

tions that may result in disfigurement and functional impairment. Other manifestations of the syndrome include neuroendocrine tumors of the duodenum (somatostatinomas) and pheochromocytomas.

Numerous mapping studies localized the NFI gene on the long arm of chromosome 17 near the centromere and led to cloning of the complete coding region (13). The NFI gene encodes an mRNA of 11-13 kb containing at least 59 exons. Four alternatively spliced NFI transcripts have been identified. NFI appears to be a tumor-suppressor gene. Its product, called neurofibromin, is a GTPase activating protein (GAP)-like polypeptide that appears to down-regulate the RAS oncogene. Over 80% of germline mutations appear to predict severe truncation of neurofibromin.

Somatostatinomas in neurofibromatosis patients are typically "pure" tumors and exhibit psammoma bodies in approximately 66% of tumors. Metastatic disease is rare (27%) and mainly confined to lymph nodes (88%)

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Gangliocytic paragangliomas of the duodenum

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Introduction

Gangliocytic paragangliomas, also referred to as nonchromaffin paragangliomas or paraganglio-neuromas, are peculiar lesions com-

posed of neuroendocrine epithelial cells, ganglionic neurons and sustentacular cells, which have been reported almost exclusively in the upper gut. Within the latter, they are found almost invariably in the duodenum, generally in the vicinity of the ampulla of Vater, although isolated reports of their presence in the jejunum have been made. Whereas these are virtually always isolated single lesions, there are sporadic reports of multiple lesions or of their association with duodenal adenocarcinoma, somatostatin-producing carcinoid tumor, patients with von Recklinghausen disease, or pancreatic rests.

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Gangliocytic paragangliomas generally appear as submucosal masses that protrude into the lumen of the duodenum where they may obstruct or bleed as a consequence of their tendency to ulcerate. They generally measure between 1 and 3 cm in maximum diameter, although rare instances of lesions measuring 10 cm in maximum diameter have been recorded. They are more common in men than in women and their age of appearance ranges between the third and the ninth decade of life, with a peak incidence in the mid-fifties. Gangliocytic paragangliomas are generally benign and, as a rule, local excision is curative. However, multiple instances of malignant behavior, with metastases to regional lymph nodes, have been reported.

Histogenesis

In view of the diversity of the elements composing gangliocytic paragangliomas, some authors have proposed that these lesions represent a hamartomatous proliferation, perhaps originating from different embryonal layers during the formation and migration of the pancreatic primordia. However, the fact that a handful of such lesions has undergone malignant transformation and produced lymph node metastases argues in favor of a true neoplastic nature. Interestingly, in one of the reported cases of lymphatic spread, only the neuroendocrine epithelial elements were present in the metastasis. This finding suggests that, even if these lesions are originally malformations derived from diverse origins, their epithelial neuroendocrine component is indeed capable of behaving as a neoplasm, and even with malignant potential.

Microscopic morphology

Light microscopy and histochemistry

Three cellular elements compose gangliocytic paragangliomas of the duodenum. Firstly, neuroendocrine cells with an epithelial appearance. These cells have a moderate amount of faintly granular eosinophilic or amphophilic cytoplasm and round to oval nuclei with delicate, stippled chromatin and generally inconspicuous nucleoli. They are clustered in variable patterns, mostly in "Zeiballen" like paragangliomas elsewhere, or in anastomosing ribbons like carcinoid tumors. Grimelius' silver stain is generally positive, whereas only exceptionally they are positive for the argentaffin stains. Secondly, ganglionic neurons, characterized by abundant cytoplasm with an irregular contour and large, vesicular nuclei endowed with prominent nucleoli. These cells are found interspersed among clusters of neuroendocrine cells or in close contact with them and their cytoplasm displays strong staining with cresyl violet, indicating the presence of Nissl substance. Apparent transitional forms between neuroendocrine and ganglionic cells have been reported. Thirdly, interstitial cells, representing Schwann cells, in contact with neurons

and sustentacular elements inserted among neuroendocrine elements. The intervening stroma consists of loose connective tissue, which contains neuronal axons, related to the ganglion cells and demonstrated with Bodian's silver technique. Amyloid deposition has been reported in a few cases.

Electron microscopy

Ultrastructural analysis of the gangliocytic paragangliomas of the duodenum reveals cell types comparable to those described by light microscopy. The neuroendocrine cells contain numerous cytoplasmic secretory granules, which are membrane-bound and which have cores of variable, generally high, electron density. Some microfilaments are seen within these cells, generally arranged in bundles. The ganglion cells, in addition to containing abundant rough endoplasmic reticulum, show the presence of neurotubules and microfilaments, together with scattered vesicles. Combined neurotubules and vesicles are also found in axons emanating from the ganglion cells. The Schwann and sustentacular cells are characterized by slender cytoplasmic projections with an electron dense background containing large numbers of intermediate filaments.

Immunocytochemistry

Numerous immunocytochemical studies have been carried out on these lesions and the results are often contradictory. The generic marker, neuron-specific enolase, is positive in the paraganglionic cells and neurons, whereas chromogranin A has been reported as positive by some and negative by others in both types of cells. Neurofilament antibodies are positive in neurons and their axons; their immunoreactivity in other cell types is, again, controversial. The interstitial cells are always positive for 5-100 protein, which is absent from the other two cell types. Numerous peptides have been investigated and detected by different authors, mostly inside paraganglionic cells and also in occasional neurons. Whereas the list of peptides reported to be contained in individual paragangliomas is very long, the most commonly found seem to be pancreatic polypeptide, somatostatin and, with lesser frequency, serotonin. The enormous variation in the immunocytochemical profiles found in the different reports may reflect in part the heterogeneity of these lesions as well as differences in technical capabilities among the authors.

Differential diagnosis

When the complete lesion of an excision specimen is observed under the microscope, the combination of the different cellular components described above is quite typical and the diagnosis is easily made. However, when the pathologist is presented with a small endoscopic biopsy, it is quite possible that a given sample may lack the neuronal elements that characterize the gangliocytic paragangliomas, and a differential diagnosis may need to be made with a carcinoid tumor of the area. Immunocytochemical investigation with S-I 00 protein antibodies is a valuable tool, since gangliocytic paragangliomas contain immunoreactive sustentacular cells, absent from carcinoid tumors.

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Duodenal lesions in patients with polyposis

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Introduction

"Polyposis" refers to well-defined syndromes in which the primary feature is the presence of multiple polyps. In the commoner 'polyposis syndromes', such as familial adenomatous polyposis (FAP) and juvenile polyposis (JP), the definition is primarily associated with the number of polyps and an appropriate clinical setting with or without molecular confirmation. The major polyposis syndromes recognized to date include FAP, JP, Peutz-Jeghers syndrome, metaplastic polyposis, Cronkhite-Canada syndrome, Cowden's syndrome and benign and malignant lymphoid polyposis. The duodenum can be involved in several of these.