



Case Report

Small Cell Esophageal Carcinoma with Merkel Cell Dysplasia: A Case Report

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Abstract

Neuroendocrine carcinoma (NEC) can rarely be associated with Merkel cell dysplasia. The clinical presentation is usually nonspecific and mild. Paraneoplastic MG is a rare autoimmune phenomenon related to esophageal NEC. We report a case of esophagus tumor having uncommon histology - (NEC) small cell type having Merkel cell dysplasia in the overlying epithelium, presenting as paraneoplastic Myasthenia gravis (MG). Neuro-muscular symptoms may be caused by paraneoplastic syndrome with underlying malignancy. The treatment options are different for esophagus squamous cell carcinoma and adenocarcinoma.

Keywords: *Esophagus, Endoscopic ultrasound, Myasthenia crises, Merkel cell dysplasia, Neuroendocrine carcinoma.*

Introduction

Neuroendocrine carcinoma (NEC) is rarely found in esophagus. The reported incidence is 0.4-2% among all malignancies of the esophagus.^[1] NEC has two histological subtypes based on tumor cell morphology - small cell and large cell types, the

latter being more common in a ratio of 1:4.^{[2][3]}

The 2010 WHO classification on histologic grading of NENs in digestive system divides them into low-grade (G1, Ki67 <2%), intermediate-grade (G2, Ki67 2-20%), and high-grade (G3, Ki67 >20%) or neuroendocrine carcinoma.

NEC are aggressive tumors, rapidly progressive and presents at advanced stage with poor survival. They are resistance to both chemotherapy and radio-therapy. These tumors frequently invade into peritumoral veins, lymphatics and nerves.^[1] The median overall survival duration is 14-28 months.^[3]

Merkel cells (MC) are normally present in the basal layer of the keratinized squamous epithelium in mid oesophagus. NEC can be associated with MC dysplasia. In esophagus MG along with other neoplasm is considered as paraneoplastic. Paraneoplastic MG is a rare autoimmune phenomenon related to esophageal NEC.

Case History

A 68-year-old man presented with recent onset dyspepsia and tight chest pain, dysphagia, weight loss. Clinical examination and Laboratory investigations (CBP, LFT, RFT, blood sugars, TSH) were normal.

An Upper GI Endoscopy revealed a non-obstructing flat focal ulcerated lesion (15mm) in mid esophagus with raised margin (Figure 1). On Narrow Band Imaging (NBI), there were abnormal tortuous vessels. Endoscopic mucosal biopsy showed poorly differentiated carcinoma, possibly of small cell NEC (Figure 2). Immunohistochemical (IHC) staining of the tumour was positive for synaptophysin and CD 56 and negative for CD 45, CK 5/6 and P40 with Ki 67 of 70%, confirming the diagnosis of small cell neuroendocrine carcinoma (Grade 3) (Figure 3). PET scan showed no uptake in esophagus. Endoscopic ultrasonography (EUS) showed focal thickening of esophagus wall with focal breach in submucosa (Figure 4). A thoracoscopic esophagectomy with gastric pull up was performed. Macroscopically, the resection specimen showed a focally raised mucosa (1.1 x 0.8 x 0.5 cm). 7 peri-esophageal lymph nodes were resected. Hematoxylin-eosin staining section show stratified squamous epithelium with diffuse areas showing marked nuclear atypia spreading

horizontally into sub-epithelium suggestive of dysplastic MC. The adjacent tumor tissue had cells arranged in nest and clusters lined by round to oval nuclei with salt and pepper chromatin having moderate amount of eosinophilic cytoplasm. The tumor cells invaded the lamina propria and muscularis mucosae and focally into the submucosa to a depth of < 200 µm was noted (pT 1) (Figure 5). A poorly differentiated NEC component was present independently. There was no lympho-vascular invasion. The resected margins of the specimen were free of tumor. On IHC staining, the tumor was focally positive for CK 20 and synaptophysin, and negative for p63 (Figure 6). The final diagnosis was small cell Neuroendocrine carcinoma with Merkel cell dysplasia without any lymph node metastases. Pathological staging (pTNM, AJCC 8th Edition) was (pT1bN0M0, Stage I). On 6th post-operative day, patient developed neuromuscular weakness with progressive breathing difficult requiring tracheostomy. He was diagnosed with Myasthenia Crisis based on positive Serum Acetylcholinesterase Receptor (AChR) Antibodies with normal serum Cholinesterase level, and negative muscle-specific tyrosine kinase (MuSK). The CT Chest showed no thymic abnormality. Patient was treated with Pyridostigmine and along with Intravenous immunoglobulins (IVIg). Most of the patients with limited neuro-endocrine esophageal carcinoma have high chance of micro-metastasis and early recurrence.^[5] Combination chemotherapy was given at 6 weeks after surgery (Etoposide + Carboplatin). Patient received 6 cycles of chemotherapy and is on quarterly follow up.

