

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.¹⁻⁴ 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.^{1,2,3,5} 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".⁶ The same theoretical problems concerning histogenesis are encountered with "carcinosarcomas" at other sites such as breast,⁷ lung,^{8,9} colon,¹⁰ and urinary bladder.^{11,12} 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.¹³ This study was undertaken to investigate whether there were morphological, cytoarchitectural, 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 μ m 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, α -1-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.¹⁴ 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.¹⁵

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

Department of
Histopathology,
Derriford Hospital,
Plymouth
T J Clarke

Correspondence to:
Dr T J Clarke, Area
Department of Pathology,
Royal Devon and Exeter
Hospital, Exeter EX2 5DY

Accepted for publication
19 October 1989

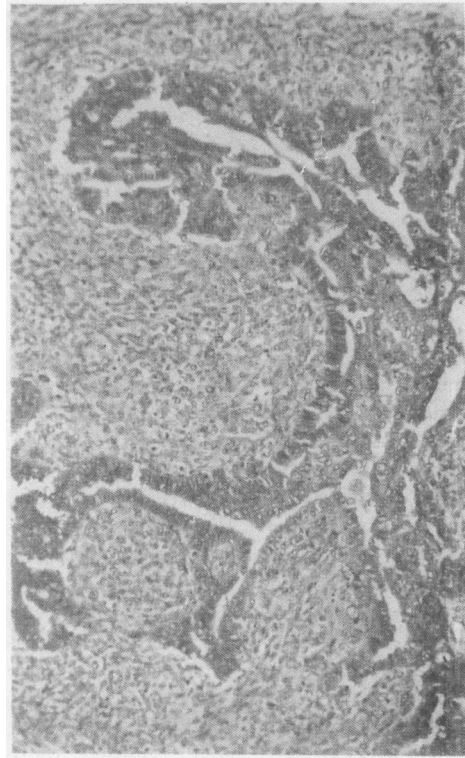


Figure 1 Ovarian malignant mixed mesodermal tumour composed of adenocarcinoma and sarcoma. (Haematoxylin and eosin.)



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

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

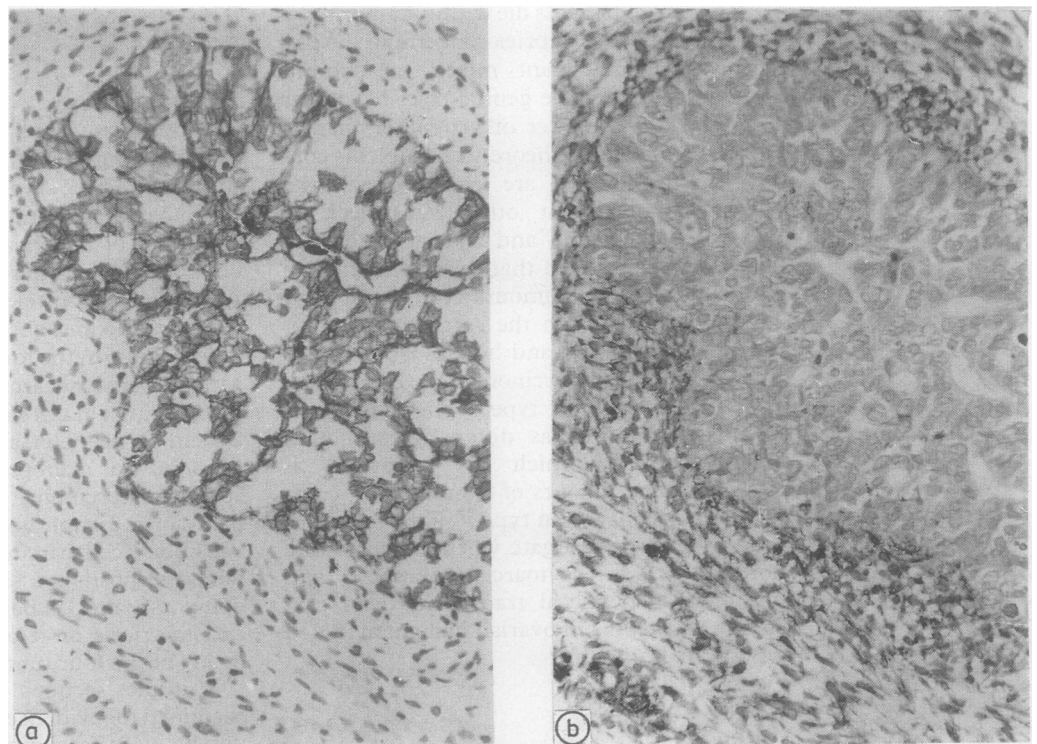
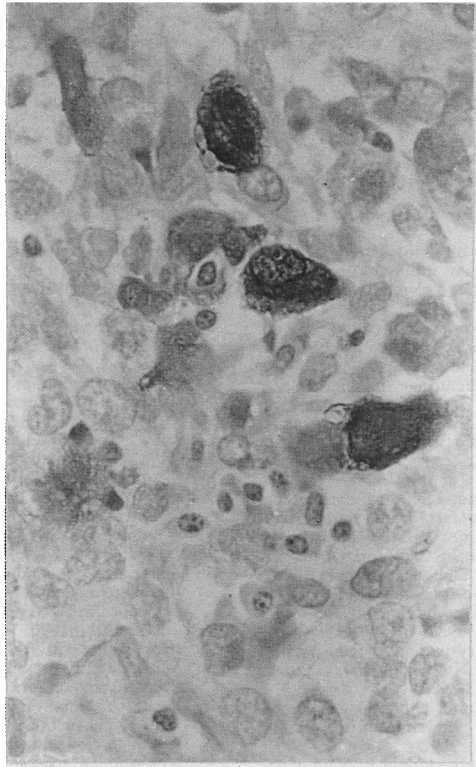


