

## Neuroendocrine Neoplasm in Cecal Appendix: A Case Report

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**Abstract:** Although neuroendocrine neoplasms are relatively uncommon entities, the appendix is a site with relatively frequent emergence of this pathology and its precise diagnosis and clinical management have been a challenge for practitioners. This paper aims to present and discuss a case report of neuroendocrine neoplasia in the appendix of a patient with acute abdomen who underwent appendectomy. A 46-year-old man referred to the Emergency Department complaining of abdominal pain in the right iliac fossa and signs of peritoneal irritation. After diagnosis of acute appendicitis, the patient underwent appendectomy. In a macroscopic analysis, an area of 1.9 cm long, hardened, irregular and yellowish shapes was noted in the distal third of the appendix. Histopathological analysis showed neoplasia consisting of invasive islands of monotonous rounded epithelioid cells, large areas of necrosis, high mitotic activity, neural and angiolymphatic invasion and extension to adipose tissue compatible with invasion of the mesoappendix. Circumferential resection was compromised, suggesting the persistence of neoplasia in the patient even after the surgical approach, which would probably recommend the need for surgical approach. Therefore, the importance of sending collected materials for anatomopathological analysis is emphasized, since it helps in the clinical evaluation, in the etiological diagnosis, guides the medical conduct in the evolution of the case, as well as assisting in family mourning in cases of mortality.

**Keywords:** Neuroendocrine tumor, Appendix, Histopathological analysis.

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## Neoplasia Neuroendócrina em Apêndice Cecal: Relato de Caso

**Resumo:** Apesar de neoplasias neuroendócrinas serem entidades relativamente incomuns, o apêndice é um sítio com relativa frequência de surgimento desta patologia e o seu diagnóstico preciso e manejo clínico têm se mostrado um desafio para os profissionais da área. Este trabalho objetiva apresentar e discutir um relato de caso de neoplasia neuroendócrina em apêndice de paciente com quadro de abdome agudo submetido à apendicectomia. Homem de 46 anos recorreu ao Serviço de Urgência com queixa de dor abdominal localizada na fossa ilíaca direita e sinais de irritação peritoneal. Após diagnóstico de apendicite aguda, o paciente foi submetido a apendicectomia. Em uma análise macroscópica, notou-se área de 1,9 cm de comprimento, endurecida, de formas irregulares e amarelas, no terço distal do apêndice. A análise histopatológica evidenciou neoplasia constituída por ilhas invasivas de células epitelíóides arredondadas e monótonas, extensas áreas de necrose, alta atividade mitótica, invasão neural e angiolinfática e extensão até o tecido adiposo, compatível com invasão do mesoapêndice. Ademais, foi demonstrado que a margem de ressecção circunferencial estava comprometida, sugerindo a persistência de neoplasia no paciente, mesmo após a abordagem cirúrgica, o que recomendaria provavelmente a necessidade de abordagem cirúrgica. Portanto, frisa-se a importância do envio de materiais coletados análise anátomo-patológica, uma vez que esta auxilia na avaliação clínica, no diagnóstico etiológico, norteia a conduta médica na evolução do caso, além de auxiliar no luto familiar em casos de mortalidade.

**Palavras-chave:** Tumor neuroendócrino, Apêndice, análise histopatológica.

### Introduction

The neoplasms of the cecal appendix correspond to about 0.5% of diagnosed intestinal tumors and are found in approximately 1% of appendectomies. It is estimated that for every 100 appendectomies performed per year, even in smaller hospitals, at least one case is related to neuroendocrine tumors (NETs) of the appendix. The incidence of this cancer is approximately 2-3 cases per million, with a preference for female sex in the ratio of 2:1, with predominant age of 40-50 years. Since most cases of appendix NETs is diagnosed incidentally, they are not related to a specific clinical presentation. The diagnosis is associated, but not necessarily, with acute appendicitis, since most of these

tumors are located at the apex of the organ. The association with carcinoid syndrome is rare and it occurs in less than 1% of the cases (Gu; Wang; Xu, 2015).

