Carcinoid tumour of the uterine cervix

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SUMMARY A carcinoid tumour of the cervix in a 64-year-old woman is described. It is the first time that this rare tumour has been associated with carcinoma-in-situ.

Carcinoid tumours of the gastrointestinal tract and lung are well recognised yet relatively uncommon neoplasms. More unusual locations of carcinoids are the ovary (Robboy et al., 1975), thymus (Rosai et al., 1976), pancreas (Hallwright et al., 1964; Patchefsky et al., 1974), liver (Primack et al., 1971), biliary tract (Shiffman and Juler, 1964), salivary gland (Nicod, 1958), breast (Cubilla and Woodruff, 1977), and the uterine cervix (Tateishi et al., 1975; Albores-Saavedra et al., 1976). Argyrophilic precursor cells have been demonstrated in most of these sites. In normal cervical mucosa these cells are very rare (Fox et al., 1964), and Tateishi et al. (1975) identified small numbers of them in 35% of instances. To date, 17 carcinoid tumours of the cervix have been documented (Tateishi et al., 1975; Albores-Saavedra et al., 1976). Another case is the subject of the present report.

Case report

A 64-year-old woman was admitted for investigation of intermittent vaginal spotting of five years' duration. Bleeding became more profuse and frequent two months before admission. She had never had gynaecological problems or a Papanicolaou smear. She had smoked one package of cigarettes per day for approximately 30 years. Physical examination, chest x-ray, and an intravenous pyelogram were normal. However, a large fungating lesion of the cervix was found. Cervical biopsy showed 'epidermoid carcinoma-in-situ' (Figs 1 and 2). Pelvic examination, after referral for rebiopsy and staging, revealed a red, fungating, friable mass, approximately 4 x 4 cm, occupying most of the external cervical os, which was displaced to the left with minimal involvement of the vaginal apex. There was nodularity of the parametrium on the left side but the pelvic wall was normal. Neither organomegaly nor lymphadenopathy was found. No abnormalities were found on sigmoidoscopy and cystoscopy. The carci

noembryonic antigen level was 72.0 ng/ml. Microscopic examination of cervical biopsy specimens was reported as 'invasive, poorly differentiated epidermoid carcinoma, large-cell non-keratinising type; epidermoid carcinoma-in-situ'.

Tentative clinical stage was IIB. However, at laparotomy one week later, tumour was found in the uterine fundus, serosa of bladder, and left ovary. Metastatic 'poorly differentiated epidermoid carcinoma' was also found in a periaortic lymph node. During the following month 4000 rads external radiation and two radium inserts (2000 rads each) were administered. On readmission two weeks later she was cachectic, listless, and dehydrated. Extension of the tumour to the lateral wall of the vagina was noted. Biopsy of slightly enlarged left supraclavicular lymph nodes under local anaesthesia revealed 'metastatic poorly differentiated epidermoid carcinoma'. Death occurred in hospital 23 days later.

PATHOLOGICAL FINDINGS
Postmortem examination revealed extensive metastatic disease in many organs. The pleural cavities together contained 700 dl of clear yellow fluid; occasional 2-mm nodules were present on the visceral and parietal pleurae. The lungs together weighed 1150 g; no obstruction or primary lesion was identified in the bronchial tree. The liver weighed 2250 g and contained several 3-cm white tumour nodules throughout. The spleen weighed 210 g and harboured several 1-5 cm tumour nodules. The heart contained an intratral tumour nodule and several epicardial ones but was otherwise normal. The combined weight of the adrenal glands was 70 g, and both were almost completely replaced by tumour. The uterus was small, and subserosal tumour nodules were present; the endometrial surface was normal. A necrotic mass of tissue, 1-0 cm in diameter, was attached to the cervical remnant. Cervical, intra-thoracic, and intra-abdominal lymph nodes were

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enlarged. Tumour nodules were present in the kidneys, pancreas, ovary, thyroid, gastric mucosa, and vertebral bone marrow. Microscopic examination confirmed the presence of tumour in the aforementioned sites.

All of the biopsy and necropsy material, with the exception of the block from the second biopsy, was available for review. The metastatic tumour was composed of sheets, nests, and strands of tumour cells with pale eosinophilic cytoplasm and nuclei.
containing dense clumped chromatin. Mitoses were plentiful and focal necrosis was not unusual. Clusters of rosettes were first noted among solid sheets of cells in the metastatic lesions (Fig. 3) and were identified in most deposits, but squamous differentiation was not found here. Close scrutiny of the second biopsy specimen and of most subsequent specimens revealed the presence of rosettes, albeit in small numbers (Fig. 4). Here tumour cells were slightly larger than those of the necropsy material. Nuclear chromatin was stippled rather than clumped, and mitoses were numerous. These cytological differences may have been due to more immediate fixation and better viability of tissue. Rosettes were not identified superficial to the limiting membrane in areas of dysplasia or carcinoma-in-situ. However, they were immediately subjacent to but not in continuity with carcinoma-in-situ. There was a moderate lymphohistiocytic infiltrate in the subepithelial stroma. Foci of in-situ cancer and some foci of microinvasive carcinoma were unmistakably squamous in type. Small foci of squamous differentiation and rosettes were also observed in separate fragments of a biopsy specimen from the uterine fundus (Fig. 5). Definite intermingling of rosettes and squamous elements was not seen. Isolated cells that reacted positively with a modified Grimalius stain (Fernandez Pascual, 1976) and rosettes were found in the supraclavicular lymph node (Fig. 6).

