Morphological and Immunohistochemical Characteristics of a case of Appendiceal Neuroendocrine Tumor (NET)

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Neuroendocrine tumor is the commonest tumor of the appendix but usually detected incidentally in appendectomy specimens. It is important to define the tumor histopathologically for proper management of such tumors. We present a case of 45 years old female who had recurrent right sided abdominal pain for last one year. She was diagnosed as a case of acute appendicitis and hospitalized for surgical intervention. Consequently, appendectomy was done. Histopathological examination revealed a neuroendocrine tumor of appendix. For prognostic and therapeutic purpose immunohistochemistry for chromogranin A, synaptophysin and Ki-67 were done. The diagnosis of appendiceal NET was confirmed by positive immunostaining for the chromogranin A and high proliferative index of Ki-67. Appendiceal Neuroendocrine tumor most often presents as acute appendicitis as it demonstrates no specific clinical presentation. It is found incidentally and diagnosis is rarely suspected before histopathological examination. A careful evaluation is further needed for appropriate medical treatment or extended surgery.

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Key words: Appendix, Neuroendocrine tumor

Introduction

Appendix is the commonest sample in surgical pathology and most of the cases the diagnosis is acute appendicitis. Primary neoplasms of appendix are identified in about 0.5% of all surgically removed cases. It is rarely suspected before the histopathological examination.[1] Carcinoid tumor represents >50% of all appendix neoplasms.[2] This tumor arise from the neuroendocrine cells of the diffuse endocrine system, which are identified in numerous locations, including the GIT (73.4%), lung (25.1%), ovaries (0.5%) and biliary system (0.2%). [3] Most of the appendiceal neuroendocrine tumor (NET) usually behaves as benign tumors. while certain lesion poses the potential for malignancy. They can metastasize also and the probability is low, 4.7% of all appendiceal tumors.[4] Lymphatic spread is the primary route and hepatic metastasis is rare. Though neuroendocrine tumor of appendix is not so common should be considered as a cause of acute appendicitis during histopathological examination.

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Case Report

A 45 years old female patient was admitted in a hospital of Dhaka city with complaint of recurrent lower abdominal pain for one year duration and an additional exacerbated attack of pain for last two days. She diagnosed as a case of acute appendicitis and consequently appendectomy was done. Macroscopically the appendix was identified 6 cm long and 1.0 cm in maximum diameter, demonstrating hyperemia and edema. On opening, lumen contained exudate. The cut surface of distal third (tip) showed a yellowish brown and firm area measuring about 0.8 cm in maximum dimension. Microscopically, the mucosa and submucosa showed lymphoid hyperplasia (Figure-1). Sections made from distal third region showed a tumor made of small cells arranged in festoon and sheets (Figure-2). The tumor cells had oval regular nuclei with inconspicuous nucleoli (Figure-3-5). These cells invaded the muscle layer. Mitotic figures were 4-6/10 HPF. Serosa and mesoappendix were free of tumor (Figure-6). For prognostic and therapeutic purpose immunohistochemistry for chromogranin A, synaptophysin and Ki-67 were done. The immunostaining for the chromogranin A was positive and synaptophysin was negative. Ki-67 was positive in 60% of the highest proliferating area which was high proliferative index and represents as high grade malignant carcinoid. The diagnosis was Appendiceal NeuroEndocrineTumor (NET) pTNM: T1aNxMx. Postoperative CT scan was revealed postoperative state of Ca appendix with hepatomegaly and cholelithiasis. No further treatment was administered and the patient was well with no discomfort.

Discussion:

In 1907, Sigfried Obendorfer, a German pathologist coined the term karzinoide, or carcinoma like to describe the tumor.[2]This tumor is originated from subepithelial Kulchitsky cell releases serotonin which is responsible for carcinoid syndrome. The Male female ratio is 1:2.4. This tumor occurs most commonly in fourth to fifth decade of life. Among all the Gastrointestinal Neuroendocrine tumors, 17% of tumors can found in appendix.[2] Neuroendocrine tumor is the commonest tumor of appendix but usually detected incidentally in appendectomy specimens.[1] It is found in 0.3%-0.9% of appendectomy specimens.[5] As it is a rare and slow growing tumor, it is important to define the correct management. This tumor commonly presents as acute appendicitis. Most tumors have largest dimension less than 1.0 cm. Metastasis risk increases up to 85% when the tumor diameter exceeds 2 cm.[5] Distal third of appendix (75%) is the commonest site.[6] Five year survival is 94% if the tumor is confined to the appendix.[7] The prognosis of Appendiceal NET is much better than midgut NET. [8] But some NETs can be highly aggressive based on location, size, grade and other factors. For these, immunohistochemical staining should be considered to confirm initial diagnosis.[9] This tumor often innocuous at the time of presentation and can Pose a diagnostic challenge. Challenges associated with the pathology of NETs are broad spectrum of biologically different neoplasm (Table I).[10] Some can be less aggressive and some can be highly aggressive. Other NETs may recur after many years and atypical histological features may confuse with adenocarcinoma. So, grade and stage are critical to predict outcome and guide therapy. Cellular pleomorphism with high mitotic index, lymphatic invasion, spread to the mesoappendix, tumor positive resection margins and lymph node involvement are bad prognostic factors.[11] Synchronous and metachronous development of colorectal carcinoma (13%-33%) can occur with this type of tumor.[12] GNETs divided into five main categories[13]

