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Case report

Multiple paraganglioneuromas

Kenji Kawaguchi[1], Touichiro Takizawa[1], Morio Koike[1], Ikuo Tabata[2], and Narihide Goseki[3]

[1] Department of Pathology, [2] Department of Medicine, [3] Department of Surgery, Tokyo Metropolitan Komagome Hospital, 3-18-22 Honkomagome Bunkyoku, Tokyo, 113, Japan

Summary. We report multiple paraganglioneuromas which occurred in a 40-year-old-man. Thirty-two tumours with similar histological appearance have been reported previously and most of them showed a striking predilection to occur in the second portion of the duodenum.

In this case, three masses were detected; one was located in the periampullary region of duodenum with a polypoid appearance, the others were well defined masses in peri-pancreatic tissue adjacent to large vessels. Histology revealed two cellular components, epithelioid cells with NSE immunoreactivity and S-100 protein containing spindle-shaped cells. Moreover, on electron microscopical examination, three different epithelioid cell types were seen. Type I was a figure differentiating to ganglion cells, type II to paraganglion cells, type III was a hybrid form of ganglion and paraganglion cells. Paraganglioneuroma revealed the histopathology of ganglioneuroma, paraganglioma and also a mixed appearance. In this respect the tumour may be considered to originate in undifferentiated neural crest cells and develop organoid differentiation.

Key words: Paraganglioneuroma – Paraganglioma – Ganglioneuroma – Gangliocytic paraganglioma – Hybrid cell

Introduction

Paraganglioneuroma is a very rare neoplasm occurring most frequently in the second portion of the duodenum. Previously 32 cases have been reported in literature as gangliocytic paraganglioma (Kepes and Zacharias 1971; Kermarec et al. 1976; Lauzon and Cadotte 1972; Reed et al. 1977), benign nonchromaffin paraganglioma (Babaryka 1978; Eugene et al. 1977; Lukash et al. 1966; Matilla et al. 1979; Taylor and Helwig 1962; Weitzner 1970),

Offprint requests to: K. Kawaguchi at the above address

ganglioneuroma (Dahl et al. 1957; Gemer and Feuchtwanger 1966; Goldman 1968) or simply paraganglioma (Friesen et al. 1974; Qizilbash 1973; Williams et al. 1980; Kheir et al. 1984). The term "paraganglioneuroma" was first described by T. Cooney (1978), who pointed out that there were two cell components (epithelioid cell and spindle-shaped cell) and a hybrid cell between them. We report a case of multiple paraganglioneuromas, whose microscopical characteristics were basically a mixed form of paraganglioma and ganglioneuroma. Electron microscopical examination also revealed a hybrid form between ganglion cell and paraganglion cells. This is the first report of multiple paraganglioneuromas and its histiogenesis has been investigated in three of the tumours by light and electron microscopy, and immunostaining methods.

Case report

A 40 year old tailor had been in excellent health one year before admission when an abnormality suggestive of duodenal tumour was pointed out by an upper gastro-intestinal (G-I) series. He was admitted to our hospital for further evaluation of this tumour. There was no history of abdominal pain, diarrhoea, weight loss, nausea, vomiting or hypertension. On examination the patient was in good health. No lymphadenopathy was found, there was no mass in the abdomen and physical and laboratory findings were normal. Amylase level was 336 IU per 100 ml, the gastrin 284 pg per ml (normal 40–200 pg per ml), the glucagon 136 pg per ml (normal 70–160 pg per ml). X ray films of an upper G.I. series disclosed submucosal tumours located in the second and third portion of the duodenum (Fig. 1). An operation was performed and three separate masses were found in the duodenum and around the pancreas.

