Small cell cancers of the ovary and cervix

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Introduction

Small cell carcinomas of the ovary and cervix are uncommon, probably constituting only 1–2% of ovarian and cervix cancers. An important issue is to distinguish pure small cell tumours from those tumours that may contain neuroendocrine differentiation. Furthermore these tumours may be associated with the ectopic production of neuropeptides which may give distinctive clinical syndromes including hypercalcaemia, hypoglycaemia and myaesthenic syndromes. These tumours are often highly aggressive and carry a poor prognosis and unless diagnosed early, are lethal.

Ovarian small cell tumours are usually pure, in contrast, the cervical tumours often arise with another more common pattern of differentiation. One of the principal difficulties in evaluating small cell tumours of this type is distinguishing them from metastatic small cell disease arising elsewhere and from other tumours which may have a subtly similar appearance. There are differences in the immunocytochemical profile but also the method of presentation and age may be relevant. Carcinoids and undifferentiated sex cord tumours may also cause confusion. Small cell carcinoma of the cervix is much more prevalent in younger women, ie under the age of 25. This diagnosis should always be considered in a younger woman presenting with advanced disease.

Small cell cancer of the ovary

These rare tumours can be classified as pulmonary and non-pulmonary in type and, confusingly, as having a typical small cell morphology or a large cell variant [1–11]. It is also important that not all small tumours are associated with hypercalcaemia. This is a further reason for specialist pathological review.

Small cell carcinomas of the ovary may often be associated with hypercalcaemia in about two thirds of cases and inspite of the aggressive treatment may well recur quickly and have a very poor prognosis. A recent review article by Harrison et al looked at 17 cases [12, 13] and showed that the best prognosis was associated with early stage disease and aggressive management including surgery, radiation and chemotherapy. Many of the ovarian tumours associated with advanced disease may commonly have liver metastases at presentation, and percutaneous liver biopsy may be the quickest way to establish a diagnosis. The development of hypercalcaemia, particularly with normal bone scan, reflects the inappropriate secretion of neuropeptides such as PTHRP or ADH (SIADH). A very recent and comprehensive review of small cell cancers of female genital tract was published at the beginning of 2007 [14].

Early cases should be investigated and managed in the usual manner with appropriate staging procedures including laparotomy for ovarian cancers and on occasions the diagnosis may only be made as an unexpected finding. However a full and thorough staging should be carried out and in cases of extensive disease in a younger woman with an atypical pattern, small cell carcinoma should be considered.

Careful review by an experienced Pathologist specialising in Gynaecological Oncology Pathology has advised an immunocytochemical profile may give important clues [9–11]. All cases should be discussed at tumour boards and if appropriate referred to regional/national referral centres [13,15]. Aggressive management with chemotherapy following optimal debulking is required for ovarian cancers. The conventional approach is to combine platinum with etoposide, as in small cell lung cancer. There is no evidence base to favour cisplatin over carboplatin but the convenience of carboplatin may make it the drug of choice. However anecdotal experience indicates that weekly Carboplatin & Paclitaxel may be considered. The importance here may be the weekly scheduling rather than the individual drugs. Unfortunately many of the patients have a short-lasting response and early relapse either with intra-abdominal disease or even cerebral metastases will occur. Consideration of prophylactic cranial irradiation should be given for those who enter complete remission. For patients who

develop early relapse further chemotherapy may be considered if they are of good performance status. The CAVE regime (cyclophosphamide, adriamycin, vincristine and etoposide) may be considered. Topotecan may also be active in small cell tumours; otherwise experimental schedules should also be discussed.

Carcinoid tumours (well differentiated neuro-endocrine tumours) may also involve the ovary but are most frequently metastatic but occasionally no other disease is located and are considered true primary carcinoids. They tend to behave like classical carcinoid tumours and may metastasize and cause carcinoid syndrome. The clinical behaviour and the histological appearance should distinguish them from small cell cancers. Poorly differentiated sex cord tumours with small cells may cause a diagnostic challenge but review by an experienced pathologist should help make the distinction.

