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Prostate-specific acid phosphatase in carcinoid tumors

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Summary. Although prostate-specific acid phosphatase (PASP) has been recognized as a specific marker of tissue of prostatic origin, several investigators have pointed out that some of the carcinoid tumours and islet cell tumours of the pancreas reacted immunohistochemically to PSAP. We investigated 50 cases immunohistochemically comprising 44 carcinoids of the G-I tract, 3 of the bronchus, 1 each of the ovary, kidney and middle ear. PSAP positive cases were, 30 in G–I tract, one each in ovary and kidney. Eighty percent of tumours of hindgut origin were positive. Apart from the immunohistochemical study, the content of PSAP in preoperative serum and tumour tissue was estimated in a case with a rectal carcinoid. Extremely elevated PSAP was confirmed in both the serum and tumour tissue. Neuroendocrine tumours such as pheochromocytoma, medullary thyroid carcinoma, and islet cell carcinoma were investigated as controls. No cells immunoreactive to PSAP were observed in these control cases. Prostate specific antigen was definitely negative in carcinoids. We would emphasize that PSAP may be an excellent marker of carcinoids especially when derived from hindgut.

Key words: Prostate-specific acid phosphatase – Carcinoid tumour – Immunohistochemistry

Introduction

Rectal carcinoids are of hindgut origin and usually have no endocrine manifestations. Recent immunohistochemical studies have, however, revealed the resemblance of rectal carcinoids to pancreatic islet cell tumours by their common multihormonal immunoreactivity and frequent staining for somatostatin, glucagon and pancreatic polypeptide (O'Briain et al. 1982). This is also true in the ovarian carcinoid (Sporrong et al. 1982). Though various kinds of peptide hormones are detected in considerable numbers of carcinoid tumours, they do not meet the standards required for tumour markers. The occurrence of multihormonal immunoreactivity is not limited to carcinoids but is detectable in other neuroendocrine tumours such as pheochromocytoma (Hassoun et al. 1984) medullary carcinoma of the thyroid gland (Kameya et al. 1983) and islet cell tumour of the pancreas (Creutzfeldt 1977).

Numerous investigators have shown that immunoreactive prostate-specific acid phosphatase (PSAP) is present in prostatic epithelial cells either in the normal gland or carcinoma and can be regarded as a specific marker of tissue of prostatic origin (Li et al. 1980; Manley et al. 1981; Nadji 1980; Nadji and Morales 1982). However, several non-prostatic tumours e.g. insulomas and carcinoid tumours (Fishleder et al. 1981; Jöbsis et al. 1981) have shown positive immunoreaction to PSAP.

The present study was designed to reveal the distribution of cells immunoreactive to PSAP in carcinoid tumours at various sites of origin. In addition, in one rectal carcinoid plasma PSAP and PSAP content in the tumour tissue were estimated.

Materials and methods

Carcinoid tumours from 50 cases were investigated. The tumours were located as follows, 28 in the rectum, 3 in the appendix, 7 in the small intestine, 6 in the stomach, 3 in the bronchus and one each in the ovary, kidney and middle ear respectively.

As controls, 2 pheochromocytomas, 4 medullary thyroid carcinomas, 5 islet cell tumours and 5 normal prostates obtained by surgery were examined.