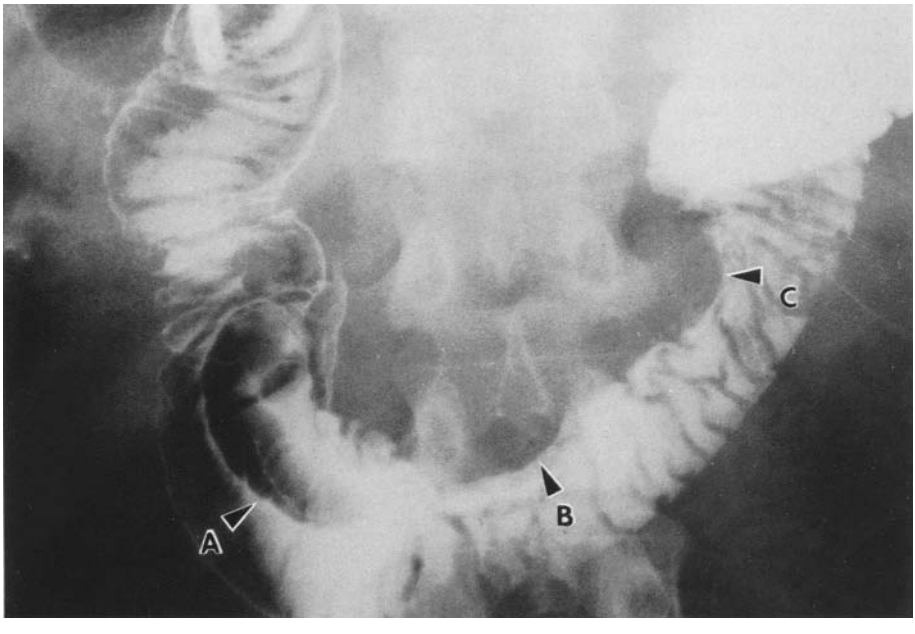


Fig. 1. Hypotonic duodenography shows either submucosal tumours or extra-duodenal compressive masses at the second and third portion of the duodenum. (*A*, *B* and *C*)

Materials and methods

Three masses were identified during the operation. The largest measuring $4 \times 4 \times 2$ cm, was located in the head of the pancreas attached to the posterior wall of the duodenum. The second, $4 \times 3 \times 2$ cm in size, was in the pancreatic body adherent to the anterior surface of the pancreas near the superior mesenteric artery and duodenal wall. These masses were encapsulated and lobulated (Fig. 2).

The third specimen consisted of a pedunculated tumour in the second portion of the duodenum, measuring $3.5 \times 3.0 \times 1.5$ cm. The surface of the tumour was almost covered by duodenal mucosa. The common bile duct and common channel were strikingly compressed but patent (Fig. 3). The cut surface of the 3 tumours showed a similar appearance of a fleshy, grayish white, slightly lobular pattern with rubbery consistency. For the light microscopic studies, these tumours were fixed in 17% neutral buffered formalin, processed routinely, and embedded in paraffin. Histological sections were stained with haematoxylin-eosin, silver impegration, periodic acid-Schiff (PAS), Grimelius for argyrophilia, Masson-Fontana for argentaffin granules, Congo red, Klüver-Barrera for Nissl staining, Bodian staining and Alcian blue-PAS. For electron microscopic studies, tissue fragments of 1 mm in diameter from the three tumours were fixed in phosphate buffered 3% glutaraldehyde, post-fixed in OsO_4, routinely processed and examined by H500 electron microscope. For immunohistochemistory, S-100 protein and neuron specific enolase (NSE) in tissue sections were carried out by Sternberger triple sandwich techniques using a 1:200 dilution of anti-S-100 protein and a 1:100 dilution of anti-NSE which were obtained from DAKO (USA).

Microscopic examination

Histopathology of the 3 masses was similar, but with some variation. The duodenal tumour was located mainly in the submucosa splitting up the neighbouring muscular layer. It was also seen in the lamina of the mucosa and in part in the stroma of the villi. It was not encapsulated but well demarcated. The others were encapsulated by fibrous connective tissue with spindle-shaped cells.

