Leading Article

Extrapulmonary small cell carcinoma

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Small cell or 'oat cell' cancer of the lung is a common disease, found in about one in four patients with lung cancer. The histological appearance of the tumour is distinctive; sheets of cells with small round, oval or fusiform nuclei and scanty cytoplasm.¹ The tumour exhibits neuroendocrine (NE) features, characterized by the presence of dense core granules, enzymes such as L-dopa decarboxylase and neurone specific enolase, and the production of a variety of hormones and neuropeptides. In the majority of cases immunocytochemistry can identify NE differentiation on the cell surface, or in the cytoplasm. The distinction of small cell lung cancer from other types of lung cancer is important because its clinical behaviour is so different. Small cell cancer spreads early and widely throughout the body, so that life expectancy in untreated cases is short. Furthermore, small cell lung cancer is more sensitive to chemotherapy and radiation than non-small cell variants. Chemotherapy has become the treatment of choice and it has extended the median survival of patients and led to cure in a few.²

Small cell carcinoma of extrapulmonary origin has been known to exist for many years. The report of two cases of small cell cancer of the oesophagus by McKeown in 1952³ has been followed by many further cases of primary small cell tumours of the stomach, small and large bowel, pancreas, salivary glands, pharynx, prostate, cervix, breast and skin. The pericardium and bone are two new sites described in this issue of *Postgraduate Medical Journal*.^{4,5} Several reviews of extrapulmonary small cell cancers have been published in the last decade.^{6–8} However, there is no general agreement as to how patients should be managed. Extrapulmonary small cell cancer is rare and its precise incidence is unknown. The certainty of the diagnosis depends on the measures taken to exclude the more common small cell lung tumour; not all patients have fibre-optic bronchoscopy or computerized X-ray tomography of the thorax. In a series of 203 fully staged cases of small cell cancer

seen between 1973–1979 at the National Cancer Institute, 8 (4%) were of extrapulmonary origin.⁶ Extrapulmonary small cell cancer occurs most commonly in the minor salivary glands or oesophagus; the frequency for the former has been estimated to be about 3.5% and 0.4–2.4% for the latter.⁸ Many patients with extrapulmonary small cell cancer have a primary tumour that can be identified with reasonable confidence. Others present with metastatic disease and a normal CT scan of the lungs and no abnormal bronchoscopic findings. In these cases cytogenetic studies are useful as they can differentiate true extrapulmonary tumours from those with an occult primary lung tumour. Deletion of the short arm of chromosome 3, a characteristic abnormality in lung cancer, is absent in extrapulmonary tumours.⁹

For many years small cell lung cancer was thought to be derived from nests of neuroendocrine cells widely distributed throughout the body. Non-neoplastic cells in these sites have biochemical features in common and they have been grouped together by Pearse,¹⁰ as amine precursor uptake and decarboxylation (APUD) cells. However, in about 5% of small cell lung cancers the population of cells is heterogeneous, with squamous or adenocarcinoma coexisting.¹¹ It is now considered more likely that small cell tumours arise from a pleuripotent endodermal cell that develops NE features. In keeping with this hypothesis a spectrum of NE differentiation is seen in small cell lung cancer. Furthermore, NE differentiation can be detected in some cells from about half the patients with non-small cell lung cancer.¹² NE differentiation is not confined to non-small cell lung cancers; it can often be detected in colorectal tumours.¹³ There are other types of small cell cancer that are regarded as being distinct from 'extrapulmonary small cell cancer'. These include small cell tumours of the bone and Ewing's sarcoma that have a different morphology and cytochemical features, as well as neuroblastoma that exhibits neural differentiation. Similarly, small cell cancer of the ovary, a rare tumour usually associated with hypercalcaemia,¹⁴ does not have neuroendocrine markers.

Biochemical abnormalities which are often seen in small cell cancer of the lung have been described

in extrapulmonary tumours. Cases of ectopic hormone production, particularly adrenocorticotrophic hormone, have been described in small cell cancer of the prostate¹⁵ and cervix.¹⁶ The Eaton-Lambert myasthenic syndrome has been reported in a patient with carcinoma of the cervix.¹⁷ Chemotherapy reduced the size of the tumour and improved the neurological disability.

The important question facing the clinician is whether the clinical behaviour of the tumour is more similar to a primary tumour without NE differentiation, or to small cell lung cancer. Many of the reported cases describe tumours which behave aggressively but this could be due to selection bias. The evidence now accumulating from published series of larger numbers of patients suggests that small cell tumours of the larynx, oesophagus, colorectum, prostate and cervix behave aggressively. They are associated with a poorer prognosis than tumours from these sites that do not have features of NE differentiation.¹⁸⁻²¹ However, the outlook for patients with small cell carcinoma of the salivary glands is better; long-term survival is not uncommon.²² It has been suggested that these tumours are not true 'oat cell' carcinomas but small cell ductal carcinomas that do not have NE features when examined by electron microscopy.²³ However, the different biological behaviour of small cell cancer is not explained solely by the presence or absence of NE

differentiation. For example, most cases of Merkel cell carcinoma of the skin, a small cell tumour with an indolent course, express neurone specific enolase.²⁴ It appears that the clinical behaviour of small cell tumours depends more on their site of origin than on the pathological features.

Knowledge of the aggressive behaviour of extrapulmonary small cell cancer and the chemosensitivity of its pulmonary counterpart has persuaded many clinicians to use combination chemotherapy as primary treatment. Responsiveness to chemotherapy has been clearly documented.^{6,17,25,26} Furthermore, it has been tentatively suggested that non-small cell tumours exhibiting NE differentiation may also be more sensitive to chemotherapy,²⁷ but the evidence is inconclusive. The use of better chemotherapeutic agents over the last decade has improved the treatment of small cell lung cancer. It would seem reasonable to use the same drugs in extrapulmonary small cell tumours, particularly in patients with metastatic disease, or in those who have tumours that are likely to behave aggressively. Remick *et al.*⁸ have estimated that in the USA only about 1,000 new cases of extrapulmonary small cell cancer are diagnosed each year. Improvement in the management of these patients can only occur if data on the outcome of patients are collected, and patients receive more uniform treatment. This can only be done in the context of a large scale clinical study.

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