ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 17, Issue, 03, pp.32265-32267, March, 2025
DOI: https://doi.org/10.24941/ijcr.48376.03.2025

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

NEUROENDOCRINE TUMOR IN CLINICALLY DIAGNOSED ACUTE APPENDICITIS

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ARTICLE INFO

Article History:
Received 20th December, 2024
Received in revised form
19th January, 2025
Accepted 26th February, 2025
Published online 30th March, 2025

Key Words:

Neuroendocrine Tumor,
Appendix, Acute Appendicitis.

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ABSTRACT

Background: Neuroendocrine tumors of appendix are rare and are mostly detected incidentally in appendectomy specimen removed for acute appendicitis. **Aim:** To report our experience of incidentally detected neuroendocrine tumors (NETs) of appendix primarily removed with the clinical presentation of acute appendicitis at our teaching hospital. **Methods:** The study was a two year retrospective study, done in the Department of Pathology, Government Medical College, Baramulla, Jammu and Kashmir, India. A total of 601 appendix specimens were examined. The data regarding age, gender, clinical-presentation, pre-operative radiological investigation and demography was collected. All cases were examined by two independent pathologists. **Results:** Out of 601 appendectomy specimens received in our department from September 2022 to September 2024, 15 (2.40%) showed histopathological features of well differentiated neuroendocrine tumor (carcinoid). Mean age at presentation was 23.72 years. The male to female ratio was 1:2. Tip was the most common location. Largest tumor diameter in our study was 2.2cm. One of the appendix had a synchronous Neuroendocrine Tumor and an epithelial-Low grade Mucinous Neoplasm. **Conclusion:** Appendiceal NET tumors most often present as appendicitis. Most of the cases are found incidentally during routine HPE and its diagnosis is rarely suspected pre-operatively, emphasizing the routine HPE of all appendectomy specimens. Ours is the first study that emphasizes this rare condition from our region so far.

Citation: Roudah Farooq. 2025. "Neuroendocrine tumor in Clinically Diagnosed Acute Appendicitis*". International Journal of Current Research*, 17, (03), 32265-32267.

INTRODUCTION

Neuroendocrine tumors are thought to be arising from the enterochromaffin cells of subepithelial neuroendocrine tissue of appendix (**1**). The worldwide incidence of neuroendocrine tumors of appendix varies between 0.9% to 1.2% (**2**). Appendiceal NET's have very indolent behavior and are mostly asymptomatic. The neoplasm is almost always benign, mostly presents as a bulbous swelling at the tip of appendix and usually detected incidentally during a surgery or histopathological examination of resected appendix. The tumor is mostly <1cm and can reach upto the diameter of 3cm. Nodal metastasis is very infrequent and distant metastasis is very rare. The studies on carcinoid appendix from our region or population is hardly documented, may be because of rarity. Here we present a series of 15 appendiceal NET's that we found in our two-year study at our tertiary care centre.

MATERIALS AND METHODS

The study was done in the Department of Pathology, Government Medical College & Associated Hospitals, Baramulla. The total of 601resected appendectomy specimens were received within the time period of two years (September 2022 to September 2024) from the Department of surgery. All the patients presented with the signs and symptoms of acute appendicitis. The data about the age, gender, clinical presentation and demography was collected. The only preoperative radiological investigation done in all patients was Ultrasonography. The received specimens were examined grossly and the representative sections from tip and base were taken. The sections were then stained routinely by Hematoxylin and Eosin (H&E), and were examined under microscope by two pathologists. The reports were made as per the CAP protocol and the tumor staging was done according to AJCC updated version (**3**).

RESULTS

Out of the 601 resected appendix specimens, 15 (2.40%) showed the features of NET tumor microscopically. All the 15 patients were operated with clinical as well as radiological diagnosis of acute appendicitis. In our series, we had 10 (66.67%) females and 5(33.33%) males. The mean age in our case series was 23.72 ±9.60 years. The age group ranging from 18 to 46 years. Out of these15 appendix specimens, 13

(86.66%) of cases had tumor size of<1cm, one (6.67%) had tumor size of more than 1 and less than 2 and one (56.67%) had tumor size of more than 2cm. The mean tumor diameter was 1.47 ±1.64 cm. On microscopic examination the tumor cells showed mostly trabecular and nesting patterns, with most of the tumors infiltrating the muscularis propria. The tumor showed less than or equal to 2 mitotic figures per 10 high power field without any evidence of necrosis. One (6.67%) out of the 15 appendix specimens showed a nodular appearance grossly. On cut section a grey white to slightly golden area was noted, involving the whole appendix. The largest diameter of the tumor was 2.2cm. The tip was dilated and filled with mucoid material and calcified plaques in the surrounding wall. On microscopic examination, synchronous neuroendocrine tumor and mucinous epithelial neoplasm was diagnosed. Our results are summarized in Table 1.