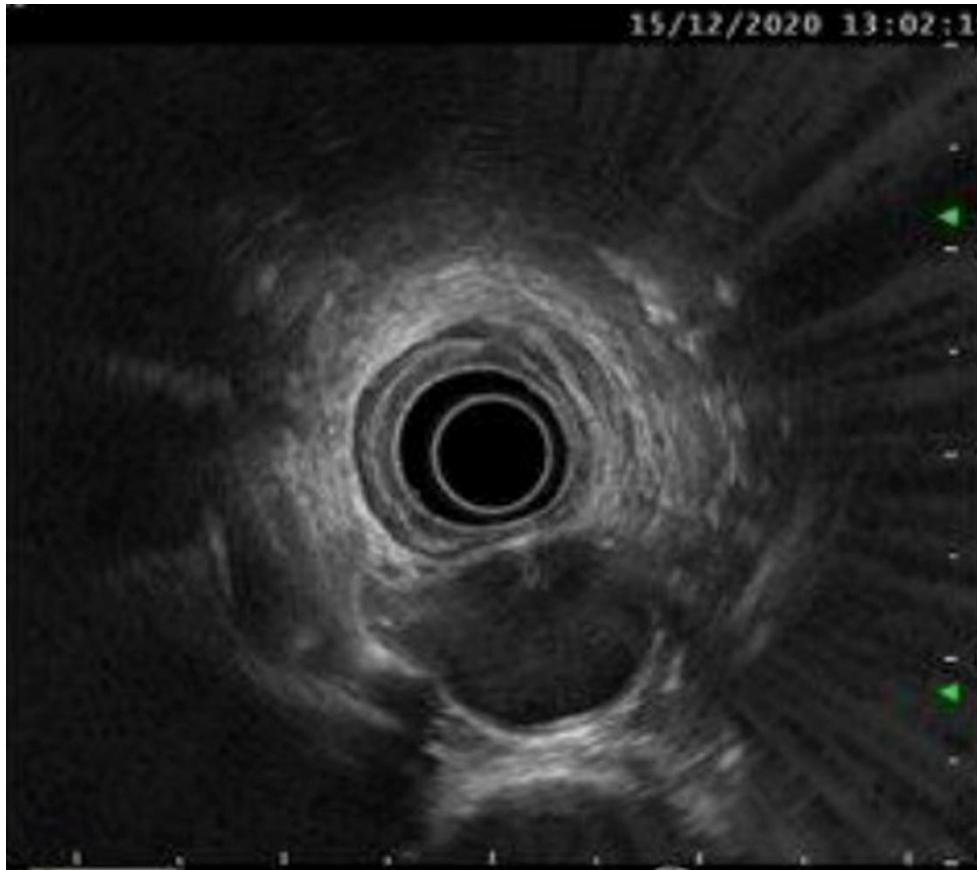


Figure 1: EUS shows focal thickening in the wall of oesophagus with breach in submucosa suggestive of T1 Lesion.



Figure 2: UGIE shows a mid-esophagus ulcer with raised margin located at 26 cm from incisors.