Small cell cervix cancer

These were first described much earlier, the first recognised report being in 1976 [16]. Historically, there is much more confusion over the terminology used in what we now call small cell cancer of cervix [17–19]. The papers in the 1990s and a consensus conference helped to address some of the issues [20–28].

Small cell carcinoma of the cervix is highly uncommon, it is said to account for less than 1% of cervix cancers. It occurs more commonly in younger females, and a woman under thirty with a poorly differentiated squamous carcinoma should be considered as having a small cell/neuroendocrine tumour. Some poorly differentiated squamous cancers may have neuroendocrine features with patchy immunocytochemical profile. This probably represents a separate disease process and may just represent the aggressive end of the spectrum of squamous cancers rather than a neuroendocrine cancer. Many of the original papers even refer to these NET type tumours as "carcinoid". HPV 18 seems to be most commonly associated (in about 50% of cases) and HPV 16 less so, but it is proposed that a different HPV virus may be associated with small cell carcinoma of the cervix.

A workshop meeting in 1997, reported by Albores-Saavedra [29] proposed that cervix (neuro)-endocrine cancers be classified into the four following categories.

– Typical (classical) carcinoid
– Atypical carcinoid
– Large cell neuroendocrine
– Small cell (oat cell) neuroendocrine

A criticism of this is that the terminology is now considered obsolescent as the WHO classification is being introduced into NET tumour care [30]. However the rarity of these tumours means they have so far not been incorporated into the revised WHO classification process. The paradox is that the term carcinoid is familiar to many and thus in practice it may be easier to understand this term.

Specialist pathological review is required with access to comprehensive immunocytochemical profile which should include staining for immunohistochemical neuroendocrine markers, p53, p16, p14, and cyclin D1 [31]. Immunohistochemical staining for CD 56 synaptophysin neurone-specific enolase and chromogranin A may be helpful. It is proposed that p16 is up-regulated or accumulated in the small cell cancers of the uterine cervix, probably caused by infection with human papillomavirus. p14 inactivation is of high prevalence and detection rate of p53 is similar to other histologic types of cervical carcinomas.

Full staging including imaging with CT, MRI or PET CT to include the chest is essential in order to exclude a primary intra-pulmonary tumour. Nevertheless even this cannot guarantee to rule out an occult primary small cell tumour of the lung. The management of these cases generates a great deal of debate and discussion and there are some experts who feel that surgery has little role to play. However some of the best results in the literature have come from a combination of surgery, radiation and chemotherapy [32–43]. Small tumours should be considered for radical hysterectomy and pelvic lymph node dissection, then followed by chemotherapy and radiation either concomitantly or sequentially. The issue of para aortic node sampling or lymphadenectomy (PALND) remains unresolved. Most would advocate sampling but there is no evidence base to substantiate routine PALND.

The larger tumours which may not be suitable for surgical resection should probably be managed with initial chemotherapy. Drug combinations similar to those used in small cell lung cancer may be considered such as Platinum/Etoposide combination with 4–6 cycles with careful monitoring followed by either radical hysterectomy, radical radiation or both. Whilst these tumours may show a high level of chemo or radio-sensitivity, early relapse is frequent and associated with an aggressive and usually lethal pattern. Patterns of relapse may be unusual with lymph node metastases in the para aortic area as first and apparently isolated site of relapse, which strengthens

the argument for lymphadenectomy at the time of initial surgery [32,40,42].

Early relapse is common and usually aggressive but occasional cases may recur 2–3 years later and if the patient is of good PS, reconsideration of surgery and chemotherapy must be given. For a longer, treatment-free interval, re-challenge with platinum is advised, in combination with etoposide or paclitaxel or even topotecan. Isolated pelvic masses may require further surgery or radiation depending on prior treatment. There is clearly further work to be done in terms of the optimal investigations, staging and management of these tumours. Because of their rarity there should be a local database and internationally agreed protocols for their management so that more information can be gained about optimum care.

Conflict of interest statement

None declared.

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