Histogenesis of ovarian malignant mixed mesodermal tumours

T J Clarke

Abstract

The histogenesis of ovarian malignant mixed mesodermal tumours, which includes the concept of metaplastic carcinoma, is controversial. Four such tumours were examined for evidence of metaplastic transition from carcinoma to sarcoma using morphology and reticulin stains. Consecutive sections were stained immunohistochemically using cytokeratin and vimentin to determine whether cells at the interface between carcinoma and sarcoma expressed both cytokeratin and vimentin. There was no evidence of morphological, architectural, or immunohistochemical transitions from carcinoma to sarcoma in the four tumours studied. This suggests that ovarian malignant mixed mesodermal tumours are not metaplastic carcinomas but are composed of histogenetically different elements.

Ovarian malignant mixed mesodermal tumours are rare neoplasms that arise typically in nulliparous, postmenopausal women. Recently they have been referred to as “mixed Mullerian tumours of high grade malignancy” or as “carcinosarcomas”. The prognosis is bleak and most patients die within 12 months of presentation. Theories concerning the histogenesis of malignant mixed mesodermal tumours of the female genital tract have been described as “a matter of art rather than of science”. The same theoretical problems concerning histogenesis are encountered with “carcinosarcomas” at other sites such as breast, lung, colon, and urinary bladder. It has been suggested that ovarian malignant mixed mesodermal tumours are “metaplastic carcinomas” in which the sarcomatous component (homologous and heterologous) arises directly from the carcinomatous component (usually glandular in type). The concept of metaplastic carcinomas differs from that of carcinosarcomas, which are regarded as heterogeneous tumours of combination, composition, or collision in type. This study was undertaken to investigate whether there were morphological, cytarchitectural, and immunohistochemical transitions from carcinoma to sarcoma in ovarian malignant mixed mesodermal tumours.

Methods

Sections of formalin fixed, paraffin wax embedded tumour tissue were cut at 4 μm and stained with haematoxylin and eosin, periodic acid Schiff (PAS) before and after diastase treatment, Caldwell and Rannie’s reticulin stain, and phosphotungstic acid haematoxylin (PTAH). Sequential sections were stained by the indirect immunoperoxidase technique using monoclonal antibodies directed against cytokeratin (PKK1 which reacts with low molecular weight cytokeratins of 44, 46, 52 and 54 kilodaltons), vimentin, α1-antitrypsin and myoglobin. Appropriate positive and negative controls, with omission of specific antisera in the latter, were performed. Haematoxylin and eosin stained sections were examined for secondary fluorescence using a Leitz Dialux 20ES microscope and mercury vapour light source epifluorescence. Four patients, aged 68, 71, 72 and 73 presented with abdominal distension and discomfort and were found to have an ovarian malignant mixed mesodermal tumour of at least FIGO stage III. Three of the women were nulliparous and the parity of the fourth was not known. Three died within one year of operation and one was alive and free from disease nine years after surgery. None of the patients received radiotherapy or chemotherapy after surgery. Necropsy was performed in one patient who died eight days after operation. This case has been reported previously.

Histopathology

The tumours were all large at initial presentation, ranging from 15 to 22 cm in maximum diameter. Three were typical, solid, and cystic ovarian malignant mixed mesodermal tumours composed of a haphazard mixture of adenocarcinoma and undifferentiated sarcoma (fig 1), with heterologous elements of rhabdomyosarcoma in one and chondrosarcoma in another. The tumour in the fourth case was a unilocular serous cystadenocarcinoma containing several discrete intramural sarcomatous nodules up to 2.5 cm in diameter and a 5-5 cm in diameter fibroma. At necropsy a separate metastatic spread of carcinoma and sarcoma was found; para-aortic lymph nodes contained metastatic squamous cell carcinoma and the liver contained deposits of sarcoma including rhabdomyosarcoma. There was no evidence of endometriosis or teratomatous differentiation in any of the four tumours. Multiple sections of each tumour were examined for evidence of morphological transition between carcinoma and sarcoma and none was found. Reticulin stains showed a crisp
demarcation in cytoarchitecture between the periglandular pattern of adenocarcinoma and the pericellular pattern of sarcoma which was invariable in each tumour (fig 2). Immunohistochemical techniques showed carcinomatous elements positive for cytokeratin set in undifferentiated sarcoma positive for vimentin (fig 3). The intramural sarcomatous nodules in the serous cystadenocarcinoma were vimentin positive and entirely separate from the cytokeratin positive, malignant epithelial lining.