The tumours were composed of two clearly distinguishable cellular elements; the first was a spindle-shaped cell and the second an epithelioid cell. Epithelioid cell nests were arranged in round cell balls, strands, lamellar structures and ribbon-like fashion (carcinoid structure), separated by delicate stroma composed of connective tissue, spindle-shaped cells, and a fine vasculature (Fig. 4, 5). The shape of the epithelioid cells varied from round or oval to markedly elongated. The large cells had often fine basophilic cytoplasmic granules on Nissl's stain and dendritic process on Bodian's silver impegration, they were reminiscent of ganglion cells. Grimelius staining demonstrated argyrophilic cytoplasmic granules in some of elongated epithelioid cells, but Fontana-Masson stain was negative. Almost all epithelioid cells were strongly immunostained by NSE antibodies, which was present in APUD (amine precursor uptake and decarboxylation) cells and neurons of the diffuse neuroendocrine system but not in other peripheral cells. Spindle-shaped cells were negative (Fig. 6a). Spindle-shaped cells were reminiscent of the satellite cells of ganglion cells or sustentacular cells of paraganglia, and had the appearance of neurinoma. These spindle-shaped cells were positive on S-100 protein by PAP methods (Fig. 6b), Schwann cells of the peripheral nerves, the satellite cells of ganglia, and sustentacular cells of paraganglia were also stained. All epithelioid cells were negative. There were occasional small calcified foci and single cell calcification. There were a few mitotic figures, but no lymphatic permeation.

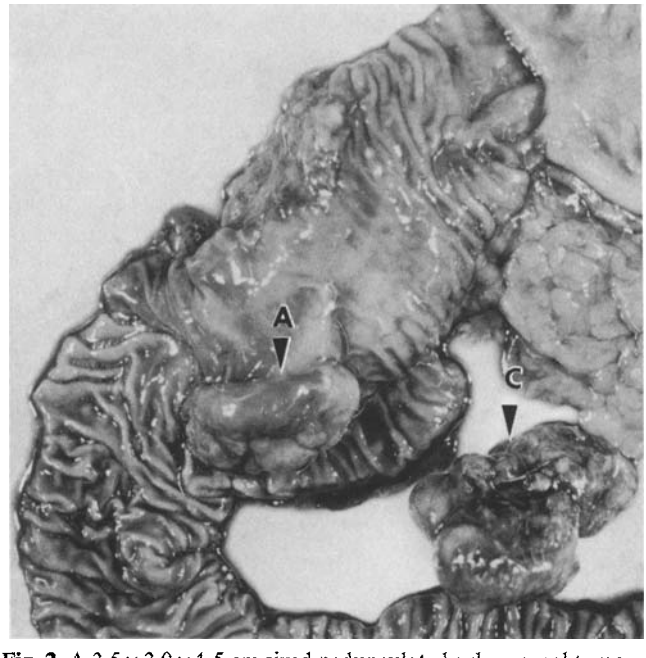


Fig. 2. A 3.5 × 3.0 × 1.5 cm sized pedunculated submucosal tumours in the periampullary region of the duodenum. (*A*)

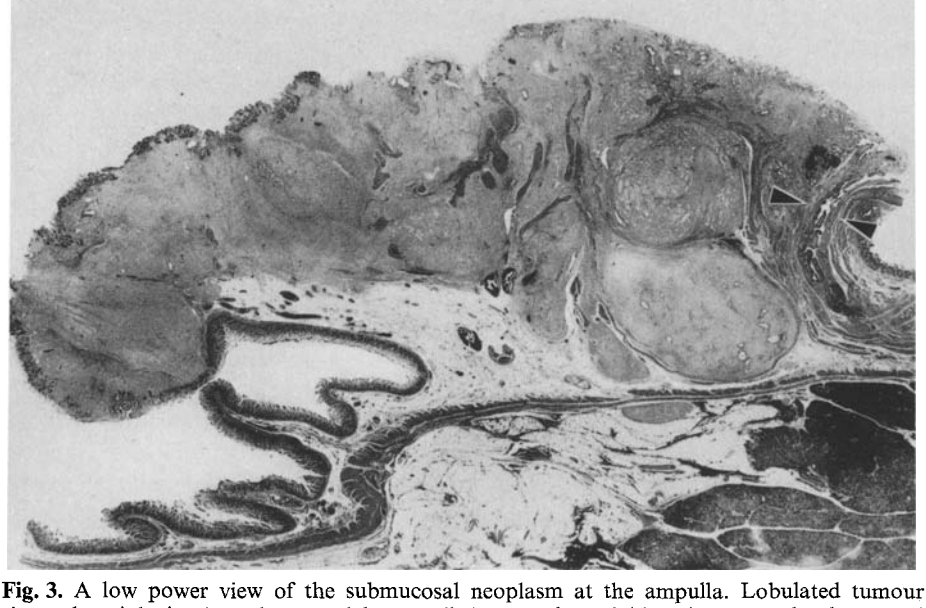
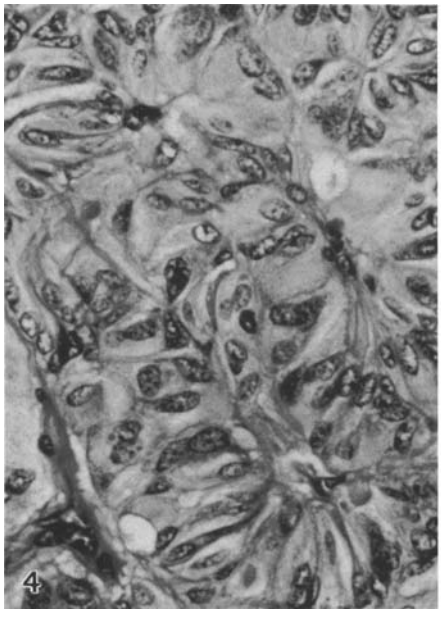


