Endocrine tumors of the pancreas and gastrointestinal tract
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CHAPTER 2

GANGLIOCYTIC PARAGANGLIOMA OF THE APPENDIX

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Abstract

Aims
A case of gangliocytic paraganglioma is reported in the appendix which, to the best of our knowledge, is the first case at this particular site to be described in modern literature.

Methods and results
A 47-year old man with signs and symptoms of acute appendicitis underwent appendectomy. In the resected specimen a tumor with a diameter of 9 mm was found, which microscopically consisted of three different cell types: (a) epithelioid cells lying in a trabecular pattern and in formations reminiscent of 'Zellballen' as seen in paragangliomas (b) spindle cells and (c) ganglion-like cells. A diagnosis of 'gangliocytic paraganglioma' was made and confirmed by immunohistochemical and ultrastructural examination.

Conclusion
Gangliocytic paragangliomas are rare tumors of uncertain histogenesis. More than 40 years ago a tumor in the appendix with features similar to our case was described by Masson as 'neurocarcinoide'. Concerning its origin, Masson, as well as other authors describing gangliocytic paragangliomas decades later, referred to the endodermal-neuroectodermal complexes found by Van Campenhout. It is felt that the current finding of a gangliocytic paraganglioma in the appendix supports the hypothesis that gangliocytic paragangliomas arise from these embryonal structures.

Introduction
The neuroendocrine system consists of neurosecretory cells, which are scattered throughout the body. It gives rise to several neoplasms with neuronal and neuroendocrine features of which neuroblastoma, ganglioneuroblastoma, ganglion-neuroma, carcinoid and paraganglioma are examples. A rare neoplasm, known as gangliocytic paraganglioma, combines elements of some of these tumors. It is characterized by the presence of three different cell types: (1) epithelioid cells, resembling paraganglioma or carcinoid tumor cells, (2) spindle cells, reminiscent of Schwann cells and (3) ganglion- or ganglion-like cells. Most gangliocytic paragangliomas arise in the duodenum and are tumors of benign nature, although in a few cases metastases to the regional lymph nodes have been described. Moreover, patients with von Recklinghausen's disease seem to have an increased risk for developing a gangliocytic paraganglioma. The histogenesis of the tumor is a matter of debate. Some authors consider gangliocytic paragangliomas as true neoplasms of neuroendocrine origin. Because of the proximity of most gangliocytic paragangliomas to (ectopic) pancreatic tissue and the occasional expression of pancreatic enzymes, others believe that
gangliocytic paragangliomas are hamartomatous lesions developing in misplaced embryonic pancreatic tissue. As we learn from the work of Perrone et al. in the first half of this century Van Campenhout described 'sympathetico-insular complexes' from endodermal-neuroectodermal origin in the ventral primordium of the pancreas. Development of gangliocytic paragangliomas from these complexes might explain why these tumors consist of both epithelioid and neural cells. Van Campenhout found other endodermal-neuroectodermal complexes in the liver, small intestine and appendix of mammalian embryos. 

We report a case of gangliocytic paraganglioma of the appendix, which, to the best of our knowledge, comprises the first case at this particular site to be described in modern literature.

Case report

A 47-year old man underwent appendectomy because of signs and symptoms of acute appendicitis. The postoperative course was unremarkable. The appendix was submitted for pathological examination. Macroscopically the appendix showed a red serosal surface, focally covered with a suppurative exudate. The dilated lumen contained feces. A tumor was not seen at gross examination. Samples from the base, the mid-zone and the tip were taken for microscopy. In the routine H&E stained slides the appendix showed acute inflammation and ulceration of the mucosa. A nonencapsulated, unsharply demarcated submucosal cellular mass (diameter 9 mm) was detected in the tip. In the lesion three different celltypes were recognized. The superficial part consisted of large cells with acidophilic cytoplasm and eccentric nuclei, resembling ganglion cells. They were surrounded by spindle cells. In the deeper part of the tumor, there was a gradual transition into a component consisting of epithelioid cells, lying in a trabecular pattern and in formations reminiscent of 'Zellballen' as seen in paragangliomas (figure 2.1).

