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RESEARCH ARTICLE

A CASE SERIESOF NEUROENDOCRINE TUMOURS IN APPENDIX: INCIDENTAL FINDINGS

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Abstract

Neuroendocrine tumors are aggressive and rare tumors which can occur almost everywhere in the body. The annual incidence of neuroendocrine tumors is 2.5-5 per 100000. We report 4 cases of appendiceal neuroendocrine tumors which were diagnosed incidentally on routine histopathological examination from the time period of December 2020 to November, 2022.The appendix is one of the most common single site for carcinoid tumor.Histopathologically, appendiceal neuroendocrine tumors (aNETs) is mostly comprised of enterochromaffin (EC) cell type and derives from a subepithelial cell population, which is different from neuroendocrine tumor in other sites. Although rare, and usually detected incidentally in appendectomy, it is considered the most common type of appendiceal primary malignant lesion, and is found in 0.3%-0.9% of patients undergoing appendicectomy.Thesetumors rarely present with metastases. In surgical practice most surgeons may encounter only one or two such tumours during their career. Therefore, it is important to define correct management of such a rare tumor. We report a series of 4 aNETs found incidentally in appendicectomy specimens and discuss about management strategies.

Introduction:-

Generally, Neuroendocrine tumors (NETs) are rare tumors comprising ~2% of all malignancies [1] with the gastrointestinal tract and the lung as the most common sites [2]. Neuroendocrine tumors (NETs) are a heterogeneous group of epithelial neoplastic proliferations arising in many body organs. Irrespective of their primary site and of their grade of differentiation, neoplastic cells share features of neural and endocrine differentiation: the “neuro” property is based on the identification of dense core granules that are similar to dense core granules (DCGs) present in serotonergic neurons, which store monoamines, and the “endocrine” property refers to the synthesis and secretion of these monoamines which is about two-thirds of NETs that arise in the gastrointestinal tract and pancreas [1, 3].The appendix is one of the most common sites for GI neuroendocrine tumours besides small intestine and rectum.

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Case series

Case 1:

A 31-year-old female presented with classical signs of appendicitis, with radiological (USG) findings of appendicitis and appendectomy was done. Tissue was sent to Pathology laboratory for routine Histopathological examination. Haematology and Biochemistry laboratory results not significant. Patient had no signs and symptoms of Carcinoid syndrome.HPE revealed a well differentiated neuroendocrine tumor in the tip of appendix and further subjected to immunohistochemistry for confirmation of neuroendocrine nature.

Case 2:

An 11-year-old male admitted in Emergency/Casualty Department with complaints of acute abdomen, tenderness in Mc Burney's point. Emergency appendectomy was performed and specimen sent as routine policy to Pathology Laboratory.Patient had elevated leucocytecount and increased C-Reactive protein. HPE revealed a neuroendocrine tumor in the tip of appendix with involvement of mesoappendix and further subjected to immunohistochemistry for confirmation of neuroendocrine nature and Ki-67 index.

Case 3:

A 41-year-old woman presented to Surgery OPD with right hypochondrial pain which had been on and off for the past one year.A clinical diagnosis of recurrent appendicitis was made and elective surgery was performed and biopsy sample sent to Histopathology lab.Routine grossing revealed a well demarcated tumour in the tip of appendix which turned out to be a neuroendocrine tumour,limited to appendix.Surrounding tissue did have features of inflammation.

Case 4:

A 52-year-old female presented with abdominal pain and vomiting with constipation for 4 days; CT of abdomen showed an enhancing mass at the ileocecal area including the appendix and she was diagnosed as having complete intestinal obstruction and underwent right hemicolectomy; histopathology report showed a well-differentiated neuroendocrine tumor of the appendix. Patient is doing well with follow-up with an oncologist. Follow-up CT of the abdomen showed a free anastomosis site.

Discussion:-

Neuroendocrine tumours(NET) have a substantial variation in both tumor biology and clinical presentation; the biology of each NET depends on its primary tumor localization, cellular morphology, and mitotic activity, and clinically, NET may manifest by the expression of autonomous hormone secretion of either a peptide hormone or biogenic amine [4].Appendiceal NETs present with an incidence of 0.15- 0.6 cases per 100000 person-years,with a slight female predominance and highest incidence before 40 years. aNETs occur mainly in the tip of appendix (in 67% of adult patients and 73% of paediatric patients).80% of cases are found incidentally after surgery for acute appendicitis. Pathogenesis is largely unknown.Molecular data is limited,rarely chromosome 18 deletion [9].