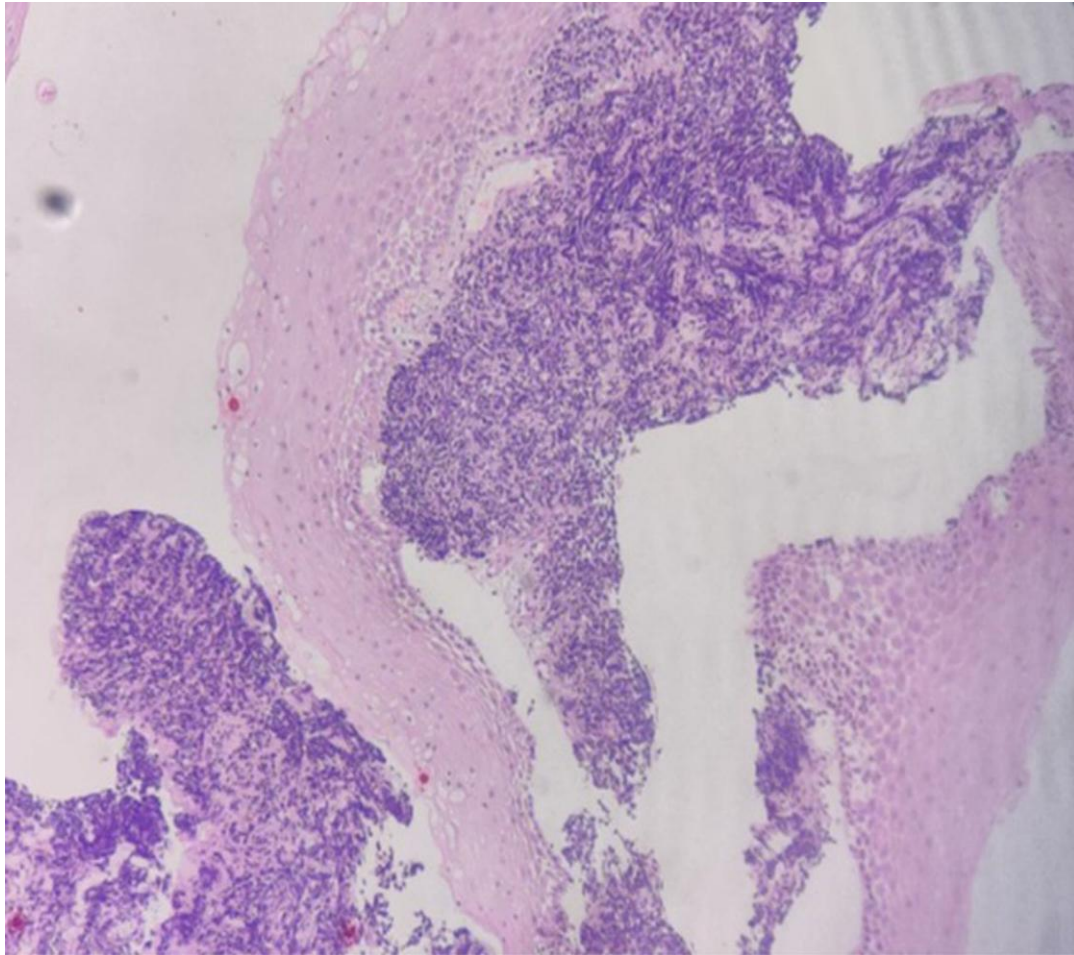


Figure 3: Esophageal Mucosa with ulceration and tumor cells expanding into the subepithelial tissue (H&E, x10).