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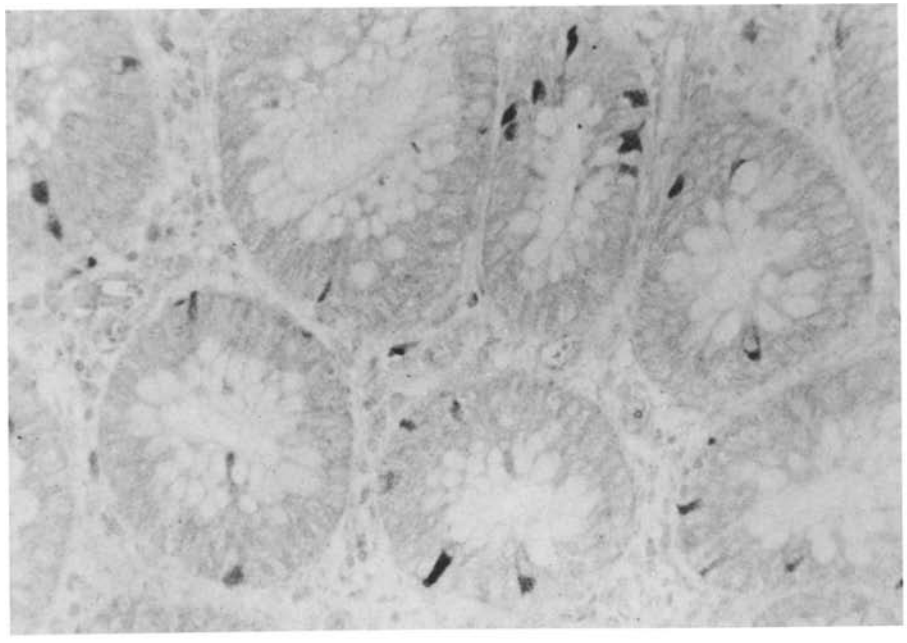

Fig. 1. Immunoreactive cells for PSAP in the normal rectal mucosa adjacent to a carcinoid tumour (ABC method, counterstained with methylgreen × 160)

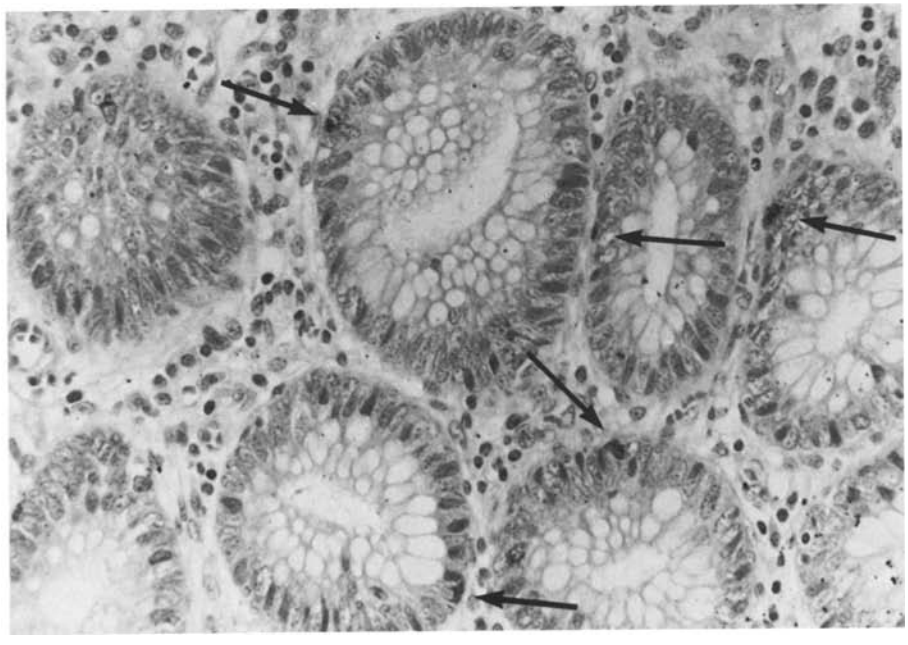

Fig. 2. Grimelius stain in the serial section. Positive cells are indicated by arrow. Note positive cells are fewer than PSAP positive cells (Grimelius stain, counterstained with Kernechtrot × 160)

Paraffin sections of 10% formalin-fixed tissues were stained with haematoxylin and eosin and Grimelius' silver impregnation.

