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Gastric Autonomic Nerve (GAN) Tumor and Extra-adrenal Paraganglioma in Carney's Triad

A Common Origin

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Carney's Triad comprises a triad of neoplasms: gastric stromal tumor, extra-adrenal paraganglioma (usually functional), and pulmonary chondroma. At least two of these are needed for the presumptive diagnosis of the Triad. This report presents a patient who had resected a gastric tumor and nonfunctional extra-adrenal paraganglioma. The gastric tumor resembled a gastric leiomyosarcoma by light microscopy, but electron microscopy revealed it to be a gastric autonomic nerve (GAN) tumor. Based on this evidence it appears that both the gastric lesions and the paragangliomata of Carney's Triad are tumors of the autonomic nervous system. Thus, the Triad may be a disorder of the autonomic nervous system rather than a multiple endocrine neoplasia syndrome or multiple hamartoma syndrome.

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In 1977, CARNEY ET AL. FIRST CALLED ATTENTION to an unusual triad of neoplasms typically arising in females: gastric leiomyosarcoma, extra-adrenal paraganglioma (usually functional), and pulmonary chondroma. Others have also observed the occurrence of these tumors in the same patient.[2–7] By 1984, Carney[8,9] had seen over 20 cases of this curious syndrome. All observers have been unable to explain the spontaneous occurrence of such apparently disparate and rare tumors. This report provides evidence that the gastric stromal neoplasms of this syndrome are probably not of smooth muscle origin but rather may arise in the autonomic nervous system and be true neural tumors. This derivation would provide a common origin for the gastric tumors and extra-adrenal paragangliomata and may explain the association of these neoplasms in patients.

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Case Report

This male patient was 16 years old when he first noted several months of easy fatigability and subcostal discomfort associated with a 15-pound weight loss. He had no headache, flushing, or palpitations, and was never hypertensive. On examination he had a right Horner's syndrome (ptosis, miosis, enophthalmos) and a palpable epigastric mass. Upper gastrointestinal series and computed tomography (CT) suggested that the mass was a large gastric tumor. An additional finding on CT was a mass in the area of the left adrenal. At celiotomy, a large gastric tumor on the

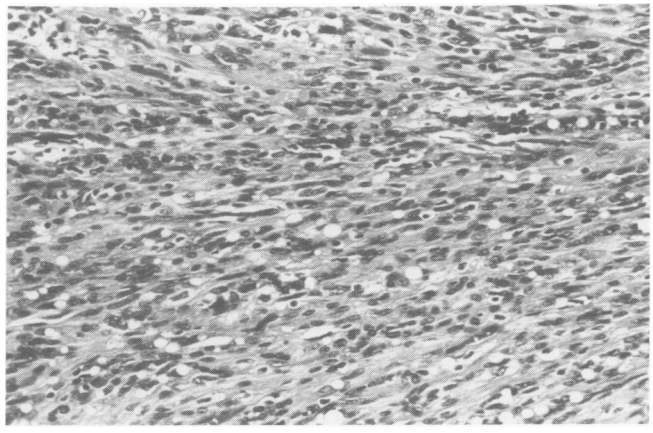

FIG. 1. Photomicrograph of the gastric tumor that is composed predominantly of spindle cells with uniform elongated nuclei. Cytoplasmic vacuolization adjacent to nuclei is evident in many cells. (Hematoxylin and eosin stain, ×210.)

lesser curvature was resected by a subtotal distal gastrectomy with a Billroth II anastomosis. The tumor was a well-demarcated, 8-cm mass attached to the serosa on the gastric lesser curvature. Microscopically, the tumor consisted chiefly of spindle cells with virtually no nuclear pleomorphism, rare mitoses (4 per 50 high-power fields), and no vascular invasion. The light microscopic impression was spindle cell tumor, probably of smooth muscle origin (Fig. 1). Immunoperoxidase studies showed positive staining of the gastric tumor with antibody to neuron-specific enolase but no staining with antibody to S100 protein. Electron microscopic examination revealed a tumor of neural origin: gastric autonomic nerve (GAN) tumor (Fig. 2). The diagnostic features of this newly recognized tumor[10] include elongated tumor cells with blunt processes and small dense core granules. Specific ultrastructural features that are diagnostic for smooth muscle cells and Schwann cells were absent.