Histological features predictive of aggressive tumor behaviour are size, histological subtype and mesoappendiceal involvement. Most of the tumour's size is smaller than 1 cm in diameter in 60–76% of patients. In tumor size 1–2 cm in diameter is 4–27% and tumor size larger than 2 cm in diameter is 2–17%. There are 4 histologic subtypes of aNETs which are goblet cell, composite cell, enterochromaffin cell and atypical cell. The risk of metastasis from tumors smaller than 1 cm is zero, while tumor size larger than 2 cm increase the risk of metastasis from 20% - 85%.[5]

Figure 1:- Gross appearance of a submucosal nodule at the tip of appendix.

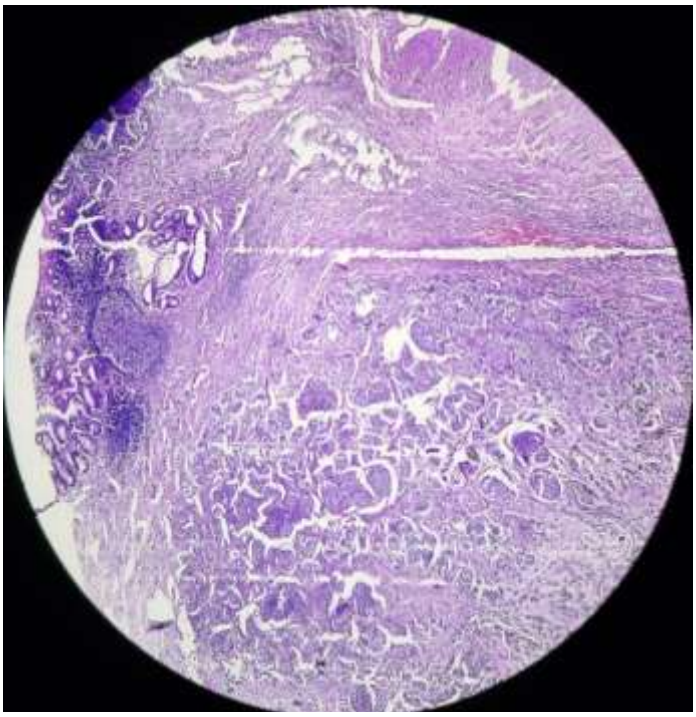

Figure 2:- Submucosal tumour ,intact mucosa H&E 4x.

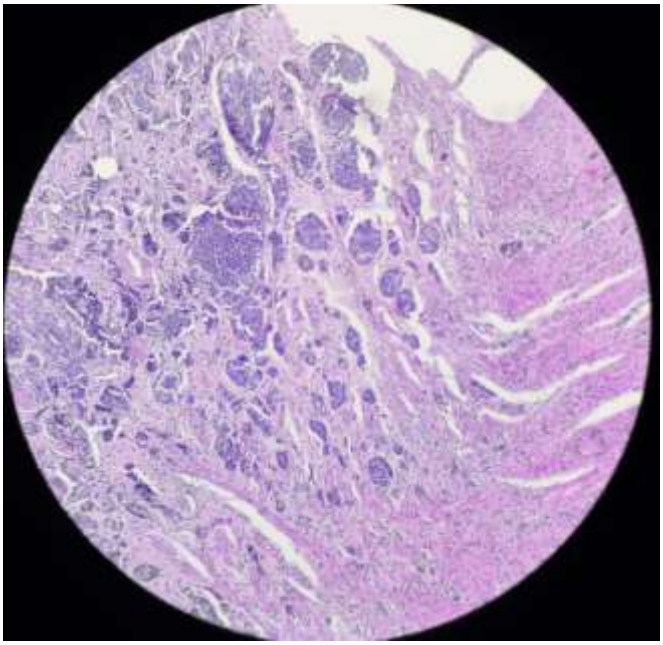

Figure 3:- Nests and cords of tumour cells reaching the muscular layer H&E 10x.

