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Case report

An incidental finding of ANET in a patient with perforated appendix: A case report

Sunil Basukala [a], Ujwal Bhusal [b,*], Shriya Sharma [b], Ayush Tamang [b], Suman Gurung [c]

[a] Department of Surgery, Shree Birendra Hospital (SBH), Kathmandu, Nepal
[b] College of Medicine, Nepalese Army Institute of Health Sciences (NAIHS), Kathmandu, Nepal
[c] Department of Pathology, Shree Birendra Hospital (SBH), Kathmandu, Nepal

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ABSTRACT

Introduction and importance: Appendiceal neuroendocrine tumors (ANETs) are incidentally found in 0.2–0.7% of appendectomies for suspected appendicitis.
Case presentation: A 29-year-old female presented with pain in the right lower quadrant of her abdomen for the past 48 h. On emergency appendectomy for suspected acute appendicitis, a perforated appendix was found. Histopathological examination showed grade 1 (low) ANET.
Clinical discussion: Appendiceal neuroendocrine neoplasms (ANENs) are commonly found at the tip of the appendix and are treated with appendectomy alone. For few ANENs located at the base, or small tumors (≤2 cm) infiltrating the submucosa, the muscularis, the subserosa layer or the mesoappendix, right hemicolectomy is recommended. However, no guidelines have been established concerning patients with appendiceal perforation in case of ANENs.
Conclusion: Although rare, ANETs should be considered in the differential diagnosis of acute appendicitis. Since, ANETs are rarely diagnosed preoperatively, subsequent patient evaluation after appendectomy is crucial for management of the patient.

1. Introduction and importance

Neuroendocrine tumors (NETs) are rare tumors accounting for about 2% of all malignancies [1]. They arise from the enterochromaffin cells found in the gastrointestinal tract and bronchopulmonary system. Appendix is the third most frequent site (16.7%) of gastrointestinal neuroendocrine tumors (GI-NET) preceded by the small bowel (44.7%) and the rectum (19.6%) [2].

Appendiceal Neuroendocrine Tumors (ANETs) are usually incidentally detected during histopathological examination following appendectomy for acute appendicitis. It is the most common type of appendiceal primary malignant lesion which is found in 0.2%–0.7% of patients undergoing appendectomy [3,4].

Here we present a rare case of incidental ANET in a perforated appendix following appendectomy for suspected acute appendicitis.

2. Method

We report this case in line with the updated consensus-based surgical case report (SCARE) guidelines [5].

3. Case presentation

A 29-year-old female patient, with past history of chronic on and off abdominal pain and infrequent loose motions, presented to emergency department with acute right lower quadrant abdominal pain for past 48 h. She gave history of pain in the periumbilical area which later on shifted to right iliac fossa. The pain was dull aching in nature, lasted for 2–3 h and was aggravated on movement and relieved on rest. She also gave history of two episodes of vomiting during the pain which was non-bilious, non-projectile, non-blood stained containing undigested food particles.

On physical examination, the patient had a body temperature of 37.6 °C, was hemodynamically stable with no signs of respiratory distress. Her abdominal examination revealed the presence of positive Rovsing, Blumberg and pointing signs and no palpable mass in the right iliac fossa. Her laboratory tests showed leukocytosis with white blood cell count: 13.3×10^3 cells/μL; neutrophil proportion of 82.2%. Her

* Corresponding author at: College of Medicine, Nepalese Army Institute of Health Sciences, Kathmandu 44600, Nepal.
E-mail address: ujwalbhusal1@gmail.com (U. Bhusal).

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hemoglobin was within a normal range while her C-reactive protein was 32.77 mg/L, sodium: 141 mmol/L, and creatinine: 1.06 mg/dL. On radiological examination, her abdominal ultrasound revealed non-compressible tubular structure of diameter measuring 10 mm probably appendix with minimal peri-appendiceal collection - the findings consistent with appendicitis. The patient underwent emergency open appendectomy. Intraoperatively, an acute suppurative appendicitis with minimal localized abscess and perforation at the tip of appendix was diagnosed. The resection of the appendix was completed. Post-operatively, the patient completed antibiotic therapy course and was discharged 5 days later with no complications.

Her histologic examination showed a circumscribed sheet of small uniform round cells arranged in small nests separated by thin connective tissue stroma (Fig 1).

There were characteristic retraction of these tumor cell clusters from the stroma. The cells had scant cytoplasm and small monotonous nuclei with acidophilic granules (Fig 2).

