Case report

Appendiceal neuroendocrine neoplasms in children and adolescents – Two case reports from a tertiary care center in coastal India

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ABSTRACT

Appendiceal neuroendocrine neoplasms (ANENs) are uncommon in children and adolescents and are incidentally diagnosed in 0.3% of appendicectomy specimens. Pediatric ANENs rarely metastasize and have excellent prognosis. We report two cases of ANENs in adolescents who presented clinically and radiologically with features of acute appendicitis for which they underwent appendicectomy. On gross examination, ≤ 2 cm lesion was identified in both the appendix. Microscopic and immunohistochemical analysis clinched the diagnosis of ANENs. Patients were followed up for 18 months and were disease free. This report emphasizes that a possibility of ANEN should be kept as a differential diagnosis even in the pediatric population presenting with acute appendicitis. A routine histopathological examination of all appendicectomy specimens is therefore crucial, as early diagnosis is associated with excellent prognosis.

Keywords: Neuroendocrine tumors; carcinoid tumor; appendiceal neoplasms.

INTRODUCTION

First described in 1907, neuroendocrine neoplasms (NENs) arise from the neuroendocrine cells found distributed along the gastrointestinal tract and broncho-pulmonary system. Appendix is a relatively rare site for primary Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) with the small intestine, colon and rectum being the more frequent tumor locations. Mean age at diagnosis is 48 years (1). While appendiceal neuroendocrine neoplasms (ANENs) are the most frequently encountered gastrointestinal epithelial tumors in children and adolescents, they are uncommon neoplasms, with an incidence of 1:100,000 children per year and often incidentally encountered in appendicectomy specimens (2,3). Herein, we report two cases of ANENs in adolescents which were incidentally detected in specimens resected for acute appendicitis.

Case 1

A 13-year-old female presented with complaints of abdominal pain. On physical examination, she was afebrile, her vitals were stable. Abdominal palpation revealed right iliac fossa tenderness. Ultrasound of the abdomen showed a grossly dilated appendix measuring 13 – 14 mm with increased vascularity in the wall pointing towards the pelvis with evidence of increased echogenicity in the adjoining mesentery and was diagnosed clinically to have acute appendicitis. Patient underwent a diagnostic laparoscopy procedure under general anesthesia. Intraoperatively, she was found to have an inflamed appendix with a tumor in the middle of the appendix that adhered to the anterior abdominal wall. Omental adhesions and an umbilical hernia of size 1 x 1 cm were also seen. An appendicectomy and adhesiolysis were performed and the specimen was sent for histopathological examination. The resected appendicectomy specimen measured 6 cm in length. It was partially received cut in the middle. The tip of the appendix appeared thickened. The cut surface showed a yellow-white, firm, homogenous nodular growth measuring 2 x 1.8 x 0.8 cm at the mid portion of the appendix.

Microscopy revealed tumor cells arranged in nests, sheets, cord, and trabeculae. These cells were small, round, and monomorphic with scanty amounts of finely granular, eosinophilic cytoplasm and round to oval nuclei with salt and pepper chromatin showing focal nuclear crowding and overlapping. The tumor was seen invading into the muscularis propria. Mitotic rate was 0-1/10 hpf. There was no lymphovascular or perineural invasion, and no necrotic areas were noted. There was a mild focal peritumoral lymphocytic infiltrate (10-20/hpf) along with an intratumoral eosinophilic infiltrate (5-10/hpf). The margins were found to be uninvolved by the tumor, although this interpretation was limited as the specimen was sent cut open and a focus of tumor tissue was seen 1 mm away from the inked margin. The regional lymph nodes could not be assessed as they were not submitted. Immunohistochemical staining with conventional neuroendocrine markers Chromogranin A (CgA), and Neuron Specific Enolase (NSE) were positive in tumor cells. The Ki-67 proliferative index

was estimated to be 2 % (Fig.1). As per the 2019 WHO classification of GEP-NENs, it was identified as a Grade 1 neuroendocrine tumor of the appendix with a TNM staging of pT_2NxMx.

