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# NEUROENDOCRINE TUMORS- A Case Series and Literature Review

**Dr. Sanjukta Padhi[*1], Dr. Bijayalaxmi Sahoo[2], Dr. Papuji Meher[3], Dr. Kusumbati Besra[4] & Dr. Sagarika Samantaray[5]**

*[1] Department of Radiation Oncology, A.H. Regional Cancer Centre, Cuttack, India
[2] Department of Radiation Oncology, A.H. Regional Cancer Centre, Cuttack, India
[3] Department of Radiation Oncology, A.H. Regional Cancer Centre, Cuttack, India
[4]. Deaprtment of Oncopathology, A.H. Regional Cancer Centre, Cuttack, India
[5]Department of Oncopathology, A.H. Regional Cancer Centre, Cuttack, India

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## *Abstract*

**Background:** Neuroendocrine tumors (NET) are extremely rare and aggressive tumor. The annual incidence of clinically significant neuroendocrine tumors is approximately 2.5 -5 per 100000.

**Case Series:** Here we report eight cases of neuroendocrine tumors of various anatomical sites which were diagnosed and treated at our institution from the time period of 2015-2016. The aim of this case series was mostly to determine the incidence, age, gender and primary site distribution of Neuroendocrine tumor at our institution. This study also helped us to evaluate the mode of treatment given according to site of Neuroendocrine tumor and also their follow up. Out of eight cases of neuroendocrine tumor three of them are from lung, one each from Urinary Bladder, Paranasal sinus, Pancreas, Mediastinum, Retroperitoneal site. Out of eight cases six were male and two were females.

**Conclusion:** Neuroendocrine tumors are extremely rare tumors and have wide range of clinical presentation according to the site of involvement. Hence it is clinically challenging in context to diagnosis and treatment. According to the clinical presentations, histopathological subtypes, immunohistochemistry and radiological finding accurate diagnosis and classification is vital for management.

## I. Introduction

Neuroendocrine tumors (NETs) are abnormal growth of some specialized cell called neuroendocrine cells. NET are rare tumors and it can occur almost everywhere in the body. Most of the NETs arise from Lung, Appendix, Small intestine, Rectum and Pancreas. NET from unknown primary is also seen.

The annual incidence of clinically significant neuroendocrine tumor is approximately 2.5-5 per 100000 and prevalence is 35 per 100000. A European investigation which included both surgical and autopsy specimen report overall incidence of 8.4 cases per 100000. [1]

Gastrointestinal tract is the most common site for occurrence of Neuroendocrine tumors (accounts 70%) followed by the Respiratory tract (accounts 25%)(2). Males are most commonly affected and patients most commonly present beyond 60 years of age.

In view of classification, the World Health Organization (WHO) has classified these tumors into 4 subtypes [3]

- Typical carcinoid (well differentiated neuroendocrine carcinoma grade 1),
- Atypical carcinoid tumor(moderately differentiated carcinoma, grade 2; large cell neuroendocrine carcinoma),

- Small cell neuroendocrine carcinoma (poorly differentiated neuroendocrine carcinoma, grade 3)
- Paraganglioma.

The optimal treatment strategy of these patients is not known but surgery, chemotherapy, radiotherapy can be used alone or as a multidisciplinary approach. With this multidisciplinary approach median survival improved from two years to more than eight years.[4]
In this study we present the clinical and histopathological features of 8 cases of neuroendocrine tumor that we come across in our institute within 1 year. We also reviewed previously published articles on the diagnosis and treatment of these neoplasms.

## II. Cases

Here we describe eight cases of neuroendocrine tumors from different anatomical sites. Out of eight cases of neuroendocrine tumor three of them are from lung, one each from Urinary Bladder, Paranasal sinus, Pancreas, Mediastinum, Retroperitoneal site. Out of eight cases six were male and two were females. The details of the patient characteristics, pathological features and treatment are summarized in the following table.[Table:1] Figure of the selected cases are given below.