Coexpression of cytokeratin and vimentin within the same cell, determined by staining serial sections alternately, was not found in any of the four tumours.

The rhabdomyoblasts in one primary tumour (fig 4) and in the hepatic metastases of another did not show cross-striations with PTAH but they did contain myoglobin. In two cases PAS positive, diastase resistant eosinophilic hyaline droplets of varying size (5-50 μm in diameter) were found mainly in the spindle

Figure 1 Ovarian malignant mixed mesodermal tumour composed of adenocarcinoma and sarcoma. (Haematoxylin and eosin.)

Figure 2 Contrast in reticulin patterns between adenocarcinoma and sarcoma. (Rannie’s reticulin.)

Figure 3 Consecutive sections stained with anti-cytokeratin (3a) and anti-vimentin (3b). (Indirect immunoperoxidase.)
Histogenesis of ovarian malignant mixed mesodermal tumours

Three tumours corresponded with the typical descriptions of ovarian malignant mixed mesodermal tumours, being composed of a disorganised mixture of carcinoma and sarcoma with a predominance of adenocarcinoma of serous type. In one case, however, the tumour was a "forme fruste" ovarian malignant mixed mesodermal tumour from which the separate metastatic spread of carcinoma and sarcoma nevertheless fulfilled the necessary diagnostic criterion. The presence of rhabdomyosarcoma in metastases alone has been noted before. Ovarian endometriosis has occasionally been described in association with ovarian malignant mixed mesodermal tumours, but none was found in this series. The eosinophilic hyaline droplets were tintorially similar to those in previous reports but did not show secondary fluorescence or contain α-1-antitrypsin.

It has been suggested that ovarian malignant mixed mesodermal tumours are metastatic carcinomas, and morphological transitions have been described. The intraperitoneal and lymphatic spread of ovarian malignant mixed mesodermal tumours is consistent with this mode of spread of a carcinoma, but the metastases are frequently sarcomatous. Masuda grew a carcinoma cell line derived from an ovarian malignant mixed mesodermal tumour in low cell density tissue culture and found that there was a loss of epithelial characteristics. This phenomenon has been described, however, in tissue culture using other cell sarcomatous component. They stained deep blue with PTAH but did not show secondary fluorescence in sections stained with haematoxylin and eosin or contain α-1-antitrypsin.

Discussion

Three tumours corresponded with the typical descriptions of ovarian malignant mixed mesodermal tumours, being composed of a disorganised mixture of carcinoma and sarcoma with a predominance of adenocarcinoma of serous type. In one case, however, the tumour was a "forme fruste" ovarian malignant mixed mesodermal tumour from which the separate metastatic spread of carcinoma and sarcoma nevertheless fulfilled the necessary diagnostic criterion. The presence of rhabdomyosarcoma in metastases alone has been noted before. Ovarian endometriosis has occasionally been described in association with ovarian malignant mixed mesodermal tumours, but none was found in this series. The eosinophilic hyaline droplets were tintorially similar to those in previous reports but did not show secondary fluorescence or contain α-1-antitrypsin.

It has been suggested that ovarian malignant mixed mesodermal tumours are metastatic carcinomas, and morphological transitions have been described. The intraperitoneal and lymphatic spread of ovarian malignant mixed mesodermal tumours is consistent with this mode of spread of a carcinoma, but the metastases are frequently sarcomatous. Masuda grew a carcinoma cell line derived from an ovarian malignant mixed mesodermal tumour in low cell density tissue culture and found that there was a loss of epithelial characteristics. This phenomenon has been described, however, in tissue culture using other cell sarcomatous component. They stained deep blue with PTAH but did not show secondary fluorescence in sections stained with haematoxylin and eosin or contain α-1-antitrypsin.

This paper is based on work presented at the Association of Clinical Pathologists' Junior Members Research Award in London on October 14, 1988.

I thank Mrs Carol Stoddard for technical assistance. Mrs G Marshall for typing the manuscript, and Professor P P Anthony for constructive criticism.