Fig. 3. A low power view of the submucosal neoplasm at the ampulla. Lobulated tumour situated mainly in the submucosal layer splitting up the neighbouring muscular layer and extending to the mucosa. Markedly compressed common bile duct (*arrow heads*) (H. & E. original magnification × 4)



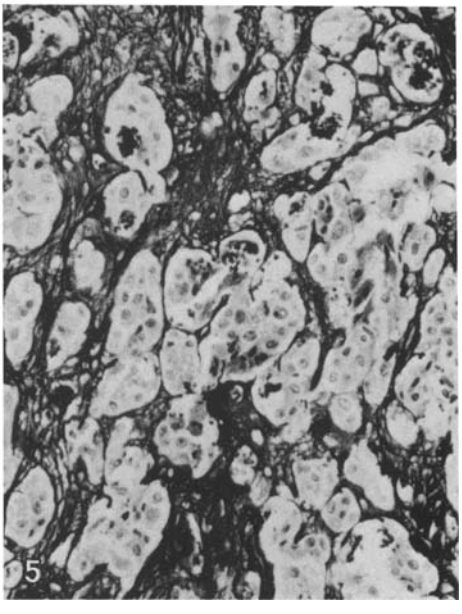
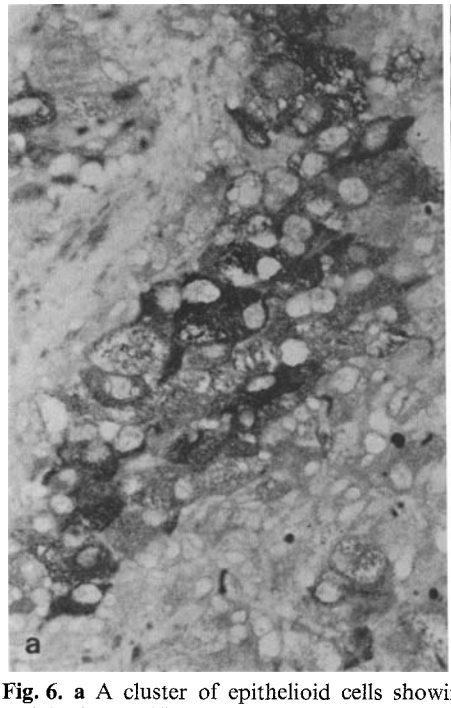


Fig. 4. Variable epithelioid cells showing oval to spindle-shaped cells. Ribbon like arrangements are seen. (H. & E. original magnification ×100)

Fig. 5. Silver impegration reveals alveolar structures of epithelioid cells (original magnification ×100)