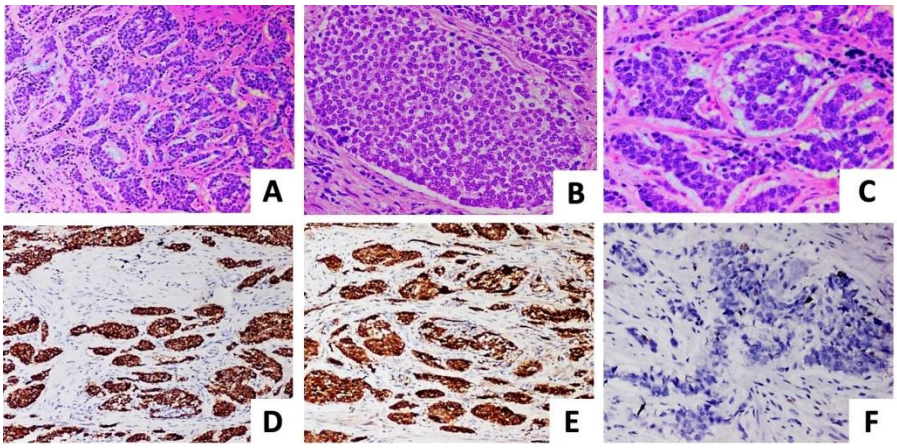

Fig. 1 (A-C): Microphotograph showing tumor cells arranged in organoid pattern, nests and few cords. (Hematoxylin & Eosin - 4x, 10x and 40x) **D:** strong cytoplasmic granular positivity to CgA (IHC - 4x), **E:** NSE (IHC 4x), **F:** Ki-67 index 2% (IHC, 10x).

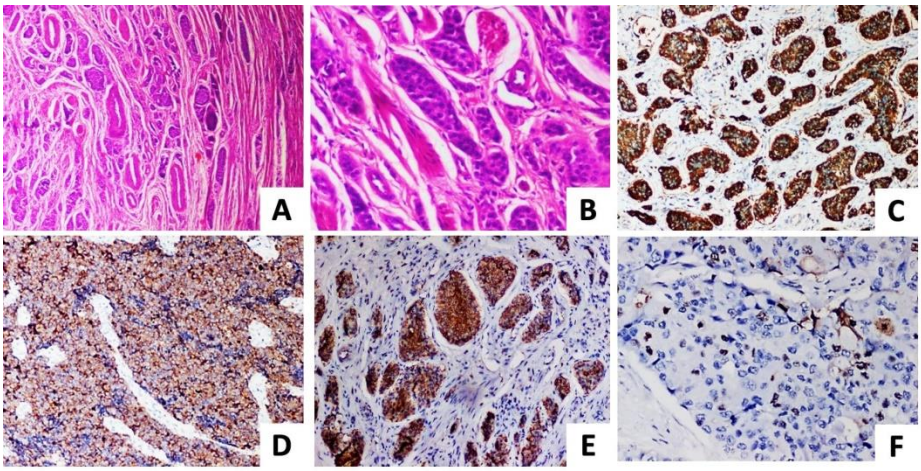

Fig. 2 (A, B): Microphotograph showing infiltrating nests of tumor cells (Hematoxylin & Eosin, 4x, 10x), **C:** cytoplasmic granular positivity for CgA (IHC, 4x), **D:** Synaptophysin (IHC, 4x), **E**: and NSE (IHC, 4x). **F:** Ki-67 proliferation index of 5% (IHC, 10x).

Case 2

A 19-year-old female came presenting complaints of lower, right-sided abdominal pain for one and a half years. On physical examination, she was afebrile, and her vitals were found to be stable and within normal limits. Abdominal examination revealed right iliac fossa tenderness. Ultrasound of the abdomen showed a grossly dilated appendix and a right ovarian cyst. A clinical diagnosis of appendicitis and right ovarian cyst was made, and she underwent an open appendicectomy with right ovarian cystectomy. Intraoperatively, the appendix was found to be inflamed and covered in exudate. The resected specimens were sent for histopathological examination.

The resected appendicectomy specimen measured 3 cm in length. An exudate was seen covering its outer surface. The cut surface revealed a pale yellow, ill-defined lesion of size 1 x 0.8 x 0.6 cm arising from the proximal half of the appendix, in the wall of the appendix and extending up to the subserosa. The lesion was at 0.5 cm from the proximal resected margin and <0.1 cm from the distal resected margin.

Microscopy showed tumor cells arranged in nests, sheets, cord, and trabeculae. These cells were medium sized, round, and monomorphic with a moderate amount of finely granular, eosinophilic cytoplasm and round nuclei with salt and pepper chromatin with some nuclei appearing hyperchromatic. The tumor was seen invading upto the subserosa without involving the visceral peritoneum. Mitotic rate was 0-1/10 hpf. Lymphovascular invasion, perineural invasion, and necrosis were absent. There was a mild peritumoral lymphocytic infiltrate (1-2/hpf) and eosinophilic infiltrate (10/hpf) along with an intratumoral eosinophilic infiltrate (6-7/hpf). The margins were found to be uninvolved by the tumor, and the closest margin was the radial margin which was less than 1 mm away from the tumor. The regional lymph nodes could not be assessed as they were not submitted. Immunohistochemical staining

showed positivity for neuroendocrine markers CgA, Synaptophysin (Syn) and NSE along with a Ki-67 proliferative index of 5 % (Fig. 2). A diagnosis of neuroendocrine tumor of the appendix - Grade 2 was made with the TNM staging being pT_3NxMx.