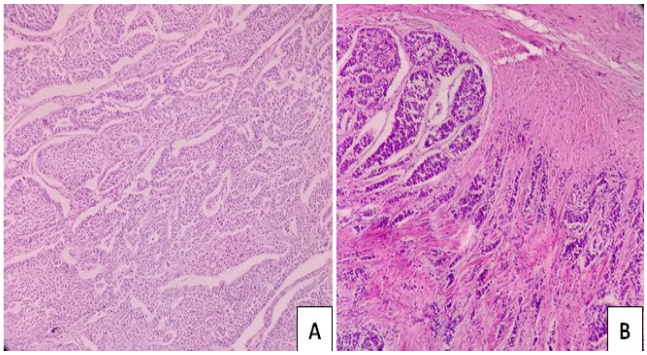

Image 1. Low power view of NET. Tumor cells are arranged in organoid /insular pattern (A), infiltrating the underlying muscularis propria (B)

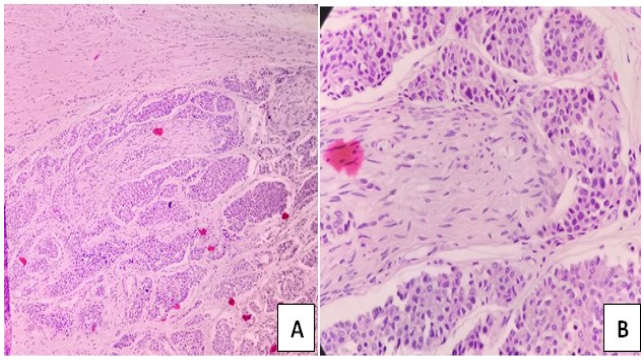

Image 2. Perineural invasion by neuroendocrine tumor – Appendix (Low power (A) and High power (B)

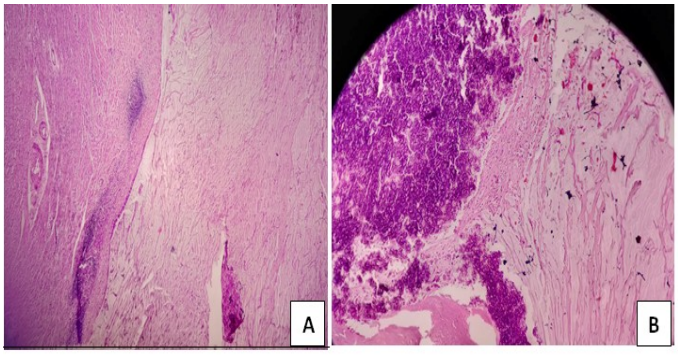

Image 3. Low power view of Mucinous Neoplasm (low grade) with fibro-inflammatory response (A) with calcifications (B)

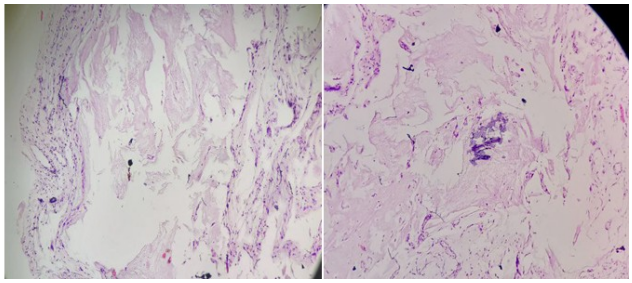

Image 4. Low powerview of mucin exending into mesoappendix (Pseudomyxoma)(A and B).

DISCUSSION

Neuroendocrine tumors of appendix comprise half of the tumors of non-epithelial origin and have a very indolent behaviour. There is no specific clinical presentation for carcinoid appendix and mostly patients present with the clinical signs and symptoms that are indistinguishable from acute appendicitis. These tumors are often found incidentally on histopathological examination. In our series15 (2.40%) neuroendocrine tumors from the 601 resected appendix were found with all cases operated for having clinical and radiological impression of acute appendicitis. The NET diagnosis was only and final impression on the histological examination. The higher percentage of NET of appendix were corresponding to the findings of Alexandraki K *et al* and Coskun H *et al*, who in their studies reported the incidence of about 0.16-2.3% of all appendectomies (4,5). McCusker M *et al* also reported the higher (9.4%) incidence of ANENs (6).Groth S *et al* reported that 50% of NET appendix are diagnosed in pathological analysis after appendectomy for acute appendicitis (7).