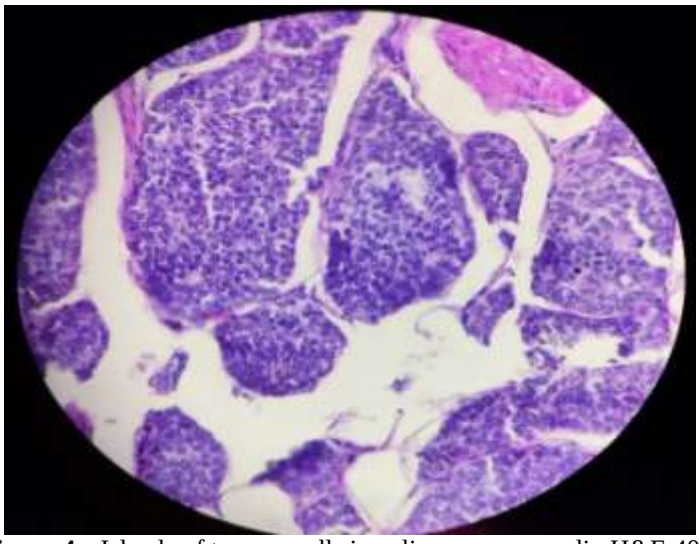

Figure 4:- Islands of tumour cells invading mesoappendix H&E 40x.

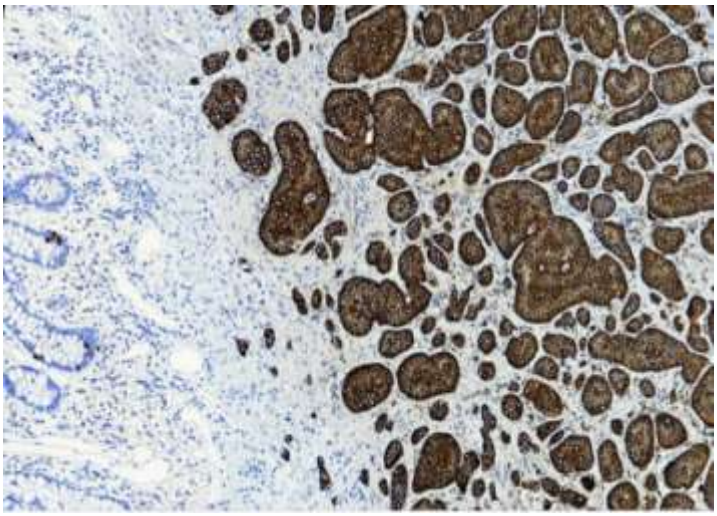

Figure 5:- Immunohistochemistry stain Chromogranin positive.

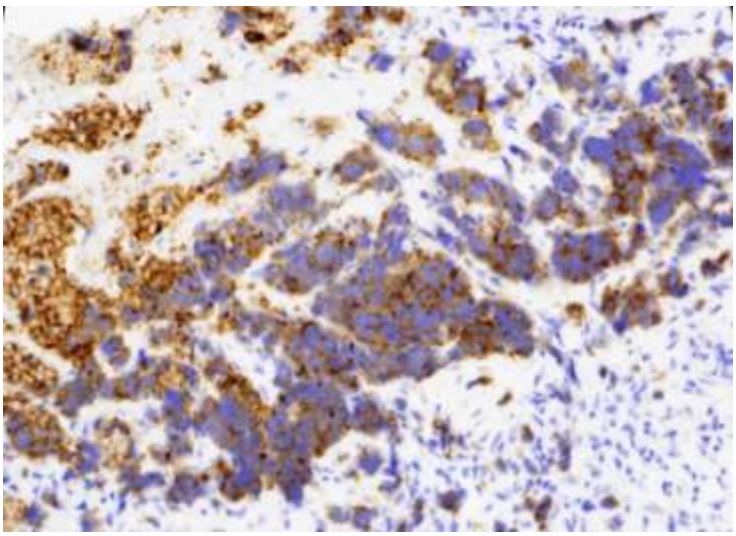

Figure 6:- Immunohistochemistry stain NSE positive in tumour cells.

In this case series, 3 of the tumors were less than 1cm and localized at the tip of appendix with no evidence of regional or distant metastases.One of the cases had involvement of mesoappendix and the last case was seen around the base of appendix. aNETs usually metastasize to regional lymph nodes rather than to the liver.[6] The aNETs distribution is heterogeneous, in which the tip of the appendix is the most frequent location 60–70% followed by in the body 5–21% and then the base of appendix 7–10% (Table 1).