1) *Well differentiated endocrine tumor (PI<2%)*
2) *Well differentiated endocrine carcinoma (PI>2% but <15%)*
3) *Poorly differentiated endocrine carcinoma (PI>15%)*
4) *Mixed exocrine-endocrine tumor*
5) *Tumor-like lesion*.

Proliferative rate is the most important feature used for grading and can be assessed in two ways-by counting mitotic figures/10 HPF/2 mm^2 or by use

of Ki 67 (Table-2)[9]. Ki 67 is acceptable as accurate mitotic count may not be possible. The pathology report is the critical tool in the management of NET. Histopathological examination of every removed appendix is important.[14] It is useful for the entire management team which includes a grade, stage and along with a reference to the specific systems being used to define these parameters. Other diagnostic procedure play important role in the diagnosis. Such as, Plasma chromogranin A which can be raised in 80-100% of NET. 24 hrs urinary level of 5-hydroxyindole-acetic acid and 111 in labeled octreotide scintigraphy are also helpful.[15]

Table I: Neuroendocrine neoplasm of the appendix WHO 2010 (Solcia et al.) [10]

Neuro Endocrine tumors (NET)	Neuro Endocrine tumors (NEC)	Mixed adenoneuroendocrine Carcinomas (MANEC)
NET G1 (Carcinoid)	Large cell NEC	EC cell, serotonin-producing NET
NET G2	Small cell NEC	Goblet cell carcinoid
		L cell, glucagon-like producing and NET
		Tubular carcinoid

Table II: Grading Systems for Neuroendocrine Neoplasm. [9]

Grade	Gastro-enteropancreatic NETs (WHO 2010, ENETS)
Low grade (Grade 1)	<2 mitoses/10 HPF, AND <3% Ki-67 index
Intermediate grade (Grade 2)	2-20 mitoses/10 HPF, OR 3%-20% Ki-67 index
High grade (Grade 3)	>20 mitoses/10 FPF, OR >20% Ki-67 index

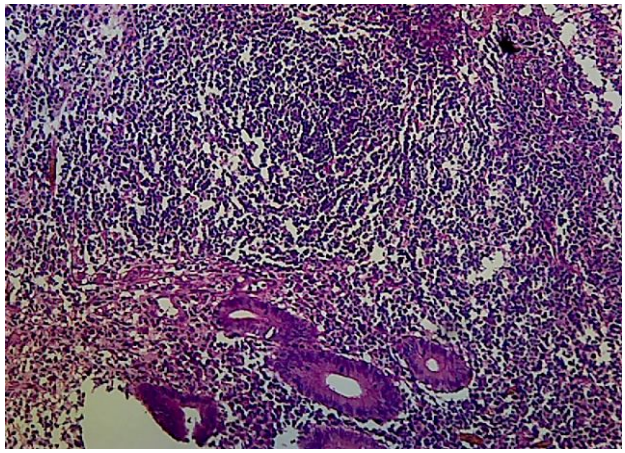

Figure: 1 The mucosa and submucosa show lymphoid hyperplasia.