Immunohistochemistry. Sections were stained by the avidin-biotin peroxidase complex method (ABC) (Hsu et al. 1981). Following blocking of endogenous peroxidase by methanol-hydrogen peroxide for 20 minutes and incubation with normal goat serum, sections were incubated for 30 minutes with the following primary rabbit antibodies at the indicated dilutions: PSAP (Miles Laboratories, Inc., 1:400, and from Biomeda Corp., ABC kit. USA), prostate specific antigen 1:100 (DAKO, USA), blood group substance 1:50 (DAKO, USA), neuron-specific enolase 1:100 (Wako, Tokyo, Japan), ACTH 1:300 (Immunonuclear, USA), Calcitonin 1:300 (DAKO, USA), Serotonin 1:100 (Ortho Diagnostic, USA) and Somatostatin 1:500 (Dr. Mouri, Tohoku University, Japan). In all instances except for serotonin, incubation with the primary antiserum was followed by incubation with biotinylated goat antirabbit IgG, ABC (both from Vector lab.) and diaminobenzidine (Dojin Kagaku, Kumamoto, Japan) as chromogens. For serotonin, a monoclonal antibody was used for staining by indirect method. Controls included replacing the primary antiserum with non-immune serum. As positive controls, specimens from the normal human prostate were used.

Specificity of the antiserum of PSAP. To check the specificity of the antiserum, tissue sections were incubated with antiserum

Table 1. Cases of carcinoid tumours with immunoreactive cells to PSAP

Location	Cases, examined	Positive cases
Rectum	28	23 (80%)
Appendix	3	2
Small intestine	7	2
Stomach	6	1
Bronchus	3	0
Ovary	1	1
Kideny	1	1
Middle ear	1	0
Total	50	30 (60%)

diluted 1:400 which had been preincubated for 1 h at 37° C and 24 h at 4° C with 15 g/ml of purified PSAP (Radioimmunoassay Incorporated, Canada). Immunoreaction failed with this absorbed antiserum in both normal prostate and carcinoid tumours.

Radioimmunoassay. Radioimmunoassay for PSAP was carried out on the surgically resected tumour tissue of a case with rectal carcinoid by Dr. J. Morikawa (Eiken Immunochemical Laboratory, Tokyo, Japan). The method is described in Morikawa et al. (1980).

Kind-King method. Serum level of PSAP from a patient with rectal carcinoid was measured with Kind-King method (Kind and King 1954) which was the conventional method for PSAP in the clinical laboratory of Tohoku Rosai Hospital.

Results

All tumours showed the typical histological features of carcinoid tumours, mostly of a mixed pattern of trabecular and insular type. Only 5 cases from stomach and duodenum showed pseudoglandular pattern. Grimelius stain was definitely positive in all cases. The size of the tumours was differed in individual cases from several millimeters to around 10 cm. Metastases were observed in 5 cases.

The immunoreactive cells for PSAP were observed in the normal rectal mucosa adjacent to the tumour. Positive cells were seen in the crypts of the Lieberkühn glands. The immunoreactive cells were greater in number than the Griemlius positive cells (Figs. 1, 2). Immunoreactive cases with carcinoid tumours are summarized in the Table 1. The frequency of the immunoreactive cases to PSAP amoung the total tumours was 60%. Immunoreactivity was extremely high in the rectum and appendix and low in the small intestine and the stomach. The 3 bronchial carcinoids were negative. In the positive cases, PSAP immunoreactivity was also observed in metastatic lesions in the liver and kidney. Positive cells showed as dark brown, fine granules in the basal area of tumour cells (Fig. 3). Thus, such tumour cells were seemingly negative when they were cut horizontally at the apical portion of the cells. The site of reaction in the cytoplasm was similar to that of Grimelius stain and different from neuron-specific enolase which demonstrated diffuse cytoplasmic reaction, especially strong around the nucleus (Fig. 4).

All of the other neuroendocrine tumours examined, i.e. pheochromocytomas, medullary thyroid carcinomas and islet cell tumours of the pancreas were negative to PSAP.