The old terminology "carcinoid tumor" (karzinoid) was originally described by Siegfried Oberndorfer in 1907 and it was used, indistinctly, to designate well differentiated neuroendocrine tumors from the gastrointestinal tract. Although these tumors are entities relatively unusual, the appendix is a place with relative frequency of appearance of NETs and its precise diagnosis and clinical management has been a challenge for health professionals. The appendix NETs are characterized by being relatively frequent among Neuroendocrine neoplasms, having small size, and generally showing indolent and less aggressive behavior. As for affected patients, there is a higher incidence in females - a fact attributed to the increased rate of surgical operations performed on women (Alexandrali et al., 2015).

Regarding molecular pathology, several transcribed genes were measured by quantitative RT-PCR in neuroendocrine neoplasms of the appendix. High levels of chromogranin A (CgA) were found in tissue samples with acute appendicitis and no evidence of tumor, implying that CgA expression may be useful in identifying occult lesions (Alexandrali et al., 2015). The symptoms are often frustrating, varying according to the endocrine production profile and tumor location, which makes it difficult to make a diagnosis based on clinical aspects. In fact, a preoperative hypothesis of neuroendocrine tumor in the appendix is rare, with no specific clinical presentation. In general, these tumors are asymptomatic, or present themselves as an acute appendicitis, which leads to an accidental diagnosis during surgery (Gu, Wang, Xu, 2015) and a confirmation postoperative to by anatomic-pathological examination.

In a nonspecific manner, patients may present painful symptoms in the iliac fossa or right flank, eventually with right testicular pain. Most of appendix NETs is located in the apex of the organ, not causing luminal obstruction and, therefore, not being related to an acute obstructive appendicitis caused by the tumor. In fact, most of the cases are diagnosed through histopathological analysis of the organ, resected in appendectomy for acute appendicitis (Abreu, 2018), which shows that the performance a post-operative pathological of the organ is coherent and necessary. For this reason, this work aims to present the anatomic-pathological findings of a case of appendix neuroendocrine tumor after clinical diagnosis of acute appendicitis.

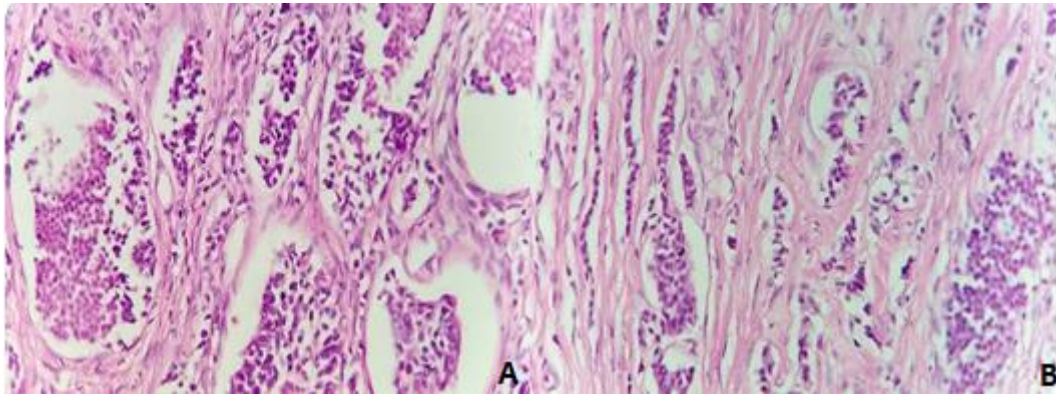
## Case Report

A 46-year-old man went to the emergency department with abdominal pain in the right iliac fossa and signs of peritoneal irritation. After diagnosis of acute appendicitis, the patient underwent appendectomy, showing intraoperative signs of advanced appendicitis and regional peritonitis. In the meantime, the material was sent to anatomic-pathological study. Macroscopic examination revealed an 1.9 cm length hardened, irregular and yellowish area in the distal third of the apêndice.

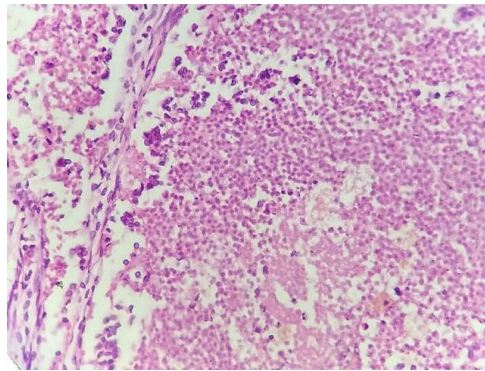


**Figure 1** - (A) and (B): Fragments of the distal third of the appendix previously fixed in formalin showing yellowish and irregular area corresponding to appendicular neuroendocrine neoplasia.