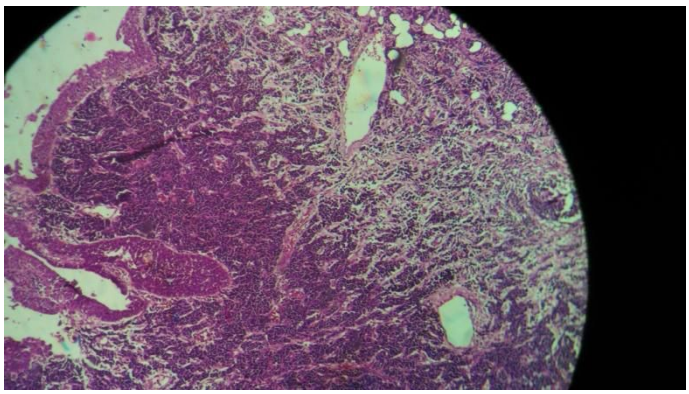


***Figure-1: Histopathology of NET of urinary bladder in low power field showing mother tissue and neuroendocrine components***

***Table 1: Clinico-pathological and radiological characteristics***

| TREATMENT GIVEN | COMPUTED TOMOGRPHY SCAN | IHC STUDY | PRIMARY HISTOPATHOLOGY | SITE OF LESION | CLINICAL FEATURES | AGE/ SEX |
|---|---|---|---|---|---|---|
| CT FOLLOWED BY RT | VESICAL MASS WITH SEMINAL VESICLE INVOLVEMENT | CD56+, CK7+ (Fig-4) | NEUROENDORINE CARCINOMA WITH UROTHELIAL CARCINOMA (Fig: 1& 2) | URINARY BLADDER | HEMATURIA, DYSURIA | 55/M |
| SURGERY, CT and RT | MASS INVOLVING NASAL CAVITY, ALL PARANASAL SINUSES (Fig-3) | NSE+ | UNDIFFERENTIATED SMALL CELL NEC OR SINONASAL UNDIFFERENTIATED CARCINOMA | PARA-NASAL SINUS | ORBITAL SWELLING | 35/F |

| | | | | | | |
|---|---|---|---|---|---|---|
| RADICAL SURGERY and CT | PANCREATIC TAIL MASS | SYNAPTOPHYSIN+, CHROMOGRANIN+ CD56+ | WELL DIFFERENTIATED NEUROENDOCRINE TUMOR | PANCREAS | PAIN ABDOMEN | 19/M |
| CT | MEDIASTINAL MASS WITH MAJOR VESSEL ENCASEMENT | SYNAPTOPHYSIN+, TTF1+, PANKERATIN+, CK7+ | MEATSTATIC NEUROENDOCRINE CARCINOMA | LUNGS WITH CERVICAL LYMPH NODE | COUGH, DYSPNEA | 45/F |
| CT and RT | ANTERIOR MEDIASTINAL MASS ABUTTING MAJOR VESSELS, MEDIASTINAL LYMPH NODE (Fig-5) | SYNAPTOPHYSIN+, CHROMOGRANIN+, NSE+ | WELL DIFFERENTIATED LOW GRADE NEUROENDOCRINE TUMOR | ANTERIOR MEDIASTINUM | CHEST PAIN, DYSPNEA | 72/M |
| CT and RT | RETROPERITONEAL LYMPH NOE DISPLACING AORTA | PANCK+, SYNAPTOPHYSIN+ | POORLY DIFFERENTIATED CARCINOMA | RETROPERITONEAL LYMPH NODES | PAIN ABDOMEN | 45/M |
| CT and RT | UPPER LOBE LUNG MASS WITH MEDIASTINAL AND AXILLARY LYMPH NODES | SYNAPTOPHYSIN+, TTF1+, PANKERATIN+, CK7+ | METASTATIC NEUROENDOCRINE TUMOR TO AXILLARY LYMPH NODE | LUNGS | CHEST PAIN, AXILLARY MASS | 64/M |
| CT | MULTIPLE CERVICAL, AXILLARY, MEDIASTINAL LYMPH NODE WITH SOLITARY RIGHT LUNG NODULE | SYNAPTOPHYSIN+, TTF1+, , CHROMOGRANIN+ | POORLY DIFFERENTIATED CARCINOMA | LUNG NODULE WITH NECK AND MEDIASTINAL LYMPH NODE | NECK AND AXILLARY SWELLING | 70/M |

N.B:- CD-Cluster of Differentiation, RT- Radiotherapy, CK-Cytokeratin, NSE- Neuron Specific Enolase, PANCK-Pancytokeratin, CT-Chemotherapy, TTF-Thyroid Transcription Factor