The mitotic activity of the lesion was low (<2 mitosis/10× magnification). Coexisting acute suppurative appendicitis was also present. The resection margin was free from neoplastic cells. Ki-67 marker was found immune reactive for 1% of the lesional cells. Hence, the tumor was reported as a well-differentiated grade 1 (low) neuroendocrine tumor based on the World Health Organization (WHO) classification for neuroendocrine neoplasms (NEN), 2019. Chromogranin A and 24-hour urine 5-Hydroxyindoleacetic acid (5-HIAA) biochemical tests were normal. Chest x-ray, CT scan of abdomen and pelvis were negative for nodal or distant metastasis. Additionally, upper GI endoscopy and colonoscopy were negative too. The case was discussed with medical oncology team and was decided for surveillance. The initial follow-up at the end of second week, monthly follow-ups until third month, at sixth month and recently at twelfth month, all showed normal Chest X-ray and CT scan of abdomen and pelvis.

4. Clinical discussion

ANENs are the most common tumor of the appendix, found in 0.2–0.7% of all appendectomies [3,4]. According to the 2019 WHO classification of Neuroendocrine neoplasms, well differentiated NENs are referred to as Neuroendocrine Tumors (NETs), while poorly differentiated NENs are referred to as Neuroendocrine Carcinomas (NECs). NETs are classified into three grading subgroups based on the mitotic activity and Ki-67 immunostaining: G1 (mitotic count <2 mitoses/2 mm^2 and/or Ki-67 index <3%), G2 (mitotic count 2–20 mitoses/2 mm^2 and/or Ki-67 index 3–20%), and G3 (mitotic count >20 mitoses/2 mm^2 and/or Ki-67 index >20%) [6].

A retrospective study by Pawa et al. [7] showed a slight female predominance for ANETs. In contrast to other appendiceal tumors and other NENs, which tend to occur in older patients [8], the mean age of the ANET patients was 33.2 (range: 7–79 years) [7]. ANENs show highest incidence rates at 15–19 years of age in women and 20–29 years in men [8,9].

The most common location for ANENs is the tip of the appendix (60–75%), followed by the body (20%) and base (<10%) [2]. Although, neoplasms located in the appendiceal base are associated with higher risk for incomplete tumor excision (R1 or R2), a clear relationship between prognosis and the location of the ANEN has not been established [3,10,11].

The classic carcinoid syndrome of NETs (flushing, diarrhea and cardiac disease) is very uncommon in ANENs (<1%) [8] and more likely to appear in patients with advanced disease. The most common presentation of these neoplasms is acute appendicitis (54%) [12], and infrequently as vague abdominal pain in the right lower quadrant or intestinal obstruction [13].

According to the European Neuroendocrine Tumor Society (ENETS) consensus guidelines 2016, appendectomy is the gold standard treatment [3,7] for stage I ENETs TNM stage tumors. Since these tumors are small in size (<1 cm), mostly limited to the appendix and diagnosed after appendectomy, like in our case, no further treatment is required.

Right hemicolectomy is indicated in cases of tumors with diameter >2 cm, or small tumors (≤2 cm) infiltrating the submucosa, the muscularis, the subserosa layer or the mesoappendix (up to 3 mm in depth) or tumors 1–2 cm especially located in the base of the appendix or those invading the mesoappendix [14]. It is also recommended for IIb ENETS TNM stage tumors which have propensity for lymph node involvement, disease relapse and distant metastases [8].

The survival rates (>95%) of ANETs is better compared to all other types of tumors of appendix [15]. The prognosis of patients even with locoregional disease remain approximately the same as those having

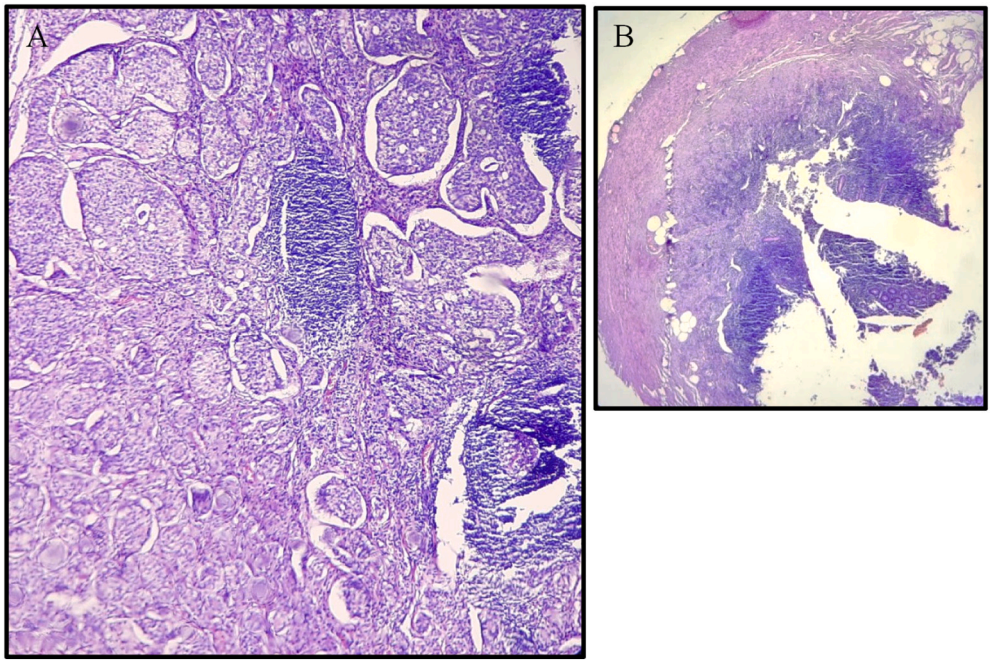

Fig. 1. H&E section of Appendix showing Neuroendocrine tumor cells in nests growth pattern (A: 10×; B: 4× magnification).

