Substance P in ovarian carcinoid

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SUMMARY A high content of substance P (124 ng/g wet tissue) was demonstrated by radioimmunoassay in lymph node metastases in a patient with bilateral ovarian carcinoid tumours. The plasma substance P level was elevated but urinary 5-hydroxyindoleacetic acid (5-HIAA) was low. It is suggested that, in some carcinoid patients, an elevated plasma substance P level may help diagnosis and follow-up when urinary 5-HIAA is normal.

Substance P (SP) is a peptide with dual brain and gut distribution (Euler and Gaddum, 1931; Powell and Skrabanek, 1979). In the gut it is found in enterochromaffin cells as well as in neural cells (Hökfelt *et al.*, 1977; Heitz *et al.*, 1977). The physiological role of SP is unknown but it has been suggested that it may play a role in the pathophysiology of the carcinoid syndrome (Skrabanek and Powell, 1978). SP has been demonstrated in ileal carcinoids (Håkanson *et al.*, 1977; Skrabanek *et al.*, 1976), in foregut carcinoids (Skrabanek *et al.*, 1978), and in medullary carcinoma of the thyroid (Skrabanek *et al.*, 1979).

In this report we demonstrate SP production by a metastatic ovarian carcinoid in a patient in whom 5-HIAA urinary excretion was undetectable.

Case history

A 41-year-old woman was admitted for tricuspid valve replacement because of carcinoid valve disease.

At the age of 29 she presented at another hospital with the carcinoid syndrome and elevated urinary 5-HIAA. At laparotomy a carcinoid tumour of the left ovary was found and resected. Two days after operation the urinary 5-HIAA was normal. At the age of 37 the patient was readmitted for recurrence of the carcinoid syndrome. She had a cyanotic malar flush, cardiac murmurs, and a palpable pelvic tumour. At laparotomy a tumour was found in the right ovary and removed. Urinary 5-HIAA, elevated before operation, became normal postoperatively. The pathological aspects of this case were discussed in detail by Coll *et al.* (1977). On her last admission at the age of 41, the patient continued to have

pulmonary systolic and tricuspid diastolic murmurs, cyanosis, and dyspnoea. Since her urinary 5-HIAA was normal and there were no signs of metastatic spread, it was decided to relieve her cardiac symptoms by operation. The patient, however, died six days after operation due to postoperative complications.

At necropsy multiple secondaries were found in the retroperitoneal and mediastinal lymph nodes. Because of the rarity of primary bilateral ovarian tumour all viscera were searched for other primary source but no other tumour was found. The total bulk of lymph node metastases was 70 g.

Methods

A plasma sample was obtained immediately before operation. SP was measured by radioimmunoassay as described previously (O'Connell *et al.*, 1976) using an antiserum directed against the biologically active end of the SP molecule (Cannon *et al.*, 1977). The sensitivity of the assay was 2 pg per tube. The normal level of SP derived from 77 normal blood bank donors was 41 ± 7 (SEM) pg/ml with a range of 20-125 pg/ml (Skrabanek *et al.*, 1976).

Tumour tissue from a lymph node metastasis and normal tissue from a control lymph node removed at necropsy and stored at -20°C until assay were homogenised and extracted into acid acetone according to the method of Chang and Leeman (1970). Dried extracts were reconstituted in assay buffer and assayed in various dilutions.

Urinary 5-HIAA was determined in 24-hour urine specimens spectrophotometrically using the 1-nitroso-2-naphthol method with a sensitivity of 10 μmol of 5-HIAA/24 hours (Tietz, 1970).

Histological sections were stained with haematoxylin and eosin, Grimelius's argyrophil silver stain, and Schmorl's ferricyanide method.

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Fig. 1 Radioimmunoassay standard curve (open circles) and serial dilution of ovarian tumour extract (closed circles).

Results

The plasma SP level was 140 pg/ml. The SP content in the tumour metastasis was 124 ng/g wet tissue. An adjacent normal lymph node contained 4.1 ng/g wet tissue. For comparison, a sample of substantia

nigra tissue was assayed for SP in the same assay, since the substantia nigra is one of the brain areas richest in SP, and the SP content was 400 ng/g wet tissue.

A close parallelism was observed between serially diluted tumour extract and serially diluted SP standard (Fig. 1).

Urinary 5-HIAA was undetectable (ie, less than 10 μmol/24 h) on two occasions.

Histologically, the tumour was a classical insular carcinoid with prominent acinar differentiation and densely sclerotic stroma (Fig. 2). Grimelius's argyrophil reaction was positive and demonstrated cytoplasmic granules.

Discussion

SP and 5-hydroxytryptamine (5-HT) share the dual brain and gut distribution and also occur together in enterochromaffin granules (Alumets *et al.*, 1977). Like 5-HT, SP is inactivated in the liver, and higher plasma SP levels may be expected in carcinoids with liver metastases or with extrahepatic drainage.

In the present report the bulk of the primary tumour was removed before the death of the patient. Even if tumour metastases in retroperitoneal and

Fig. 2 Metastatic carcinoid tumour showing islands of tumour cells surrounded by a fibrotic stroma. Haematoxylin and eosin $\times 750$.

mediastinal lymph nodes continued to produce 5-HT, the amount was too low to cause a significant elevation of 5-HIAA in urine. However, at the same time, the plasma SP was elevated, suggesting that the growth of carcinoid metastases could be monitored by SP assay even before detectable elevation of urinary 5-HIAA.

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