The patient recovered uneventfully from surgery but the Horner's syndrome persisted. A CT series obtained 3 months after operation showed enlargement of the left adrenal mass. He again had no headaches, flushing, or palpitations, and was never hypertensive. Because of the concern of metastasis, he had exploratory surgery again and the mass was excised along with a portion of the left adrenal gland that was in-

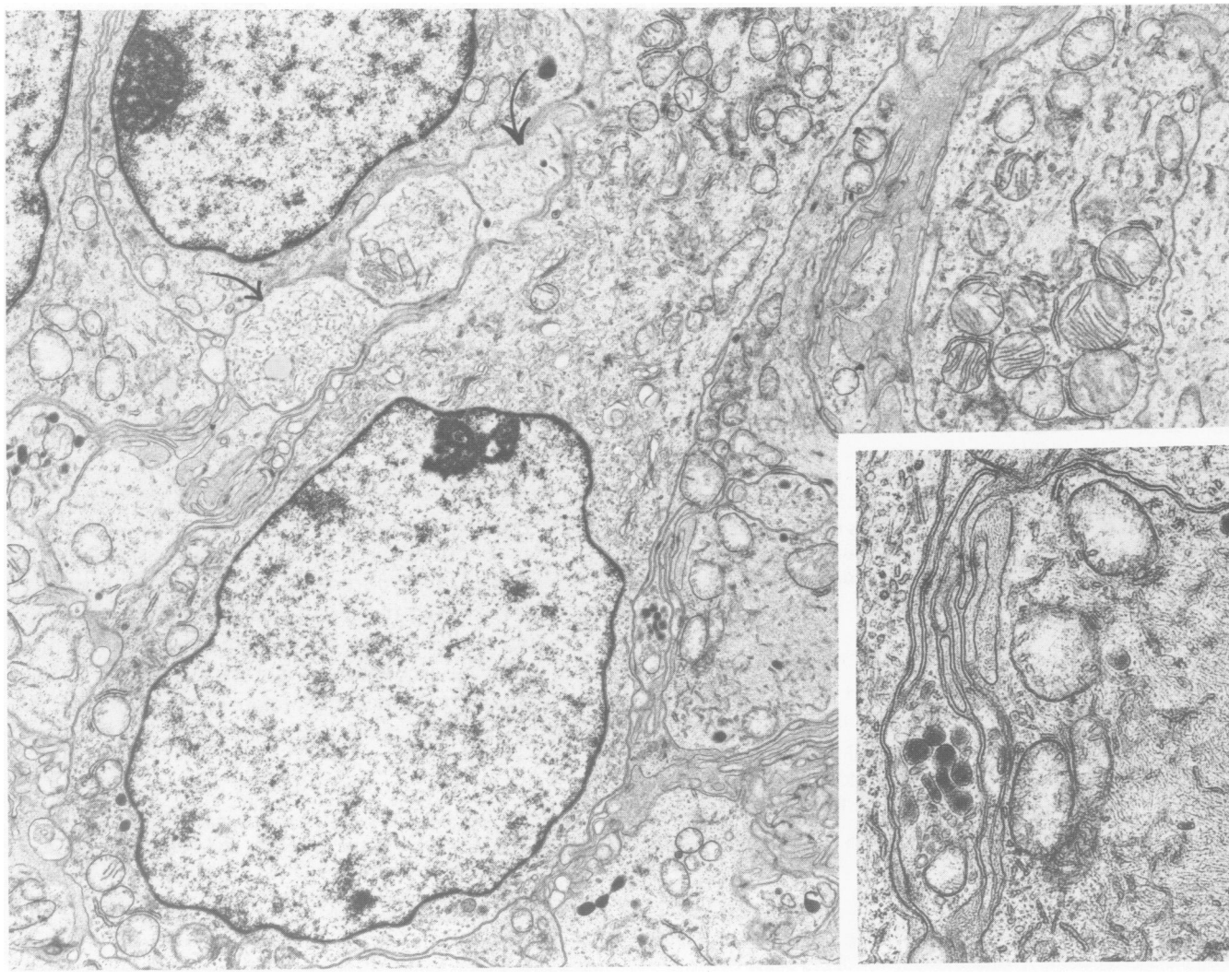

FIG. 2. Electron micrograph of GAN tumor shows a tumor cell with an elongated blunt process surrounded by numerous tumor cell processes and axons. Tumor cells have dense core granules that cluster in axons (inset) connected by synaptic densities. Some axons are filled with neurotubules (arrows) as well as a few dense core granules. (×8000; inset ×19,000.)

extricably bound to it. At pathologic examination, the tumor was clearly separate from the adrenal gland. The mass was firm, tan, and 3.5 cm in diameter. Microscopically, it consisted of cords and nests of large, moderately pleomorphic cells with scattered mitoses, embedded in a vascular stroma. The impression was that this mass was a paraganglioma (Fig. 3). Immunoperoxidase studies revealed this tumor to show positive staining with antibody to chromogranin. Ultrastructural examination of this retroperitoneal paraganglioma revealed large tumor cells that were filled with large, swollen mitochondria and attached by junctions (Fig. 4). Some tumor cells contained medium-sized lightly dense granules analogous to those described as containing epinephrine.[11] Nearly all tumor cells also contained small dense core granules identical to those present in the gastric tumor. However, granules identical to the norepinephrine granule type present in adrenal medullary pheochromocytomas were absent.[11] This latter granule type is the one most often seen in functional pheochromocytomas. Their absence in this case then correlates with the clinical absence of evidence of a functional paraganglioma.