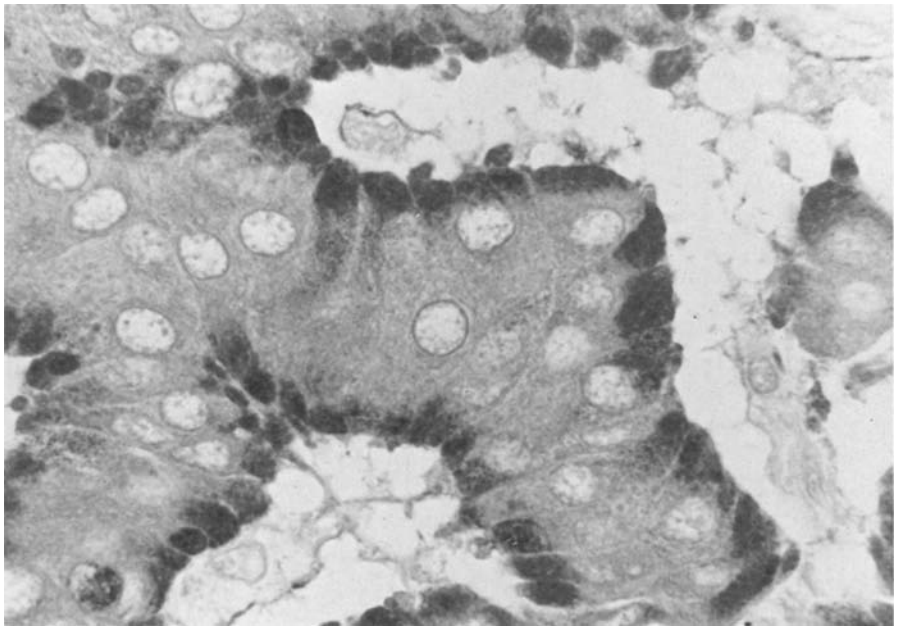

Fig. 3. Immunoreactive cells for PSAP in a rectal carcinoid tumour. Most of the tumour cells are positive. Infranuclear regions are strongly reactive with dark, granular staining (ABC method, ×400)

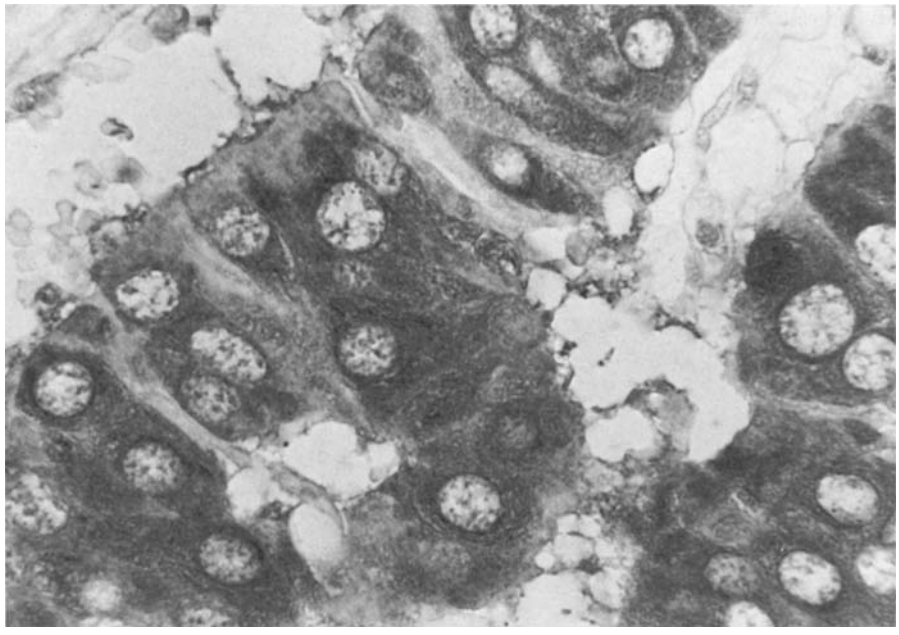

Fig. 4. Immunoreactive cells for neuron-specific enolase in a rectal carcinoid tumour. Diffuse cytoplasmic reaction, especially strong around nuclei is observed (ABC method, ×400)

Both of the prostate specific antigen and blood group substance were negative in carcinoid tumours. Neuron-specific enolase was detected in all carcinoid tumours.

