sibship were not specified. In an important review of 150 cases, Young *et al*¹⁰ reported a case similar to ours where three sisters were involved. Remarkably, these three patients presented with bilateral ovarian tumours which is in favour of a genetic predisposition. These same investigators reported that the mother of one of the patients in their series had died at 31 years from "ovarian carcinoma" but the histology slides could not be re-evaluated to determine the precise type of tumour. Lastly, one recent case reported such a cancer in a mother and daughter, aged 40 and 21 years respectively.²⁰ It is of course impossible to confirm genetic determination in such a small number of familial cases. However, because of the rarity of the tumour and its recent identification, familial forms may have gone unrecognised and may in fact be more frequent. Also, because of the early age at onset and the commonly fatal outcome, in case of genetic determination and dominant pattern of inheritance, familial clusters of cases will be rare. If we assume that genetic determination is involved, our case and that reported by Young *et al*¹⁰ in three sisters, apart from other involvement in parents and relatives, could be compatible with transmission of an autosomal recessive trait. However, this mode of transmission is unusual in syndromes with genetic predisposition to cancer and the two cases involving two first cousins¹⁹ and a mother and daughter²⁰ tend to

support an autosomal dominant mode of inheritance.

These few cases lead us to believe that, in addition to familial forms of epithelial cell tumours of the ovary, especially those related to BRCA1 and familial forms of germ cell tumours, there exists a distinct category of familial ovarian tumour corresponding to a specific histological type, the small cell carcinoma of the hypercalcaemic type. A large number of cases will be needed to support the hypothesis that these familial clusters of cases may be genetically determined.

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