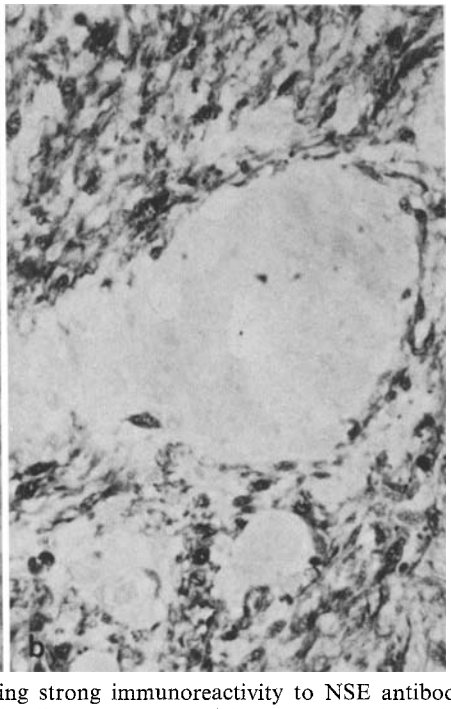


Fig. 6. a A cluster of epithelioid cells showing strong immunoreactivity to NSE antibodies (original magnification ×125). **b** Epithelioid cell nest surrounded by S-100 protein-positive spindle cells (original magnification ×125)

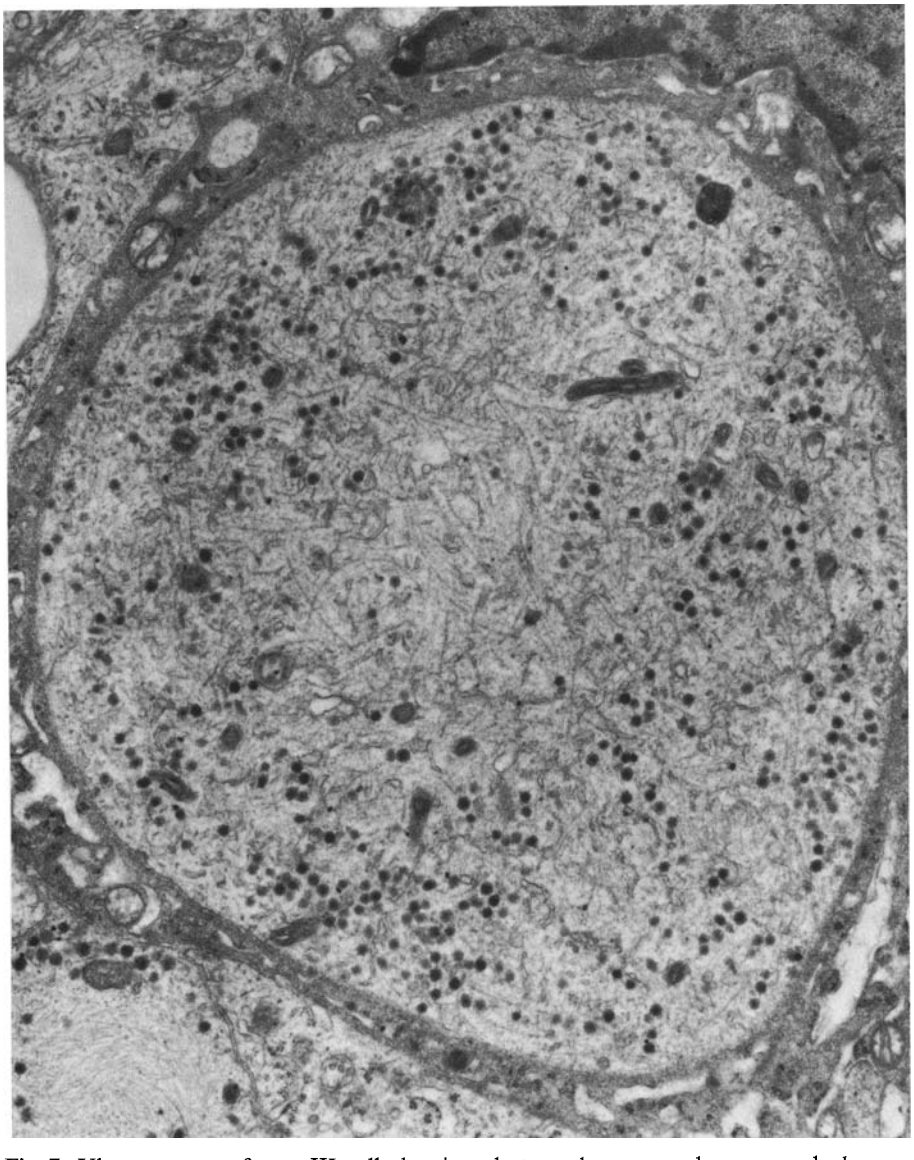


Fig. 7. Ultrastructure of type-III cell showing electron dense granules arranged along cell membrane and numerous fibrillary structures (× 18,000)

Electron microscopy

Electron microscopy revealed 3 different types of epithelioid cells.

