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Neuroendocrine Tumours of Appendix mimicking acute appendicitis- A case report

Shivani[1], Moudgil Ashish[2], Shakeel Summaiya[1], Shakya Avaneet Kiran[3], Kale Ravi[4]

1 Junior Resident Department of General Surgery, SMS&R, Sharda University
2 Assistant Professor Department of General Surgery, SMS&R, Sharda University
3 Senior Resident Department of General Surgery, SMS&R, Sharda University
4 Professor, Department of General Surgery, SMS&R, Sharda University
Corresponding Author e-mail: drashishmoudgil@gmail.com

Abstract:
Introduction: *Neuroendocrine tumors (NETs) are rare neoplasms arising from neuroendocrine cells. Incidental appendiceal neuroendocrine tumors occur in 0.2%-0.7% of surgical resection for suspected appendicitis. They often present with nonspecific symptoms, posing diagnostic challenges.*
Case Summary: *A 25-year-old female presented to the emergency room with vomiting, migratory abdominal pain, anorexia, and fever. Initially diagnosed with acute appendicitis based on clinical evaluation and imaging findings, the patient underwent open appendectomy. Intraoperatively, an inflamed retrocecal appendix was found with a healthy caecal base. Histopathological examination surprisingly revealed a neuroendocrine tumor of the appendix*
Discussion: *European Neuroendocrine Tumor Society(ENETS) consensus guidelines for neuroendocrine neoplasm of appendix states appendectomy may be sufficient for tumor <2cms and they are associated with good long-term outcomes as seen in our case.*
KEYWORDS: *Appendicitis, Neuroendocrine*

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I. Introduction:

Neuroendocrine tumors (NETs) are cancers that begin in specialized cells called neuroendocrine cells. These cells have traits of both hormone-producing endocrine cells and nerve cells. They are most commonly found in the gastrointestinal tract with the small intestine, rectum, and appendix as the sites most at risk of developing NETs [1, 2].

Appendiceal NET accounts for ~19% of all NETs and is the most common type of appendiceal cancer. They usually progress indolently and the majority are detected in the third or fourth decade of life while other NETs are usually diagnosed in the sixth decade of life (3, 4). More than 80% of appendiceal neuroendocrine tumors (aNETs) are diagnosed incidentally in appendectomy specimens and are found in approximately 0.5% to 1% of all appendectomies. [1]

Here, we present a case of appendiceal NET masquerading as acute appendicitis.

Case Report: A 25-year-old female patient presented to the Emergency department of Sharda Hospital with complaints of pain in the right iliac fossa for 2 days which initially started around the umbilicus and then shifted to RIF. Pain was sudden in onset, continuous, sharp aching, and associated with 2 episodes of vomiting and anorexia. The patient had a history of low-grade fever for 1 day. The patient had no history of bowel or urinary symptoms. She had regular menstrual cycles with the last menstrual cycle 7 days back and had no significant past history.

The patient was febrile with tachycardia of 102 bpm. Examination revealed a soft abdomen with tenderness and rebound tenderness present over the right iliac fossa with a positive Rovsing sign. The rest of the abdomen examination and systemic examination were unremarkable.

Her blood investigations showed leucocytosis of 12.4 x 103 with neutrophilia. Her ALVARADO SCORE was evaluated to be 8/10.

Ultrasonography (USG) of the whole abdomen showed features suggestive of acute appendicitis with an appendiceal diameter of 9mm with the peri-appendiceal fluid collection and fat stranding. Consequently, informed surgical consent was taken and the patient underwent emergency open appendectomy by standard Grid iron incision approach.

Intraoperatively, a retrocecal non-perforated appendix was identified, which was elongated, edematous, and inflamed with few pus flakes, however, no mass through the entire length of the appendix was palpable. The base of the appendix was mildly inflamed with a healthy caecal base (fig1). The appendix was removed and sent for histopathological examination as routine protocol. No nickel diverticulum was found. The postoperative period was uneventful. The patient tolerated the oral diet well with regular bowel and bladder habits. The patient was discharged on Post-op day 3.