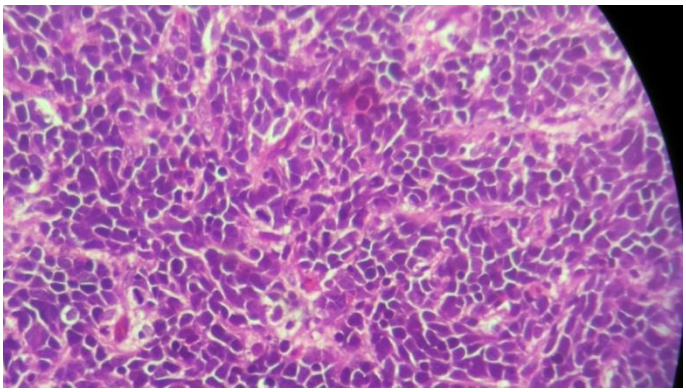


*Figure-2: Histopathology of NET of urinary bladder in high power field showing small round cells with prominent nuclei and scant cytoplasm, focal salt and pepper chromatin appearance with mitoses*

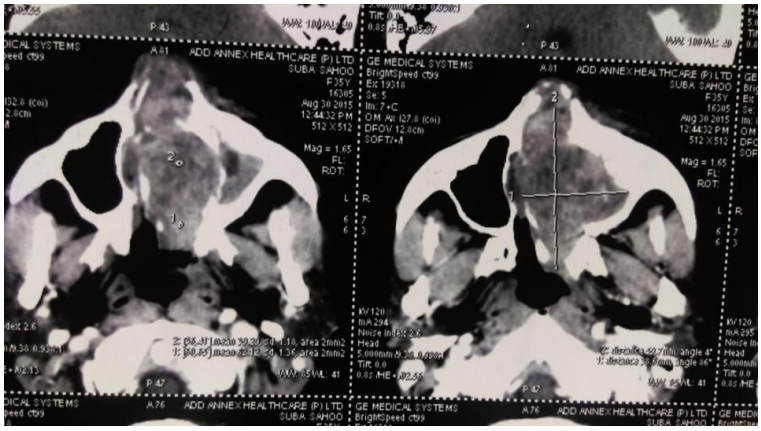
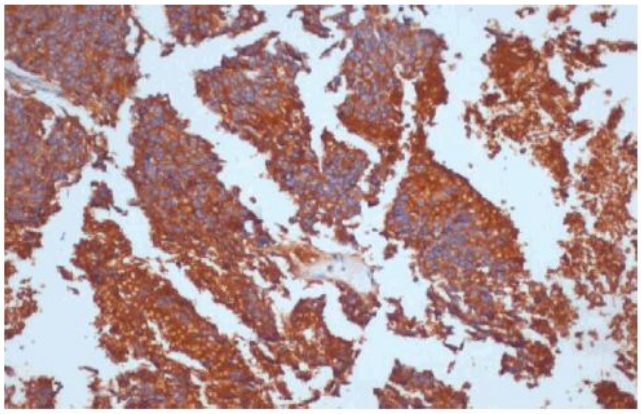


*Figure-3: CECT Scan of NET paranasal sinus showing mass in left maxilla extending to orbit and nasal cavity*



CD56 (X200): Immuno-reactivity reactivity for CD56

*Figure-4: Immunohistochemistry for NET of urinary bladder showing positivity for CD56*

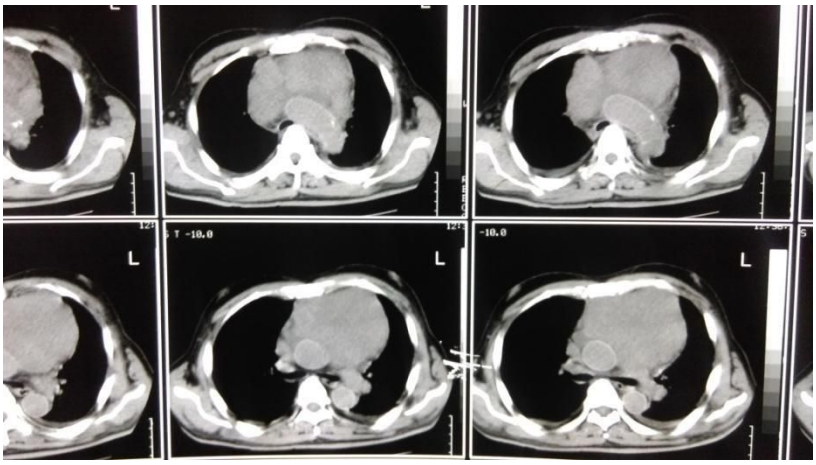


***Figure-5: CECT scan of NET mediastinum showing anterior mediastinal mass abutting major vessels and mediastinal lymph nodes.***

## III. Discussion

Neuroendocrine tumors (NET) are very rare tumors and a controversial topic in literature. NETs are mostly derived from primitive stem cell in Gastrointestinal tract (GIT) and lungs; but it can derived from any organ in the body(5).Most common site for NETs is GIT (70%) followed by lungs(20%).(2).Appendix is most common site in children. These are mostly benign and indolent but malignant form often exists.