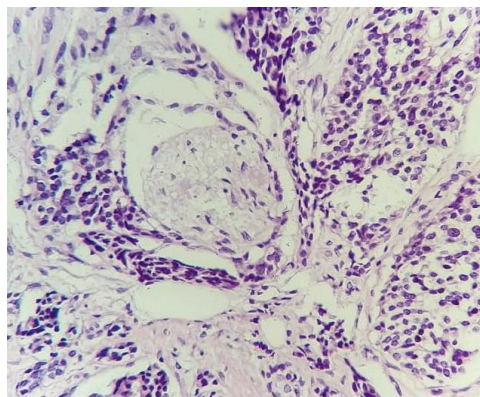
Histopathological analysis showed neoplasm formed by islands of invasive, rounded and dull epithelioid cells, large areas of necrosis, high mitotic activity, neural and angiolymphatic invasion and extension reaching the fat tissue, compatible with invasion of mesoappendix. Furthermore, it was demonstrated that the circumferential resection margin was compromised, suggesting the persistence of the neoplasm in the patient even after the surgical approach, which implies a likely need of a new surgical approach.



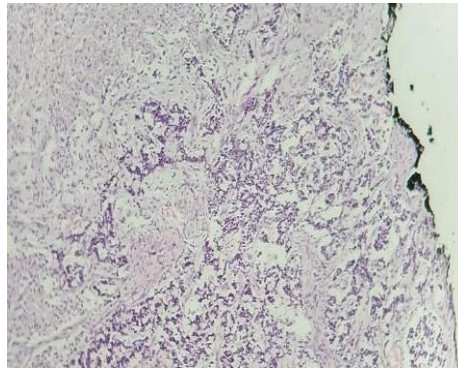
**Figure 2 -** (A) Nests off neoplastic cells with insular pattern (B) Cordonal pattern areas



**Figure 3-** Tumor necrosis



**Figure 4 -** Perineural Invasion



**Figure 5-** India ink adhering to the neoplastic cells (Circumferential Margin Involvement)

## Discussion

Neuroendocrine neoplasms of the appendix correspond to the third most common type (16.7%) of neuroendocrine tumors of the gastrointestinal tract, with the small intestine (44.7%) and the rectum (19.6%), occupying, respectively, the first and second positions. They are predominantly female and usually manifest themselves between 15-19 years in women and 20-29 years in men (Morais et al., 2019). The clinical presentation of these tumors is indistinguishable from acute appendicitis in more than 54% of patients (Alexandralli et al., 2015), which leads to the need for surgical resolution.

In the reported case, we observed a different epidemiological pattern than expected, since it is a male patient over 29 years old. Regarding the clinical presentation and the diagnosis, we observed the follow-up of a pattern: patient complaining of abdominal pain in the right iliac fossa, diagnosed with acute appendicitis, showing intraoperative advanced appendicitis and regional peritonitis; on macroscopic examination, the presence of a yellowish and hardened area, 1.9 cm long, with irregular margins, which, after histopathological analysis, was confirmed to be a lesion with morphological characteristics of malignancy, with invasion of the mesoappendix and circumferential resection margins compromised.

Neuroendocrine neoplasms, in general, may be present in several locations, including lung (25.1%), ovaries (0.5%), biliary system (0.2%) and gastrointestinal tract (73.4%). In the latter case, regarding the appendix, we can observe the occurrence of these neoplasms mainly in the apex of the organ (75% of cases), in the base (5%) and in the intermediate region (20%), with lesions of average size of 6 mm (Morais et al., 2019).

Appendix neuroendocrine tumors (NETs) originate from subepithelial neuroendocrine cells, present in the lamina propria and submucosa of the organ wall. These cells are more numerous at the tip of the appendix, unlike neuroendocrine epithelial cells, which are evenly distributed throughout the organ. The characteristics that differ neuroendocrine tumors in the appendix from neuroendocrine tumors originating from other sites are attributed to their histological origin and may be related to their more favorable prognosis as well as their smaller size (Alexandrali et al., 2015).