Figure 3 Consecutive sections stained with anti-cytokeratin (3a) and anti-vimentin (3b). (Indirect immunoperoxidase.)

Figure 4
Rhabdomyoblasts stained
with anti-myoglobin
(Indirect
immunoperoxidase.)



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.² 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.² Ovarian endometriosis has occasionally been described in association with ovarian malignant mixed mesodermal tumours,^{1-3 16-20} but none was found in this series. The eosinophilic hyaline droplets were tinctorially similar to those in previous reports²¹⁻²³ but did not show secondary fluorescence²³ or contain α -1-antitrypsin.²¹⁻²³

It has been suggested that ovarian malignant mixed mesodermal tumours are metaplastic carcinomas, and morphological transitions have been described.^{1,2} The intraperitoneal and lymphatic spread of ovarian malignant mixed mesodermal tumours is consistent with this mode of spread of a carcinoma,²⁴ but the metastases are frequently sarcomatous.² 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.²⁵ This phenomenon has been described, however, in tissue culture using other

epithelial cell lines.²⁶ It is due to decreased cell to cell contact²⁷ and is, therefore, not proof of metaplasia. When examined by electron microscopy, two ovarian malignant mixed mesodermal tumours showed no evidence of transitional cell forms or discontinuity in the basal lamina separating carcinoma from sarcoma.²⁸ Electron microscopy was not used in this series but the difference in reticulin patterns between the two components supports the previously reported ultrastructural findings. The biphasic pattern of cytokeratin and vimentin expression has been described before²⁹ but immunohistochemical transitions between the two elements were not investigated.

The light, electron microscopic, and immunohistochemical findings suggest that ovarian malignant mixed mesodermal tumours are not metaplastic carcinomas—that is, tumours in which the sarcomatous component derives from the carcinomatous. Meyer classified carcinosarcomas into collision, combination, and composition types.¹³ There is no evidence to suggest that ovarian malignant mixed mesodermal tumours are collision tumours formed following coalescence of two separate tumours; moreover, ovarian carcinomas are common and sarcomas are rare.¹⁶ In a combination tumour the carcinosarcoma is thought to arise from a precursor stem cell (Ahnzelle) which differentiates along two divergent pathways. There is evidence from tissue culture experiments using cells from malignant mixed mesodermal tumours to support³⁰ and refute³¹ this; but, again, extrapolation from tissue culture work is fraught with difficulties. In a composition tumour there is synchronous malignant change in adjacent epithelium and stroma. This change was evident in the forme fruste ovarian malignant mixed mesodermal tumour in this series. The other three tumours may have been either of combination or composition in type.

In conclusion, examination of the general morphology, cytoarchitecture, and immunohistochemistry of four ovarian malignant mixed mesodermal tumours produced no evidence to suggest that such neoplasms are metaplastic carcinomas, and it is suggested that carcinosarcomas at other sites be reexamined in the manner described in this study.

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.

- 1 Dehner LP, Norris HJ, Taylor HB. Carcinosarcomas and mixed mesodermal tumors of the ovary. *Cancer* 1971;27:207-16.
- 2 Fenn ME, Abell MR. Carcinosarcoma of the ovary. *Am J Obstet Gynecol* 1971;110:1066-74.
- 3 Dictor M. Malignant mixed mesodermal tumor of the ovary: a report of 22 cases. *Obstet Gynecol* 1985;65:720-4.
- 4 Barwick KW, LiVolsi VA. Malignant mixed mesodermal tumors of the ovary: a clinico-pathologic assessment of 12 cases. *Am J Surg Pathol* 1980;4:37-42.
- 5 Hanjani P, Petersen RO, Lipton SE, Nolte SA. Malignant mixed mesodermal tumors and carcinosarcoma of the ovary: report of eight cases and review of the literature. *Obstet Gynecol Surv* 1983;38:537-45.