**Discussion**

This patient's symptoms were not unusual, and in view of the long history of bleeding it is unfortunate that she never had cervical smears. The long survival after the onset of symptoms compares with two of the cases reported by Albores-Saavedra et al. (1976). Both were considered to have well differentiated tumours and the patients survived five and six years as opposed to three to 24 months' survival for those with poorly differentiated carcinoids. Endocrine changes were not found in this case, and estimations of serum polypeptide hormones or amines were not performed. Elevated levels of carcinoembryonic antigen have been reported in squamous cell carcinoma of the cervix (DiSaia et al., 1975; Kjorstad and Orjaser, 1977) but the level found in this case is very high.

All carcinoid tumours, irrespective of the degree of differentiation, are potentially lethal neoplasms derived from the clear neuroendocrine cells of Feyrter (1952), which are now commonly referred to as APUD cells of Pearse (1974). The most benign tumours are those of the ileocaecal region with a high cure rate and very long survival (Moertel et al., 1961). Oat cell (small cell) carcinoma probably represents the most malignant state of this cell type. Between these limits lie neoplasms of varying grades of malignancy, depending on the degree of differen-

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**Fig. 3** Metastatic tumour in liver showing rosette formation. (H and E x 400)
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Fig. 4 Rosette formation in second cervical biopsy specimen. In other fields the tumour was monotonous, and severe dysplasia with carcinoma-in-situ was present in the superficial epithelium. (H and E × 100)

Fig. 5 Focus of squamous differentiation in uterus. (H and E × 1000)

Differentiation and on their location. Thus oat cell carcinomas have been described in the same sites as carcinoids with the interesting exception of the small intestine and appendix. It is very likely that many undifferentiated small cell carcinomas of the cervix are in reality types of carcinoid tumour. More widespread application of silver stains and ultrastructural examination should reveal more of these tumours, especially in those cases that lack definitive histological features. Unfortunately in this case
the only tissue that might have been suitable for electron microscopy was not available. Stains for argyrophilic cells also require excellent fixation, and tissue of borderline viability is obviously unsuitable.

The histological pattern encountered in oat cell carcinomas of the lung (Azzopardi, 1959) and carcinoid tumours (Williams and Sandler, 1963; Soga and Tazawa, 1971) is distinctive and aids in their recognition even without recourse to special techniques. Both may share common patterns, depending on their location, but generally oat cell carcinomas are composed of small round or spindle cells. Cells may be arranged in ribbons, festoons, trabeculae or nests. Pseudorosettes and true rosettes may also be present (Azzopardi, 1959; Soga and Tazawa, 1971). The latter have been described in carcinoids of many sites, including the cervix (Albores-Saavedra et al., 1976), thymus (Rosai et al., 1976), and breast (Cubilla and Woodruff, 1977) and in oat cell carcinoma of the lung (Azzopardi, 1959); they correspond to the acini that are commonly found in midgut carcinoids. The presence of these structures lends a distinctive appearance to these tumours. Morphologically they are distinguishable from glandular formation in adenocarcinoma (Azzopardi, 1959; Hattori et al., 1972). As in the present case, intracytoplasmic, intraluminal, and intercellular PAS-positive material has been found in carcinoids and oat cell tumours (Azzopardi, 1959; Soga and Tazawa, 1971; Tateishi et al., 1975; Albores-Saavedra et al., 1976).

It is difficult to exclude the concurrence of squamous cell carcinoma and carcinoid tumour in this case. Thus, this could be a collision tumour. The clinical history and anatomical findings weigh heavily against a primary tumour of the lung. Neoplastic changes in the ectocervix were typically squamous and diffuse and did not resemble intraepithelial spread of the type seen in Paget's disease or malignant melanoma. Squamous metaplasia in the uterus could be explained if the neural crest origin of the precursor cell in this location was disregarded in favour of a mesodermal origin, that is, from endocervical glands. However, this is only because uterine adenocarcinomas may harbour benign or malignant squamous elements. Microscopic foci of 'epidermoid differentiation' were found in three of the 12 cervical carcinoids reported by Albores-Saavedra et al. (1976), and Tateishi et al. (1975) found 'squamous metaplasia' in two of five tumours. Squamous elements are a rare but accepted feature of carcinoid tumours (Rosai et al., 1976). Carcinoma-in-situ has not been described in any of the 17 reported cases of cervical carcinoid (Tateishi et al., 1975; Albores-Saavedra et al., 1976). This case is not without precedent as bimorphic features have been recognised in other carcinoid tumours, notably those of the gastrointestinal tract (Azzopardi and Pollock,
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1963; Hernandez and Reid, 1969). To explain this one could postulate: (1) a common precursor cell with metaplasia, (2) a collision effect with mixing of two elements, or (3) permanent phenotypic conversion with variable expressivity through gene transfer or cell hybridisation. All explanations are highly speculative and lack experimental verification.

References


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