DISCUSSION

First described in the late 19th century and recognized as a significant separate entity by the German pathologist Siegfried Oberndorfer who coined the word carcinoid (‘*karzinoide tumoren’*) in 1907, neuroendocrine tumors are rare, slow-growing neoplasms (4,5). ANENs are most encountered in individuals in their third and fourth decades. In children and adolescents, the most common age at presentation is 12-13 years (2,6,7). In our cases, the ages at diagnosis were 13 and 19 years. There is a slight female preponderance seen in adult ANENs. Studies comparing the incidence in boys and girls of a similar age group either reflect this observation or are equivocal (8,9). Both our cases were of female patients.

In the pediatric and adolescent age group, appendiceal NENs are reported in nearly 3 out of every 1000 appendicectomy specimens that are resected for acute appendicitis (2,10,11). Our cases presented with features of acute appendicitis and the tumor was not detected by imaging. The majority (60-75%) of appendiceal NENs arise from the tip of the appendix and less frequently from the body of the appendix (5-20%) and its base (<10%) (2,9,12,13). Studies have shown that tumors involving the distal portion of the appendix always present with features of acute appendicitis, but those arising from the proximal appendix may present clinically with features of peritonitis (14). The tumors in our cases were in the middle and distal appendix respectively (15). As in our second case, some patients present with a chronic vague right lower quadrant abdominal pain (16). This is regarded to be due to an intermittent partial or complete obliteration of the lumen of the appendix by the tumor, especially in cases where the tumors were found to be located more proximally. However, in our second case the tumor was found located in the distal appendix, so a symptomatic luminal obstruction is doubtful.

According to the 2019 WHO classification, NENs are graded into G1, G2 and G3 with respect to their mitotic activity as well as their ki-67 index (17). Those tumors with <2 mitoses/ 2 mm^2 and having a ki-67 proliferative index of <3% are classified as low grade or G1 tumors. Those with 2-20 mitoses/ 2 mm^2 and a ki-67 proliferative index of 3-20% are classified as intermediate grade or G2 tumors. Low grade or G3 tumors show >20 mitotic figures/ 2 mm^2 as well as a ki-67 proliferative index of >20%. Based on this classification, our cases would be classified as G1 and G2 respectively.

Although right hemicolectomy was once regarded the standard surgical procedure for all appendiceal NENs, both the North American Neuroendocrine Tumor Society (NANETS) as well European Neuroendocrine Tumor Society (ENETS) now recommend it only in cases of tumors measuring >2 cm diameter or displaying a mesoappendix invasion greater than 3 mm (12). This may allude to the fact that ANENs that measure greater than 20 mm have a higher propensity to metastasize (11). In all other cases, an appendicectomy would suffice as appropriate surgical management. Since both our cases are not greater than 2 cm in their largest dimension, the surgical management has been appropriate.

Due to the paucity of studies on ANENs in children and adolescents, there are no standard guidelines on and the duration of post-operative follow up. Both the NANETS and ENETS guidelines may have limitations as they were established based on adult ANENs. The ENETS suggests following up patients with specific risk factors such as tumors >2 cm size and with known metastasis at 6 months and 12 months post operatively, and a yearly follow-up thereafter (11). On the other hand, some studies have challenged the requirement for follow up in the pediatric age group and deemed it unnecessary (12).

ANENs carry an excellent prognosis. Numerous studies, particularly the more recent ones, have shown five-year and ten-year overall survival rates across all age groups to be close to 100% (9,10,17,18). This may be attributed to several factors including and especially improved diagnostic methods and overall knowledge of the disease. Most pediatric and adolescent ANENs are of <2 cm size and are either G1 or G2 at the time of presentation and therefore show a low tendency to metastasize at this stage, further lowering disease morbidity and mortality (2,9).

CONCLUSION

Although encountered in nearly 0.1-0.3% of resected appendicectomy specimens, ANENs are generally diagnosed incidentally in children presenting with clinical manifestations of an acute appendicitis. Despite its apparent rarity, a clinician must be mindful of it as a possible differential diagnosis, especially since an early diagnosis and surgical removal has been linked with an excellent prognosis and a low risk of metastasis. A routine histopathological examination of the resected appendix specimen is therefore paramount in every case of acute appendicitis.

CONFLICT OF INTEREST

Authors declare no potential conflicts of interest.

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