Proper staging is important to establish good therapy, follow-up and prognosis of patients. It is necessary to evaluate the size, location, histopathological features, mesoappendix invasion, vascular invasion and the presence of distant metastases (Abreu, 2018). The World Health Organization (WHO) categorizes neuroendocrine tumors (NETs) by their prognosis, considering histopathological features and proliferative index (Riechelmann et al., 2017). According to the current classification of WHO and ENETS (European Society of Neuroendocrine Tumor), the NET-G1 type neuroendocrine tumor would have a mitotic count of  $<2$  by  $2 \text{ mm}^2$  (in a 40x magnification) and a Ki-67 (proliferative index)  $<2\%$ . NET-G2, on the other hand, would be represented by the group with a mitotic count of 2 to 20 by  $2 \text{ mm}^2$  or Ki-67 of 3 to 20%, and, finally, NET-G3 would represent tumors with a mitotic count.  $> 20$  by  $2 \text{ mm}^2$  or Ki-67 index  $> 20\%$  (Morais et al., 2019).

In this context, it is important to analyze the classification of the injuries as well as the decisions taken before them. In most patients with appendix neuroendocrine neoplasm with a tumor diameter  $<1 \text{ cm}$ , isolated appendectomy is sufficient for treatment, as they rarely metastasize (Gu; Wang; Xu, 2015). Tumors smaller than or equal to  $2 \text{ cm}$  that infiltrate the submucosa, muscle, subserosa and mesoappendix (at least  $3 \text{ mm}$  deep) are considered to be stage IIa by the TNM classification of ENETS - European Neuroendocrine Tumors Society (Moris et al., 2018) and should be treated with right hemicolectomy, not just appendectomy.

Other situations which favor right hemicolectomy (and not just appendectomy) as treatment of the lesion are those in which there was no complete tumor excision. It's said that there was an R0 resection when there is no compromised margins around the lesion; R1 resection when there are microscopically affected margins and R2 resection when there are micro and macroscopically affected margins. Therefore, in cases of resection in which the margins were not clear after the procedure (R1 and R2), appendectomy is not the

appropriate treatment and, therefore, extended surgery should be performed (Silva et al., 2010).

Regarding the follow-up of these patients, the literature shows that regular follow-up is required for tumors between 1 and 2 cm with high risk factors for lymphatic spread of the disease, as well as in cases of mesoappendix invasion of more than 3 mm, localization of the injury at the base of the appendix, vascular infiltration or intermediate differentiation (Moris et al., 2018).

Regarding the case, a yellowish and hardened area, 1.9 cm long, with irregular margins was observed, which, after histopathological analysis, was confirmed to be a malignant lesion, with invasion of the mesoappendix, whose circumferential resection margins post-appendectomy were compromised, which frame the tumor as a stage IIa; thus, it is possible and necessary to perform a right hemicolectomy for the appropriate treatment of the patient. Appendectomy is the gold standard for the treatment of stage I tumors (Moris et al., 2018), which does not fit this case.

Postoperative follow-up for patients with tumor excision larger than 2 cm in diameter is indicated, including follow-up with anamnesis and physical examination every 3 months for one year after the resection and every 6 months for up to 10 years, considering imaging and laboratory markers such as 5-hydroxy indole acetic acid or chromogranin A (Gu; Wang; Xu, 2015).

## **Conclusion**

Cecal appendix neuroendocrine tumors are uncommon and the prognosis is generally favorable. Simple appendectomy is the routine surgical treatment for tumors up to 1 cm without invasion of adjacent areas, providing cure in most cases. In cases of tumors between 1 and 2 cm with mesoappendix invasion, as presented in the case described, the best therapeutic option would be to perform a right hemicolectomy with adequate excision of the tumor and the tumor margins. Therefore, the importance of sending collected materials for anatomic-pathological analysis is emphasized, since it helps in the clinical evaluation, in the etiological diagnosis, guides the medical decisions in the evolution of the case and also helps in family mourning in cases of mortality.



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