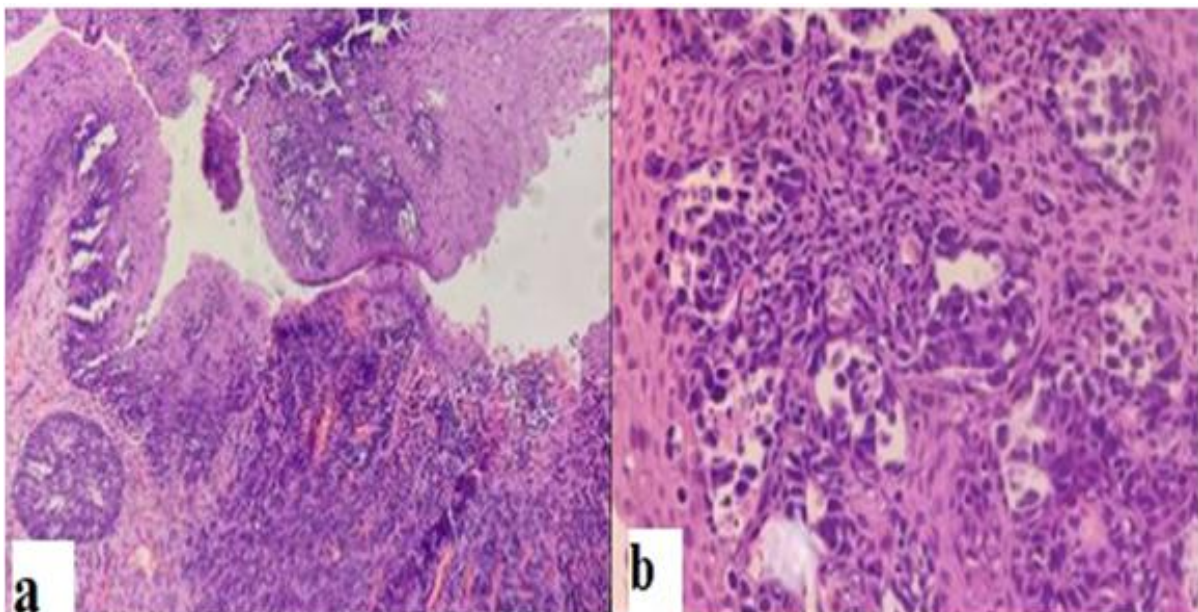


Figure 4: (a) Horizontally spreading tumor infiltrating the submucosal layer to a depth of $< 200 \mu\text{m}$ (H&E, x10) (b) Stratified squamous epithelium with diffuse areas showing marked nuclear atypia (Dysplastic Merkel cell) (H&E x40).

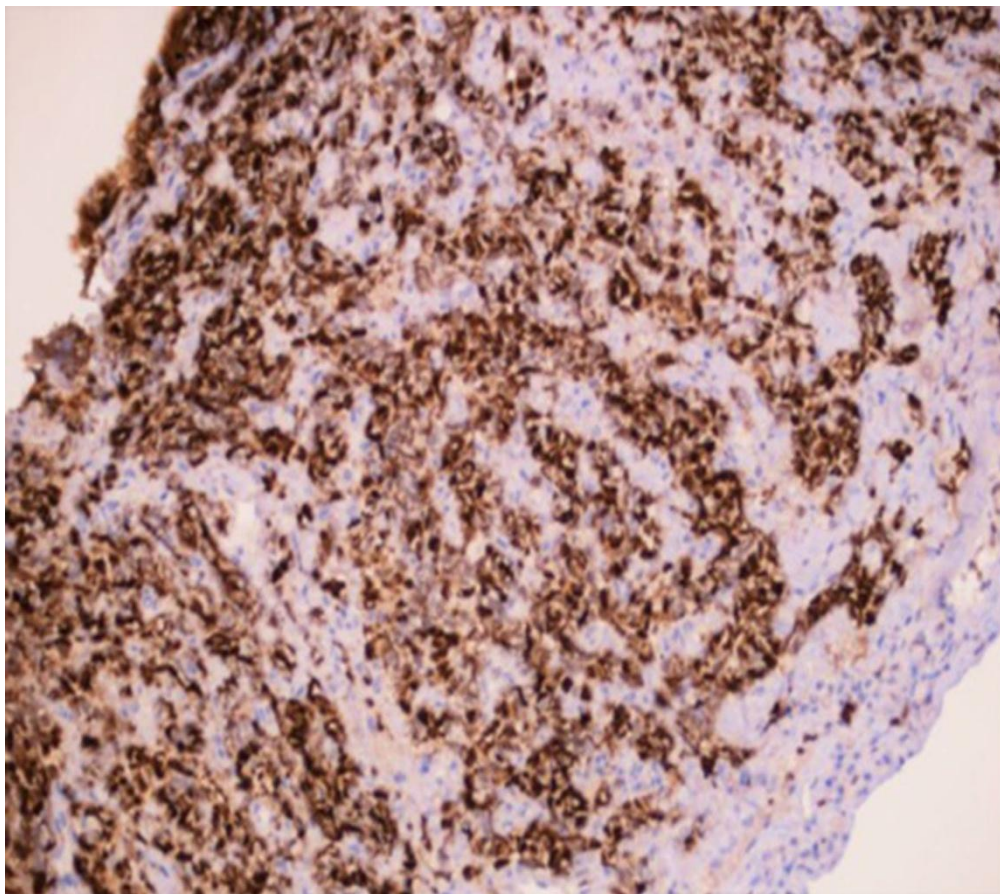


Figure 5: Ki-67 -70 % (x40)