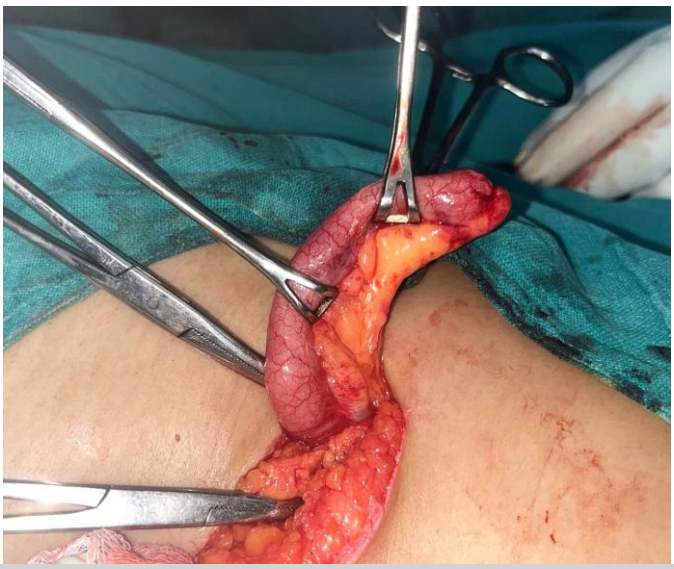


Fig 1- a retrocaecal non-perforated appendix, edematous and inflamed, base of appendix inflamed, caecal base healthy.

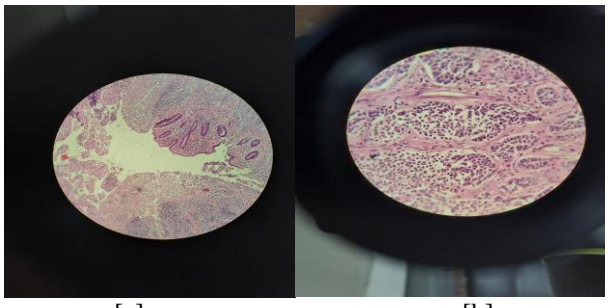
Histopathological Findings:

On gross examination, the appendix measured 6 cm in length and 0.8 cm in diameter with the attached mesoappendix measuring 1.5x1x1 cm. The external surface was congested. On the cut section, a well-demarcated tan firm lesion was seen at the tip measuring 1.3 cm in diameter.

Microscopically, the tip of the appendix showed a tumor disposed in nests, trabeculae, and cords and was seen predominantly in the submucosa reaching up to the subserosal layer. The tumor nests showed relatively monomorphic cells with enlarged nuclei and stippled chromatin. Mitoses were very sparse (2/10 HPF)with no evidence of necrosis. The cut margin of the appendix was negative for tumor cells.(fig 2a,b)

On Immunohistochemistry, the tumor was positive for synaptophysin and chromogranin A and ki-67 proliferative index:<3% with a mitotic index of <2.

Findings were suggestive of low-grade neuroendocrine tumor, appendix with staging- pTNM: pT3 Nx Mx



[a] [b]

Fig 2- a-section from the lumen of the appendix, b- b-section from the tip of the appendix showing features of neuroendocrine tumor

Retrospective evaluation for any symptoms associated with functional NETs was done. The patient had no complaints of diarrhoea, flushing, constipation, or cardiac complaints. Postoperatively patient underwent a 68 Ga-Dotatate PET scan which was reported negative. The patient is doing well on 3-month follow-up and advised subsequent regular follow ups 6 monthly.

II. DISCUSSION

NETs are identified in numerous locations, including the gastrointestinal tract (73.4%), lungs (25.1%), ovaries (0.5%), and biliary system (0.2%) [5]. There has been a large increase in the incidence of gastrointestinal NETs, and the elderly population is more susceptible to poorer outcomes in regard to overall and disease-specific survival. Appendiceal NETs are located most commonly at the tip of the appendix—in 75% of cases, at the base of the appendix in 5%, and in the mid-section in 20% [3], with a mean tumor size of about 6 mm (range 0.4–14 mm) [4]. Often times NETs of the gastrointestinal tract do not have characteristic symptoms that are unique to their diagnosis. About half of the patients present with symptoms of localized disease such as suspected appendicitis, abdominal pain with no diagnosis, and GI bleeding with anemia. Classic carcinoid syndrome (flushing, diarrhoea, and cardiac disease) is very uncommon (<1%) [6] and is more likely to appear in patients with advanced disease. The histopathological diagnosis of NETs includes the determination of the immunohistochemistry profile of the tumor in regard to synaptophysin and chromogranin A (CgA), as well as the proliferative marker, the Ki-67 index []. The overall prognosis for NETs of the appendix is good, with tumor size being one of the important determinants of prognosis. Studies have shown an association between raised Ki-67 index and decreased survival [7].