Type I had a relatively uniform round to oval nucleus with prominent necleoli. The cytoplasm contained scanty rough endoplasmic reticulum and few mitochondria. This type of cell had a few electron dense secretory granules, varying in size from 100–200 nm, in the cytoplasm.

Type II showed convoluted and lobular nuclei. The cytoplasm of these

cells, however, appeared electron dense with large number of mitochondria, rough endoplasmic reticulum and free ribosomes. Many electron dense granules were also present.

Type III cells contained electron dense granules arranged along the cell membrane. The rest of the cytoplasm was filled with an extensive fibrillary structure, probably consistent with neurofilaments (Fig. 7).

These cells closely interdigitated with other cells by means of intercellular junctions such as desmosome and hemidesmosome.

Discussion

Paraganglioneuroma is an extremely rare tumour. The term "paraganglioneuroma" was first described by T. Cooney (1978). He reported a case of duodenal submucosal tumour containing epithelioid cells with a "Zellballen" structure, and spindle-shaped cells. On electron microscopic examination, his descriptive terms "light" and "dark" cells refered to the granule-containing epithelioid cells and the neurofilament-containing spindle-shaped cells, respectively. Furthermore, he indicated that the "hybrid cell" with both neurofilaments and secretory granules was the key element of this tumour. In the most extensive series reported to date, similar tumours have been described as "gangliocytic paraganglioma", "benign nonchromaffin paraganglioma", "ganglioneuroma", or simply "paraganglioma".

The previously reported 32 tumors in 32 cases, all of which were benign, involved the second portion of the duodenum with the exception of 4 tumors in the third and fourth portion of the duodenum and the jejunum. The present report is, to our knowledge, the first description of simultaneous occurrence of three tumours.

In the present case, the 3 tumours were located in the periampullary portion of the duodenum and peripancreatic tissue, close to large vessels. Histological examination revealed 2 types of cell components, the first epithelioid cell with "Zellballen" architecture, the other spindle-shaped among neurofibers and epithelioid cell nests. The proportion of these elements was different in each tumour.

Grimelius positive argylophilic cells scattered in epithelioid cell nests showed a resemblance to paraganglioma. Ribbon-like structures composed of elongated epithelioid cells were reminiscent of carcinoid tumour. From these light microscopic findings and the immunoreactivity of neuron specific enolase, the epithelioid cells probably had the characteristics of ganglion cells, APUD cells or neuroendocrine cells.

On electron microscopical examination the epithelioid cells revealed 3 types; the first type might differentiate to ganglion cell, the second to a paraganglion cell or carcinoid cell, the third, having elements of both ganglion cells and paraganglion cells.

S-100 protein positive spindle-shaped cells also disclosed a transition from Schwann cell to sustentacular cells or satellite cells.

The varied morphological structure of these tumours give rise to an interesting question concerning histogenesis. Two patterns are mixed in varying proportions, each compatible with paraganglioma or ganglioneur-

oma and there are transitional forms from the former to the latter. Furthermore there are transitional forms to carcinoid tumour.

Paraganglioma and ganglioneuroma are derived from cells of neural crest origin, which give rise to the cranial and spinal sensory ganglia. Migrating cells from neural crest differentiate to the para-vertebral and visceral autonomic ganglia, the chromaffin system, the Schwann cells investing all peripheral nerves, the leptomeninges, and some of the melanoblasts of the skin.

We believe that the morphological variation in paraganglioneuroma is an expression of differentiation by a pluripotent stem cell from aberrant undifferentiated or imcompletely developed cells originating from neural crest.

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