Table 1:- Classifications and staging of aNETs according to the TNM system.

Stage	T	N	M
I	T1	N0	M0
II	T1	N1	M0
	T2	N0	M0
III	T2	N1	M0
	T3	Any N	M0
IV	Any T	Any N	M1

T1: Tumor < 2 cm
T2: Tumor ≥ 2 cm but < 3 cm
T3: Tumor ≥ 3 cm
N0: No lymph node metastases
N1: Regional lymph node metastases
M0: No metastases

Regarding the treatment modalities of appendiceal neuroendocrine tumours, there is still debate and review of literature reveals different views. The size of the tumor and histological patterns are the most important factors that contribute to the selection of the surgical treatment. For aNETs lessthan 1 cm in diameter size, it is unlikely to have metastasized. Therefore, a simple appendectomy with clear margin would suffice. However, if the aNETs measures more than 1 cm and less than 2 cm in diameter size, with no muscular invasion or lymph node involvement a simple appendectomy with surgical margins free of tumor [7]. However, Moertel[5] suggested in aNETs greater than 2 cm in diameter size with lymph node involvement and high-grade malignant carcinoids (including those with cellular pleomorphism and a high mitotic index, more than 2 mitoses/10 HPF), extension of the tumor into the mesoappendix, subserosal lymphatic invasion, tumor location near the base of the appendix or close to the cecum with potential involvement of its wall, and tumor-positive resection margins then this should be managed with right hemicolectomy.[2,6] Meanwhile, in elderly age group and in high risk patients a simple appendectomy may be adequate for surgical resection of tumors larger than 2 cm in diameter in size (Table 2).[5]

Tumor size	Risk for lymphatic spread	Further characterization	Predictive validity for malignancy	Type of evidence source	Treatment recommendations
< 1 cm	0	None (positive margins)	Accepted	Retrospective series (Conclusive)	Appendectomy
1-2 cm	0-1%	Serosal invasion Mesoappendiceal invasion Vascular invasion Mitotic activity (>2 cells/mm²) Proliferation markers (i.e. Ki67)	Not predictive (accepted) Controversial Controversial Not proven	Retrospective series Retrospective series Retrospective series Common sense evidence' (data from different NETs applied to appendix)	Individual risk evaluation: High risk (elderly) patient: Appendectomy 'High risk' tumor, low risk (younger) patient: Right hemicolectomy
		Localization at base of appendix Positive margins	Accepted	'Common sense evidence'	
>2 cm	30%	None	Accepted	Retrospective series	Right hemicolectomy

				(Conclusive)	
Any size gobletcell tumor	10-20%	None	Accepted	Retrospective series (Conclusive)	Right hemicolectomy

It is worthy to mention that the term carcinoid has been criticized because it was used to describe different tumors distinct in their aetiology, prognosis, and management, leading to terminological confusion and diagnostic unreliability. This term is considered to be a misnomer as the malignancy of this tumor group can be confirmed on the basis of local invasion prior to metastases [9] and not all benign. The term carcinoid should be used whenever there are the symptoms of this syndrome which are watery diarrhoea, flushing, bronchospasm, hypotension, and right-sided heart disease that correlates with serotonin hypersecretion since properties of serotonin include vasodilation, bronchoconstriction, and smooth muscle contraction [8]. In our case series, none of the patients presented with secretory symptoms and all of them presented with a clinical picture of acute appendicitis.
Singh S et al[7] proposed an algorithm of treatment and follow up depending on size, immunohistochemistry,biochemical and radiological findings given in figure 7.