The guidelines set by The North American Neuroendocrine Society (NANETS) recommend right hemicolectomy for tumors originating at the base of the appendix, tumors >2 cm in size, lymphovascular or meso-appendiceal invasion, positive lymph node metastases, and for intermediate or high-grade tumors [8,9].In regards to those tumors between 1 cm and 2 cm, there is no clear consensus. There have been reports of both lymph node metastases in neoplasms under 1 cm in size that underwent right hemicolectomy, and tumors greater than 2 cm in size but negative lymph nodes [8]. NANETS recommends that for tumors intermediate in size, high-risk characteristics of the neoplasm be taken into account for decision on right hemicolectomy and node dissection [10].

According to the current WHO (World Health Organization) and ENETS (European Neuroendocrine Tumor Society) grading systems, NET-G1 is labeled by a mitotic count of <2 per 2 mm2 (40× magnification) and Ki-67 ≤2%; NET-G2 by a mitotic count of 2–20 per 2 mm2 or Ki-67 of 3–20%; NET-G3 by mitotic count of >20 per 2 mm2 or Ki-67 index >20%. Many parameters have to be taken into account for the distinction of tumors with a mild clinical course from those with a more aggressive potential carrying a higher risk for locoregional relapse and distant metastasis, including the tumor size and its exact location, the extent of infiltration of the appendix wall or possible vascular invasion and the proliferative rate [2].

With regards to follow-up on tumors smaller than 1 cm in size, NANETS recommends 3–6 months after resection with curative intent and every 6 months to 1 year for the next 7 years. For more advanced tumors, follow-up is advised every 3–6 months and potentially lengthen the interval for patients who show absence of any disease after 12 months [10]. Although NANETS recommends follow-up for tumors <1cm.

ENETS guidelines suggest long-term follow-up, only when lymph node involvement is present, locoregional disease is identified postoperatively, and when the tumor is of high stage. Regular monitoring is necessary for patients with tumors sized between 1 and 2 cm with features indicating a higher risk for lymph node dissemination of the disease, such as mesoappendiceal invasion >3 mm, localization in the base of the appendix, vascular infiltration or intermediate differentiation (G2) [2]. Furthermore, follow-up is also not mandatory for tumors larger than 1 cm for which a right hemicolectomy was performed and if no additional risk factors were present such as lymphovascular invasion [8]

NET is a rare disease with a reported good prognosis, but it can still be fatal if not handled appropriately. Pathology on appendix specimens should always be complete and follow-up should be done if it's feasible. SEER (Surveillance, Epidemiology, and End Results) database studies report 5-year survival rates of 94% for confined lesions, 84.6% for locoregional disease, and 33.7% when distant metastasis is present [,

All appendectomy specimens must be sent for routine histopathological examination to identify and diagnose incidental appendiceal NETs. In this clinical case, the patient experienced acute pain in the right iliac fossa which started in the paraumbilical region initially. Laboratory investigations and imaging studies aided in the diagnosis of acute appendicitis and underwent. On histopathological examination, appendiceal NET of size 1.3cm in diameter was identified with a Ki-67 index of < 3% and a mitotic index of <2. Accordingly, the tumor was classified as NET-G1. The tumor was located at the tip of the appendix with no features of lymph node dissemination. In retrospect, classical symptoms of appendicitis, in this case, correlates with the fact that gastrointestinal NETs present with localized symptoms rather than systemic ones, as discussed earlier. As per recent guidelines and accepted global standards, the decision for an appendectomy was sufficient in the said case. Although regular monitoring is not warranted in our patient given the location of the tumor at the tip and no features of lymph node dissemination, follow-up is being done periodically.

Conclusion: Neuroendocrine tumors of the appendix are rare entities that can mimic acute appendicitis clinically. Clinicians should maintain a high index of suspicion for unusual presentations of appendicitis,

especially in cases where symptoms are atypical or not responsive to standard treatment. Prompt histopathological evaluation is essential for accurate diagnosis and appropriate management of such cases.

Conflict of Interest: The authors declare no conflicts of interest regarding the publication of this case report.

Informed Consent: Informed consent was obtained from the patient for the publication of this case report and accompanying images.

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