- 6 Marshall RJ. Mixed Mullerian tumours of the gynaecological system other than endometrial tumours. In: Williams CJ, Kirkorian JG, Green MR, Raghavan D, eds. *Textbook of uncommon cancer*. Chichester: J Wiley, 1988:65-75.
- 7 Oberman HA. Metaplastic carcinoma of the breast: a clinicopathologic study of 29 patients. *Am J Surg Pathol* 1987;11:918-29.
- 8 Huszar M, Herczeg E, Lieberman Y, Geiger B. Distinctive immunofluorescent labelling of epithelial and mesenchymal elements of carcinosarcoma with antibodies specific for different intermediate filaments. *Hum Pathol* 1984;15:532-8.
- 9 Addis BJ, Corrin B. Pulmonary blastoma, carcinosarcoma and spindle-cell carcinoma: an immunohistochemical study of keratin intermediate filaments. *J Pathol* 1985;147:291-301.
- 10 Weidner N, Zekan P. Carcinosarcoma of the colon: report of a unique case with light and immunohistochemical studies. *Cancer* 1986;58:1126-30.
- 11 Young RH. Carcinosarcoma of the urinary bladder. *Cancer* 1987;59:1333-8.
- 12 Fromowitz FB, Bard RH, Koss LG. The epithelial origin of a malignant mesodermal mixed tumor of the bladder: report of a case with long-term survival. *J Urol* 1984;132:978-81.
- 13 Meyer R. Beitrag zur verstandigung uber die namengebung in der geschwulstlehre. *Zentralblatt für Allgemeine Pathologie und Pathologische Anatomie (Jena)* 1919;30:291-6.
- 14 International Federation of Gynaecology and Obstetrics. Classification and staging of malignant tumors of the female pelvis. *Acta Obstet Gynaecol Scand* 1971;50:1-7.
- 15 Clarke TJ. Sarcoma-like mural nodules in cystic serous ovarian tumours. *J Clin Pathol* 1987;40:1443-8.
- 16 Azoury RS, Woodruff JD. Primary ovarian sarcomas: report of 43 cases from the Emil Novak Ovarian Tumour Registry. *Obstet Gynecol* 1971;37:920-41.
- 17 Cooper P. Mixed mesodermal tumor and clear cell carcinoma arising on ovarian endometriosis. *Cancer* 1978;42:2827-31.
- 18 Saunders P, Price AB. Mixed mesodermal tumour of the ovary arising in pelvic endometriosis. *J Roy Soc Med* 1970;63:1050-1.
- 19 Marchevsky AM, Kaneko M. Bilateral ovarian endometriosis associated with carcinosarcoma of the right ovary and endometrioid carcinoma of the left ovary. *Am J Clin Pathol* 1978;70:709-12.
- 20 Ricci M, Santini G, Mazzoleni G, Gelli MC, Bazzocchi F. Malignant mixed mesodermal tumours of the ovary: a clinico-pathological study of four new cases. *Arch Anat Cytol Pathol* 1987;35:41-3.
- 21 Dictor M. Ovarian malignant mixed mesodermal tumor: the occurrence of hyaline droplets containing α_1 -antitrypsin. *Hum Pathol* 1982;13:930-3.
- 22 Dictor M. Alpha-1-antitrypsin in a malignant mixed mesodermal tumor of the ovary. *Am J Surg Pathol* 1981;5:543-50.
- 23 Dervan PA. Alpha-1-antitrypsin haematoxylin and eosin fluorescence: a rapid, useful screening technic. *Am J Clin Pathol* 1984;82:188-90.
- 24 Czernobilsky B, LaBarre GC. Carcinosarcomas and mixed mesodermal tumor of the ovary: a clinicopathologic analysis of 9 cases. *Obstet Gynecol* 1968;31:21-32.
- 25 Masuda A, Takeda A, Fukkami H, Yamada C, Matsuyama M. Characteristics of cell lines established from a mixed mesodermal tumor of the human ovary. *Cancer* 1987;60:2696-703.
- 26 Ben-Ze'ev A. Differential control of cytokeratin and vimentin synthesis by cell-cell contact and cell spreading in cultured epithelial cells. *J Cell Biol* 1984;99:1424-33.
- 27 Lane EB, Hogan BLM, Kurkinen M, Garrels JI. Co-expression of vimentin and cytokeratins in parietal endoderm cells of early mouse embryo. *Nature* 1983;303:701-4.
- 28 Geisenger KR, Dabbs DJ, Marshall RB. Malignant mixed Mullerian tumours: an ultrastructural and immunohistochemical analysis with histogenetic considerations. *Cancer* 1987;59:1781-90.
- 29 del Poggetto CB, Virtanen I, Lehto V-P, Wahlstrom T, Saksela E. Expression of intermediate filaments in ovarian and uterine tumors. *Int J Gynecol Pathol* 1983;1:359-66.
- 30 Takeda A, Matsuyama W, Kuzuya K, Chihara T, Tsubouchi S, Takeuchi S. Mixed mesodermal tumor of the ovary with carcinoembryonic antigen and alkaline phosphatase production. *Cancer* 1984;53:103-12.
- 31 Centola GM. Long-term growth of a heterologous mixed Mullerian tumor of the ovary. *Invasion Metastasis* 1986;6:123-32.