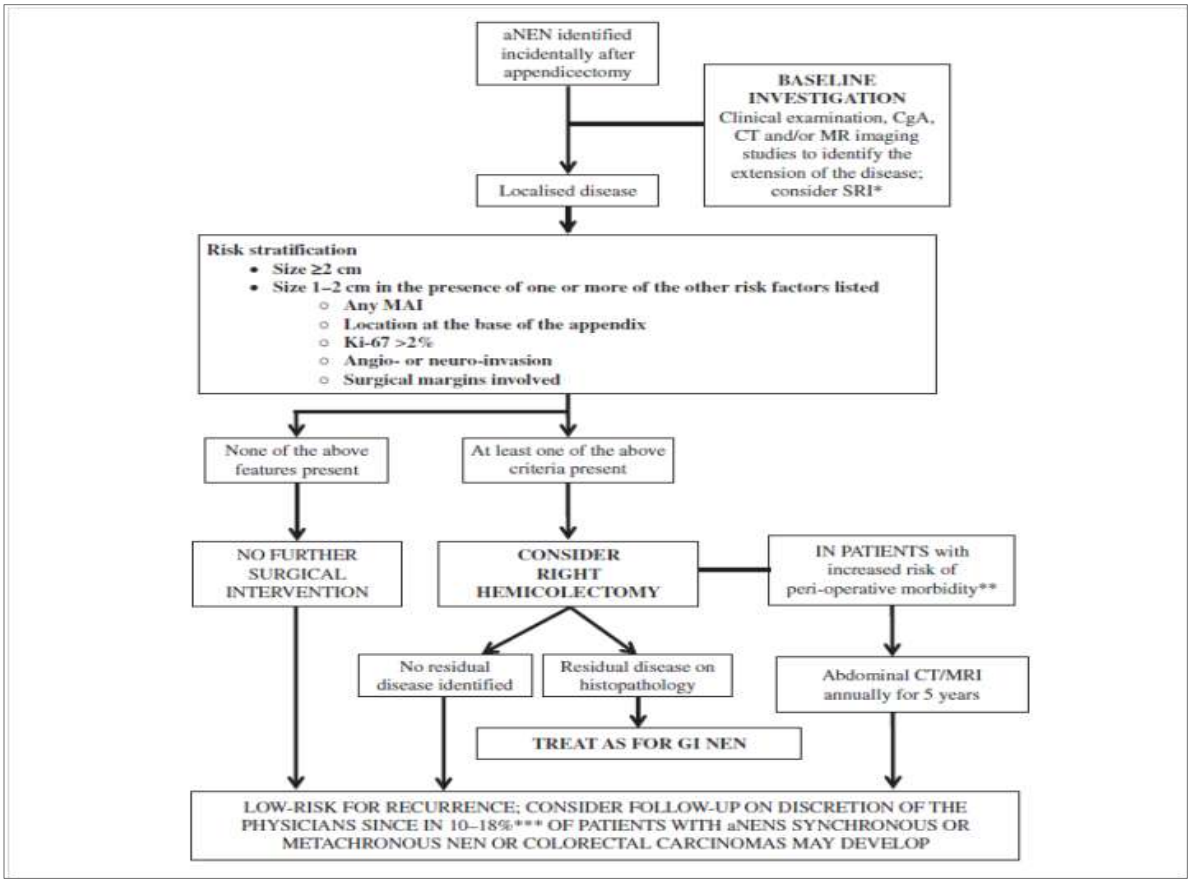

Figure7 Algorithm for appendiceal NETs therapeutic and follow-up in incidentally found after appendicectomy for acute appendicitis, aNETs, appendiceal neuroendocrine neoplasms; MAI, mesoappendiceal fat invasion; MRI, magnetic resonance imaging; NEN, neuroendocrine neoplasm; SRI, somatostatin receptor imaging; US, ultrasound scan.

Fortunately, 3 of our patients were diagnosed in early stages and these 3 patients were treated radically aiming for cure and they underwent radical surgeries; one of the cases was expected to upfront right hemicolectomy, and all cases underwent appendectomy, whereas the last case underwent appendectomy, but based on the histopathological findings and the discussion of the case, right hemicolectomy was done. Based on the clinical picture and staging of these 4 cases, no adjuvant treatment was required. One case presented with involvement of mesoappendix, and he

presented in poor general condition, and referred to a cancer hospital. All patients who did radical surgery were followed up; follow-up consists of clinical examination and abdominal imaging (6 months after imaging and then as clinically indicated).

Conclusion:-

Despite the increasing number of patients diagnosed with GIT NET and also the increasing knowledge within this field, still, most of the cases are diagnosed incidentally; thus, a higher incidence of suspicion is required. Also, there are still some controversies regarding the sequence of systemic treatments used in the management of GIT NET that needs a consensus.

Compliance with Ethical Standards

Conflicts of Interest

The authors declare that they have no conflict of interest.

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