The patient again recovered uneventfully from surgery. The Horner's syndrome persisted. Another CT series revealed a nodule in the left neck

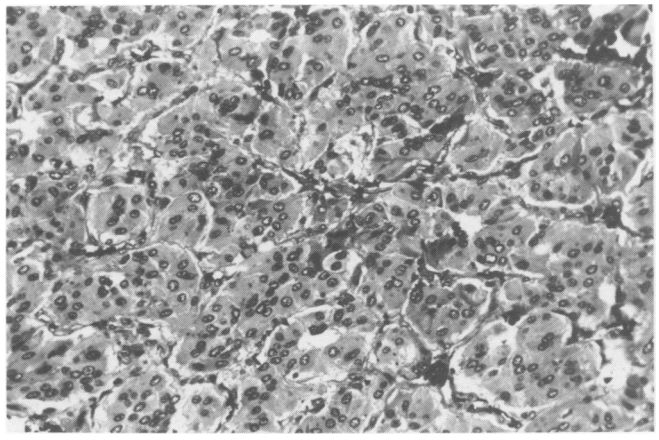

FIG. 3. Photomicrograph of the retroperitoneal paraganglioma. The tumor consists of nests of moderately pleomorphic cells separated by a delicate fibrovascular stroma. (Hematoxylin and eosin stain, ×210.)