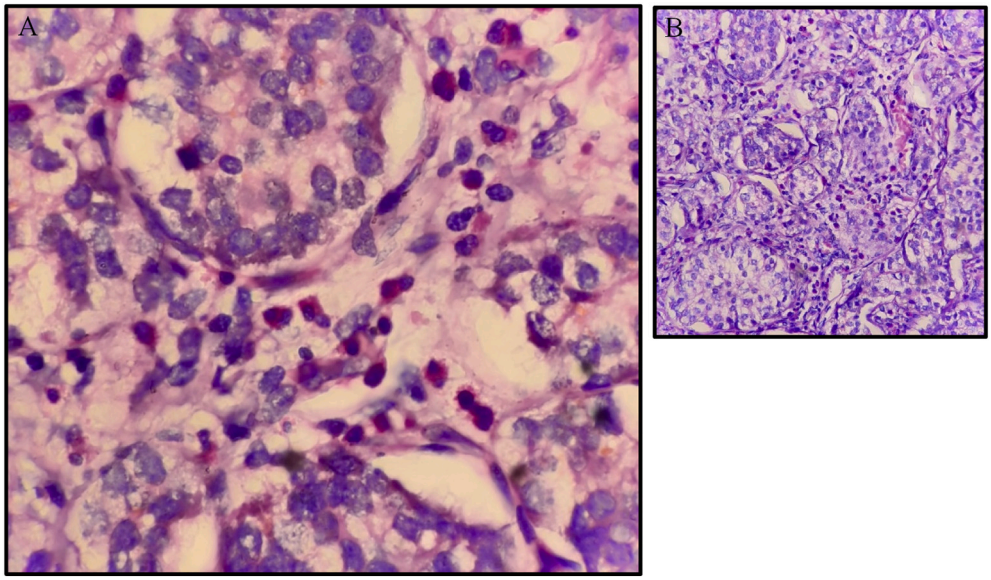

Fig. 2. H&E section of Neuroendocrine tumor of Appendix showing tumor cells composed of monomorphic uniform size nuclei with salt and pepper chromatin. (A: 100×; B:40× magnification).

tumors limited to the appendix [15]. In few studies which found rare cases of relapse [16,17], the primary tumor was greater than 2 cm with regional metastasis.

According to the ENETs guidelines, no observation is suggested for low-risk patients: <1 cm maximal diameter of the tumor, tumor excision in clear margins (R0), no meso-appendiceal invasion, low Ki-67 index and localization in the tip or body of the appendix [3]. However, long-term follow-up is recommended in cases of lymph node involvement, locoregional disease or high stage tumor [3].

There are no guidelines till date concerning patients with appendiceal perforation in the case of ANEN. A case reported by Marthur et al., suggested supplemental right hemicolectomy as a means of minimizing the possibility of disease dissemination [18]. For our patient, after consulting with the medical oncology, radiology and pathology team, we decided not to conduct a complementary right hemicolectomy. A systematic review by Madani, et al. [19] including 103 cases of classical carcinoids and associated perforation, found no peritoneal recurrence or death, although follow-up data were often unspecified or scarce. They concluded that perforation has no influence on prognosis of classical appendiceal carcinoid. Despite the low incidence of ANETs, larger studies and clear guidelines need to be established for appendiceal perforation in the case of ANETs.

5. Conclusion

In our case, ANET was incidentally found after appendectomy of a perforated appendicitis. Although rare, ANETs and other malignancy should also be considered in the differential diagnosis of acute appendicitis. Since, ANETs are rarely diagnosed preoperatively, subsequent histopathologic, biochemical, and radiologic evaluation after appendectomy is crucial.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Ethical approval

The case report is exempt from ethical approval in our institution.

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CRediT authorship contribution statement

Sunil Basukala (SB), Suman Gurung (SG) = Conceptualization, Supervision.

Ayush Tamang (AT), Shriya Sharma (SS), Ujwal Bhusal (UB) = Writing - original draft.

SB, SG, AT, SS, UB = Writing - review & editing.

All the authors read and approved the final manuscript.

Declaration of competing interest

All authors declare that they have no conflict of interest.

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