Figure 2.1 A: The part of the tumor, formed by epithelioid cells lying in a trabecular pattern and in aggregates reminiscent of 'Zellballen'. B: The part of the tumor, consisting of ganglion-like cells surrounded by spindle cells.
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Figure 2.2 Immunohistochemical staining for S100 in the neural part of the tumor (A), showing positivity in the spindle cells and in the epithelioid part of the tumor (B), showing S100-positive sustentacular cells.

The epithelioid component infiltrated into the muscularis propria and reached the serosal surface of the appendix. Given the above three cell types, the criteria for the diagnosis 'gangliocytic paraganglioma' were met. Additional immunohistochemical stainings were performed. All three cell types showed weak expression of neuron-specific enolase (NSE). The spindle cells and the cells surrounding the 'Zellballen', the so-called sustentacular cells, showed S100 positivity (figure 2.2).

The epithelioid and ganglion-like cells were chromogranin and synaptophysin positive. A part of the epithelioid cells was positive for pancreatic polypeptide (PPP). Immunostaining for CAM 5.2, keratin-7, LU-5, vimentin, HMB-45, serotonin, glucagon, somatostatin, substance-P and gastrin was completely negative in all three cell types.

The diagnosis 'gangliocytic paraganglioma' was confirmed by ultrastructural examination of the paraffin-embedded material. In the epithelioid part of the tumor, the cytoplasm of the epithelioid cells contained variable numbers of neuroendocrine granules, ranging from only a few dispersed granules to massive numbers of granules, virtually filling the whole cytoplasm. In addition, there were numerous intermediate filaments, often arranged in large whorls. Slender sustentacular cells, surrounding and traversing the cell groups, could also be recognized. In the part of the tumor that consisted of large ganglion-like cells, neural differentiation was evident from the presence of prominent stacks of cisternae of rough endoplasmatic reticulum, corresponding to Nissl bodies and numerous intermediate filaments. Between the ganglion-like cells, there were many axon-like cell extensions containing filaments. The epithelioid and neural components of the tumor were not strictly separated. For example, both the ganglion-like cells and the axon-like structures contained neuroendocrine granules.
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Discussion
Gangliocytic paraganglioma is a rare entity of uncertain histogenesis. Of the cases described in modern literature, none concerns a gangliocytic paraganglioma arising in the appendix. A search of older documents drew our attention to Masson's original description of a ‘neuro-carcinoïde’ of the appendix, which showed remarkable similarities to the lesion that we now know as gangliocytic paraganglioma. In fact, this lesion described by Masson was mentioned previously, when it was postulated by Perrone et al. that gangliocytic paragangliomas are derived from Van Campenhout's sympathetico-insular complexes; these endodermal-neuroectodermal complexes can be found in the appendix of mammalian embryos and in that regard our case supports the postulated hypothesis concerning the origin of gangliocytic paragangliomas from Van Campenhout's complexes.

The fact that the appendix contains neuroendocrine cells could be used as an argument in favor of the theory that a gangliocytic paraganglioma is a neoplasm of neuroendocrine origin, but it does not explain the presence of the three different cell types in the tumor. When we compare the tumor in the appendix of our patient to Masson's description and pictures of the 'neuro-carcinoïde' of the appendix, we believe that it is indeed the same lesion and that therefore Masson can be considered the first who described a gangliocytic paraganglioma of the appendix. Our data do not support the hypothesis that a gangliocytic paraganglioma is a hamartomatous lesion that necessarily arises from (embryonic) pancreatic tissue. The tumor was found in a part of the gastrointestinal tract that is not very close to the pancreas and that is not derived from the foregut. Moreover, the appendix did not contain ectopic pancreatic tissue. A part of the epithelioid cells was PPP-positive. Although the name pancreatic polypeptide suggests that this peptide is specific for pancreatic tissue, expression of PPP has, for example, been described in paragangliomas and does not necessarily mean that the cells are of pancreatic origin.

Interestingly, Masson apparently concurs with a derivation of the lesion from the endodermal-neuroectodermal complexes as when referring to Van Campenhout, he states that: 'Ainsi, l'hypothèse d'un neurendoderme reçoit un début, au moins, de confirmation.'

References
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