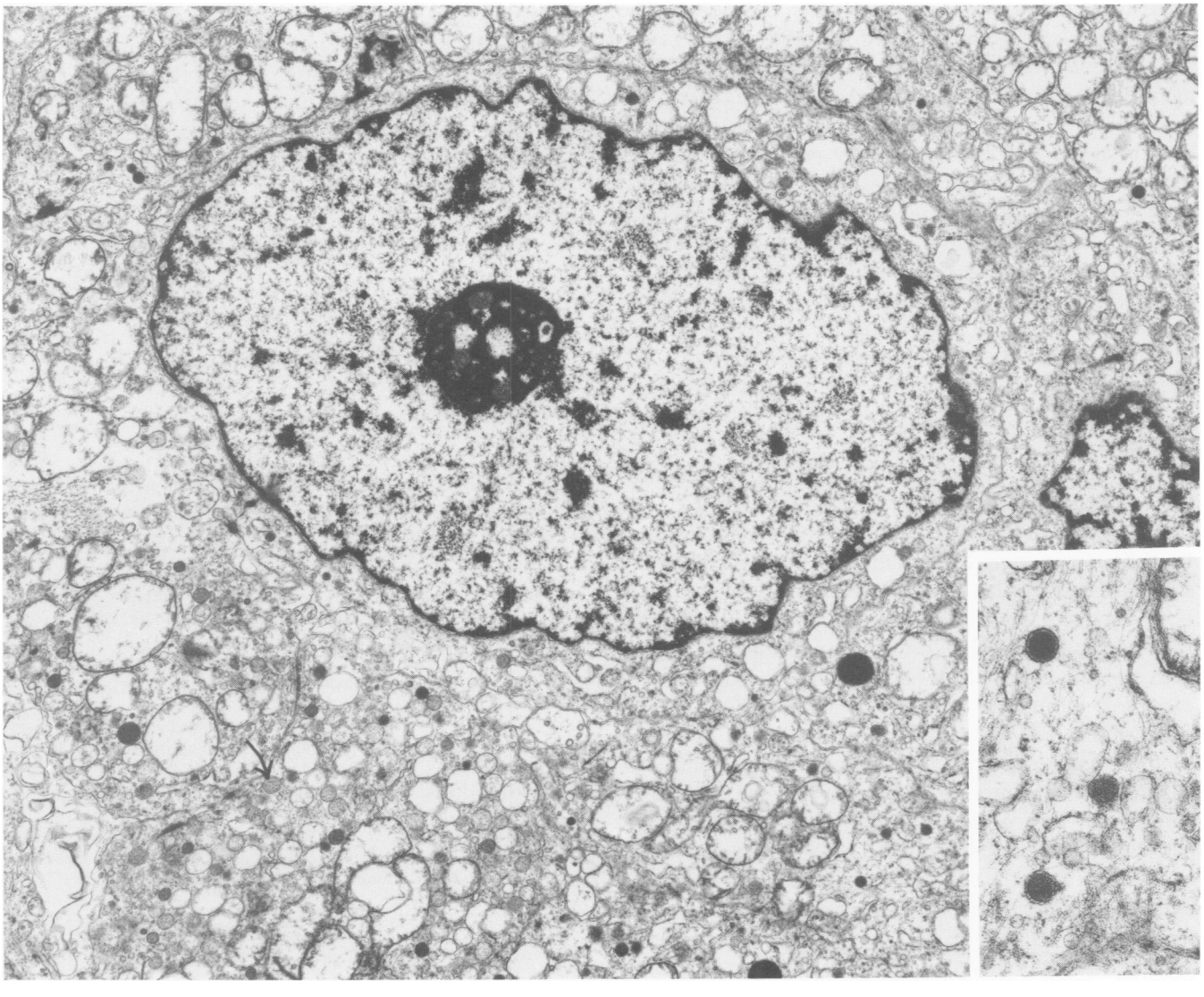

FIG. 4. Electron micrograph of paraganglioma shows a large tumor cell attached to others by junctions and filled with swollen mitochondria. The nucleus has an open chromatic pattern and a large nucleolus. Small dense core granules (inset) and large less dense granules (arrow) are present. (×8000; inset ×24,500.)

at the level of the third cervical vertebra displacing the external carotid artery anteriorly and the internal carotid artery posteriorly, but no masses were palpable on physical examination. This nodule did not enhance with contrast, a finding not typical for paragangliomata.[12] CT of the thorax did not disclose any pulmonary or mediastinal lesions. The patient continues to be asymptomatic with no elevation in urinary metanephrine or vanillyl mandelic acid (VMA) levels. A portion of the paraganglioma was assayed for nerve growth factor[13] and was found to have none. No amplification of the neuroblastoma-associated oncogene *N-myc* was found in the paraganglioma.[14]

Discussion

The classification of gastric tumors is undergoing great change with the use of electron microscopy for the study of these lesions. For example, Walker and Dvorak[10] have suggested that some lesions previously believed to originate in smooth muscle are actually neural in origin because nests of the tumor cells mimic the ultrastructural appearance of the enteric autonomic nervous system. The small dense core granules noted in this patient's gastric lesion are identical to the noradrenalin-containing granules of the enteric nervous system.[15,16] In our case these granules were found in Golgi synthetic areas as well as close to tumor cell surfaces. Tumor cells displayed elongated processes and axons with synaptic densities that also contained dense core granules, neurofilaments, and clear vesicles. The ultrastructural features in this case are the same as those recently described by Walker and Dvorak under the heading of GAN tumor.[10] A similar neoplasm has been described by Herrera et al.[17] in the small bowel, and they termed it a plexosarcoma. In addition, the immunocytochemical demonstration of neuron-specific enolase in the tumor adds support to the concept of its neural origin.[18]

Our patient has two of the three neoplasms that comprise Carney's Triad. Carney does not mention electron microscopic examination of the gastric specimens, and by light microscopic examination, the lesions were described as gastric leiomyosarcomata. This would have been the diagnosis in our patient if not for the electron microscopic findings that instead demonstrated the neural origin of the tissue. Only half of Carney's patients had extra-adrenal functioning paragangliomata. Our patient clearly has at least one extra-adrenal paraganglioma, albeit nonfunctional. Electron microscopy and immunocytochemistry confirmed the presence of neurosecretory granules in the paraganglioma.[19] The majority of the paragangliomata described as part of the Triad are located in the neck and thorax, not the abdomen as with our patient. However, the Horner's syndrome and the neck mass seen on CT may be evidence of a lesion in the neck. The occurrence of the nodule and the Horner's syndrome on opposite sides suggests there may be bilateral lesions. Although 80% of Carney's patients have had pulmonary chondromas, our patient continues to have a normal chest radiograph. However, it is important to note that all three lesions need not be present to make the provisional diagnosis of Carney's Triad.[9] If a pulmonary lesion develops, we will entertain the possibility that the mass represents a benign chondroma rather than a metastatic tumor.

We believe that two of the three tumors comprising Carney's triad may be neoplasms of autonomic nerve cell origin that are manifested as GAN tumors and extra-adrenal paragangliomata. Confirmation of our hypothesis will have to await re-examination of previously reported gastric lesions using the electron microscope. The reason for the association with pulmonary chondromas remains unclear. Paragangliomata are believed to be true neoplasms of the chief cell elements of paraganglia rather than hyperplasia or hamartomatous change because the cellular elements resembling the normal sustenticular cells of paraganglia are rare and the normal relationship of nerve fibers to chief cell nests is lacking.[20] Rather than a multiple endocrine neoplasia syndrome or multiple hamartoma syndrome, this once curious admixture of tumors can now be better understood as a manifestation of multiple tumors of similar origin, *i.e.*, the autonomic nervous system.

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