In addition to immunohistochemical study, one case with rectal carcinoid was investigated for PSAP in preoperative serum and the tissue contents of the tumour were determined. Laparotomy revealed a rectal carcinoid measuring 5.5 × 3.5 × 3.5 cm in size and extensive metastases in the liver. Total acid phosphatase and PSAP in the preoperative serum were 29.0 U/l/37° C (normal < 5.2) and 26.1 U/l/37° C (normal < 1.5) respectively. Tissue content of PSAP in the tumour was 1,310 ng/mg protein. The serum level of glucagon was also high at 330 pg/ml (normal: 40–180 pg/ml). Immunohistochemical study revealed strong immunoreactivity to PSAP in most of the tumour cells. No cells immunoreactive for serotonin, somatostatin, ACTH or carcitonin were observed.

Discussion

Cells immunoreactive for PSAP in carcinoid tumours have been reported by Jöbsis et al. (1981) and Fishleder et al. (1918). Fishleder et al. (1981) noticed that all of 6 rectal carcinoid tumours reacted immunohistochemically to PSAP. They considered that this phenomenon was cross-reactivity probably secondary to contamination of the prostatic extract used to immunize the rabbit by argentaffin or argyrophil cells, or both, which have been reported to be present in the normal prostate (Azzopardi and Evans 1971; Kazzaz 1974). Capella et al. (1981) reported that about one-third of the 40 prostatic carcinomas contained endocrine-paracrine cells. Recently Azumi et al. (1984) reported an interesting case of a primary prostatic carcinoid tumour which showed argyrophilia, dense-core granules and immunoreactive prostatic acid phosphatase, together with prostate specific antigen in the same tumour cells. However, their case is an exceptionally rare case and may not have the antigenic determinant of the various antibodies available from several different laboratories.

Are any substances produced in both prostatic tissue and carcinoid tumours apart from PSAP? Immunoreactive cells for ACTH and β-endorphin were identified in the prostatic carcinomas (O'Briain et al. 1982). Though various kinds of peptide hormones are generally produced by carcinoid tumours, ACTH and β-endorphin are quite rare in rectal carcinoids (in preparation). In the present study, simultaneous measurement of serum levels with rectal carcinoid revealed a high level of glucagon. Immunoreactive cells for glucagon are, however, usually not observed in prostatic tumours (Capella et al. 1981). Chromogranin is another substance which may be present, and is widely distributed in the neuroendocrine tissue (O'Conner et al. 1983). In our control study, no immunoreactive cells to PSAP were observed in pheochromocytomas, which always contain a large amount of chromogranin. Therefore, the possibility of cross reaction of PSAP with chromogranin can be ruled out. Absorbed antiserum showed no im-

munoreaction in either prostate or carcinoids, therefore interpretation of cross-reactivity with any other known antigen can be ruled out.

In our study, serum PSAP was directly examined by the Kind-King method. Both methods of radioimmunoassay and the Kind-King revealed extremely high level of PSAP in the serum and tumour tissue of the rectal carcinoid.

The clinical utility of PSAP as tumour marker for carcinoids has not been established since the PSAP excess signis not known. In addition, most gastrointestinal carcinoid tumours are detected when small and may not produce enough PSAP to elevate the plasma level. However, as shown in the case presented here, careful estimation of serum PSAP may be valuable in both diagnosis and in post therapy monitoring of patients with carcinoid tumours. Furthermore, a location for the carcinoid tumour may be suggested since PSAP is preferentially produced by hindgut carcinoids.

Ovarian carcinoids are regarded as being of teratoma tous origin and to be similar to carcinoids of endodermal origin (Kimura and Sasano 1986) particularly the rectal carcinoid (O'Briain et al. 1982) by immunohistochemical studies of polypeptide hormones. This is based on the finding that positive immunoreaction for somatostatin, pancreatic polypeptide and glicentin are often seen. Positive immunoreaction for PSAP in ovarian carcinoids provides additional evidence of the similarity to rectal carcinoid. Analysis of tumours producing substances including PSAP may support new concepts of histogenesis.

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