Neuroendocrine tumors of appendix occur more commonly in younger patients and usually shows female predominance (8,9).In our study, we had same findings of female predominance, with male to female ratio of 1:2. The mean age in our case series was 23.72 ±9.60 years, ranging from 18to 46years.Bayhan Z *et al* reported that majority of the cases of NET of appendix are diagnosed in adults between the age group of 20 to 50 years (10). Hsu C *et al* also reported that appendix NET are common in women as compared to men (11). NET appendix mostly have a benign behavior and usually do not metastasize but do possess a metastatic potential. The characteristics of the carcinoid tumors that predict their aggressive behaviour include size of the tumor, histological type or grade of the tumor and involvement of the mesoappendix/periapendiceal fat. In our case series, 13 (86.66%) out of 15cases had tumor size of less than 1cm, one (6.67%) had tumor size of more than 1 and less than 2 and one (56.67%) had tumor size of more than 2cm. the mean tumor diameter was 1.47 ±1.64 cm. All 15 (100%) NET had low tumor grade. 33.33% (n=5) had perineural invasion and only 13.33% (n=2) showed vascular emboli. O'Donnell ME *et al* also demonstrated from their study that 80% of neuroendocrine tumors of appendix had tumor size of less than 1 cm and only 6% had tumor size larger than 2 cm (12). Most of the patients with NET appendix do not require any further intervention or investigation and benefit from simple appendectomy. Patients who need further work-up or screening are those, with high – grade tumor (even if <1cm), patients with tumor size between 1 cm to 2 cm or tumor size more than 2 cm, and patients with positive surgical resection margin and metastatic disease(13).

Tumors >2cm possess the metastatic potential and patient may require right hemicolectomy (14). In our series one (6.67%) of the cases out of 19 had a tumor with largest diameter of 2.2cm involving the whole of the appendix with positive base/surgical resection margin. The patient presented with acute appendicitis in the emergency department and open appendectomy was done. The patient had a long history of intermittent abdominal pain, diarrhea and cutaneous flushing which persisted after the procedure as well. On microscopic examination the tumor cells showed organoid, insular and trabecular pattern, separated by thin fibrovascular septae. The histological grade appeared low and well differentiated, involving the mucosa, submucosa, muscularis propria and periappendiceal adipose tissue (Image 1). Extensive perineural invasion was present (Image2). Lymphovascular emboli were not seen. The mitotic activity was ≤ 2/10 hpf with no evidence of necrosis. On immunohistochemistry, the tumor cells expressed Cytokeratin (CK), Synaptophysin and Chromogranin. The Ki-67 labelling index was found to be <2%.

The tip of the appendix was dilated and filled with mucoid material and had calcified plaques. On microscopic examination the wall showed columnar lining epithelium with presence of goblet cells. The tumor exhibited a low grade morphology. The islands of acellular mucin showed an extensive fibro inflammatory response and calcifications (Image 3). The mucin was also seen dissecting through the wall, with extravasation onto serosal surface (Pseudomyxoma) (Image 4).

The diagnosis was made as a Synchronous malignancy of well differentiated neuroendocrine tumor and low grade appendiceal mucinous neoplasm (LAMN) of appendix and further radiological workup was advised for the further definitive management. O'Donnell ME *et al* demonstrated that NET appendix is associated with a higher incidence of metachronous and synchronous lesions, requiring investigation and surveillance of the gastrointestinal tract (12). The prognosis of NET appendix is much better than the midgut NE tumor. The 5-year survival rate of patients with local disease is reported to be 92% and 81% of those with regional metastasis and 31% of those with distant metastasis, respectively (15,16). In our case series only one patient presented with persistent symptoms of diarrhea and cutaneous flushing, rest of the 18 patients were doing well post appendectomy. No recurrence was seen among theses 19 cases within the study time period in our study.

CONCLUSION

NETs of appendix are rare and are mostly found incidentally in the resected appendix of patients presenting with acute appendicitis. A routine HPE of all resected appendix is highly recommended for the patient well-being. In our study we found 15 (2.40%) NET out of 601 resected appendix. The overall prognosis of NET appendix is favourable. Histological grade and size of tumor plays an important role in tumor behaviour. At times further workup may be needed to rule out associated malignancies particularly in colon. A larger multicentre study is needed from our region to validate the increased incidence observed in our study.

Conflicts of interest and disclosures: None.

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