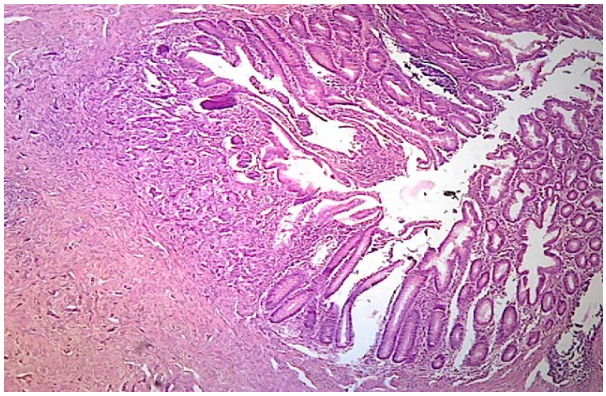

Figure: 2 Sections made from distal third (tip) show the tumor made of small cells arranged in festoon, sheets and clusters

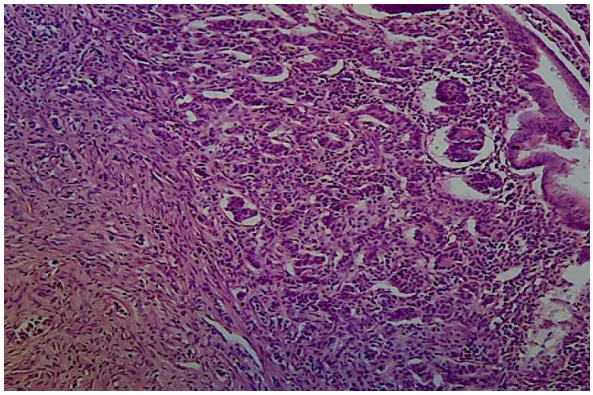

Figure 3. The tumour cells are arranged in groups

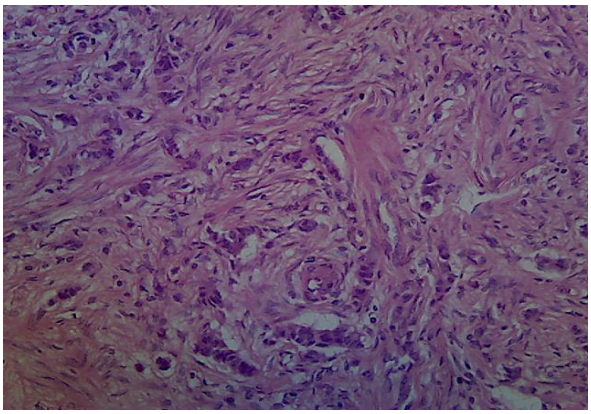

Figure 4. The tumors have finely distributed nuclear chromatin with inconspicuous nucleoli.

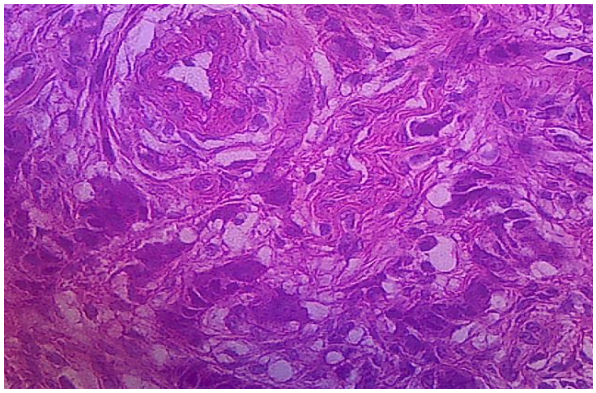

Figure 5. The tumor Cells are nested close to blood vessels

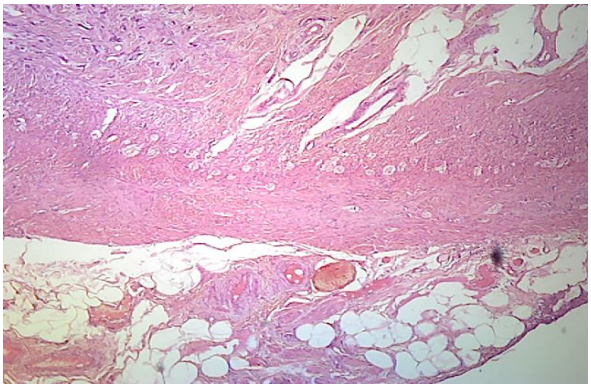

Figure: 6 Serosa and mesoappendix are free of tumor

Conclusion

Appendiceal Neuroendocrine tumor most often presents as acute appendicitis as it demonstrates no specific clinical presentation and often innocuous at the time of presentation. As its diagnosis is rarely suspected before histopathological examination can pose a diagnostic challenge. The prognosis of Appendiceal NET is generally favorable, however it can be quite variable and related to the location of the primary tumor, extent of metastatic disease at initial presentation and time of diagnosis. For these, immunohistochemical staining should be considered to confirm initial diagnosis as well as for prognosis. Extended surgery or further medical treatment must be planned for patients with defined risk factors.

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