NETs generally have slight male predominance but it can affect either sex. Similarly in our study six out of eight cases were males, and rest were females. Mostly NETs present in the age group of 50 -60 years (6). In our study four out of eight cases were below 50 years of age and one neuroendocrine tumor of pancreas presented at a very early age of 19 year and another case of NETs of paranasal sinus presented at 32 years of age.

NETs are generally diagnosed based on clinical, radiological and Immunohistochemistry features. Tumor cells show a large hyperchromatic pleomorphic nuclei with punctate chromatin and little cytoplasm. Mitotic figures are common. NETs are highly invasive tumor with lymphovascular and perineural spread. Hematoxyllin and eosin [H&E] stains are generally not sufficient for diagnosis so IHC is mostly confirmatory [7, 8].

Immunohistochemical markers of NET include Cytokeratin(CK), Chromogranin, Synaptophysin and Neuron specific enolase(NSE). Antibody against Protein convertase(PCs) also been used as an endocrine cell marker(9). Thyroid transcription factor-1(TTF-1) is a nuclear transcription protein and it show differentiation in thyroid, lungs and selected brain tissue(10). TTF-1 positivity is found in 40% cases of large cell neuroendocrine carcinoma of lung(11) and its absence indicates a poor prognosis(12). In our study two cases showed CD56 positivity, three cases CK-7 positive, three cases Chromogranin and two cases NSE positive, but six cases out of eight show Synaptophysin positivity and three case show TTF-1 positivity. So Synaptophysin positivity was found in most of the cases.

Primary NETs of urinary bladder is very rare and constitutes less than 1% of all bladder neoplasms. Small cell NETs of bladder were first described in 1981 and large cell NETs of bladder in 1986. NET of bladder is highly aggressive disease and 24% of patient show distant metastasis and 5% of patient show multiple lymph node metastasis at the time of presentation (13). Our patient presented with disease restricted to urinary bladder without any metastasis.

NETs of paranasal sinuses (PNS) have an incidence of 1 per 100000 person per year (14). These tumors have very poor prognosis. So despite aggressive management, local recurrence and distant metastasis occur within 2 year after treatment (15). Median survival of these patients for limited disease is 1.4 years and for extensive disease is 0.7 year (16).Our case is now on follow up for 3 months after completion of treatment.

Pancreatic NETs are rare slow growing tumors which constitute less than 2% of all pancreatic neoplasms. Pancreatic NETs have an incidence of 1 per 100000 individual per year. Generally NETs are diagnosed in older age but in our study it presented at an early age of only 19 years.

NETs of lungs account for only 1.6 -3% of all lung cancers [17]. Garcia-Yuste et al reported that two-thirds of them occurred in the periphery of lungs [18].Another case series by Paci et al show that only one out of forty eight cases

was in central location [19]. In our study the lesion was in the central part of lungs which is a rare presentation.
NETs of mediastinum account for less than 5% of all anterior mediastinal neoplasms and are mostly malignant almost accounting 82% of cases [20].Chromogranin is one of the most important marker in such tumors [21].
Various treatment modalities are available for NETs. These include radical excision, radiotherapy and chemotherapy with Etoposide and Cisplatin. Earlier, excision followed by Radiotherapy was the preferred modality of treatment [22]. But in late 1990s combination of Chemotherapy and Radiotherapy with or without surgery has produced encouraging results [23]. NETs mostly recur after 3 years in 70% of cases with median age of recurrence being 37 months.
NETs are highly aggressive tumors with poor prognosis because of high risk of distant metastasis. The most common site of metastases are brain, lungs, bone and skin. Two of our patients are upfront presented with cervical lymph node metastasis and one with upfront axillary node metastasis. Rest of the patients have not shown any metastases till now.

## IV. Conclusion

NETs are highly aggressive neoplasms with poor prognosis. Lower incidence and diagnostic difficulties hinder the proper elaboration of early diagnostic criteria and management protocols. So this case series with our review literature gives an overview of presenting symptoms, radiological and pathological features for early diagnosis and proper treatment of neuroendocrine tumors.

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