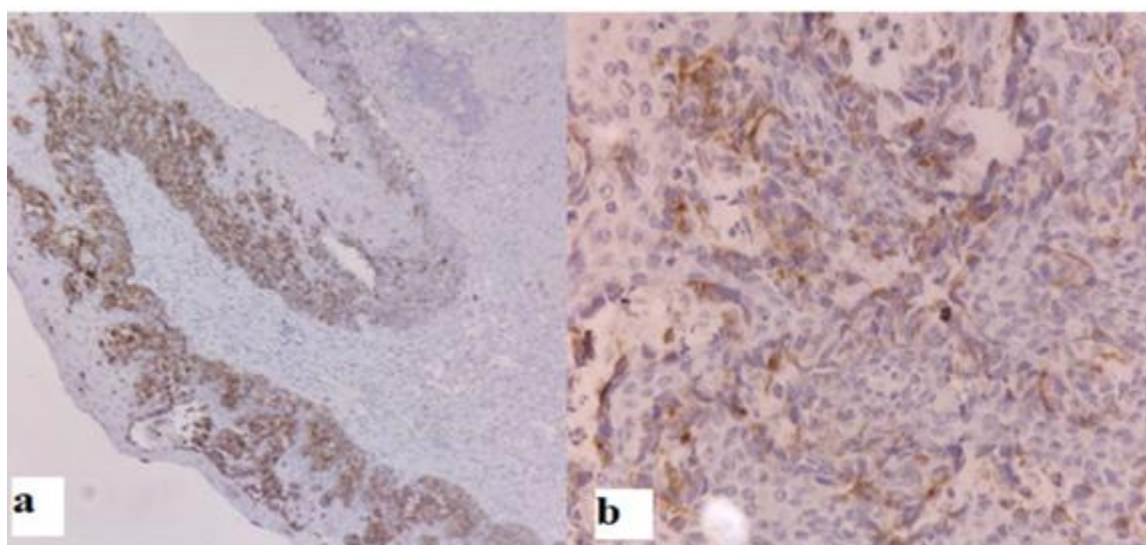


Figure 6: (a) CK20 highlights Merkel cells (x10)
(b) CK20 focal positive in tumor cells (x40).

Discussion

The first description of small cell carcinoma of the esophagus was reported in 1952 by McKeown.^[2] Neuro-endocrine neoplasms (NEN) often pose a diagnostic challenge on standard microscopic examination.

Esophageal NEC are commonly diagnosed in 7-8th decade, having a male predominance. They are usually diagnosed in advanced stage. Our patient had late onset dyspepsia as a presentation. Interestingly PET scan usually do not show uptake.

Most of esophageal NECs are in the middle or lower esophagus may be related to the presence of endocrine cells in the glands at esophageal cardia.

^[6] Classic macroscopic features of NEC include submucosal growth, with intact overlying epithelium, with or without central ulceration. The cell of origin of NEC of esophagus is unclear, however MC and Stem cells are considered likely origin. Markedly increasing gradient of MCs towards the middle of the esophagus suggests possibility of NECs arising from the Merkel cells, presence of MC in small cell neuroendocrine tumor has been reported in few prior studies. ^[7]

IHC profiling of the tumor is essential to differentiate small cell NECs from squamous cell carcinoma and adenocarcinoma. Also synchronous malignancy along with NEC of the esophagus have been reported. ^[8] Multipotent neoplastic stem cells are possible common precursors for SCC, NEC, Adenocarcinoma of esophagus. Also, esophageal NEC arising from Barrett's oesophagus has been reported. ^[9]

In the index case Negative immunostaining for p40 and cytokeratin 5/6, and CD45 markers, exclude the diagnosis of squamous cell carcinoma and lymphoma. Positive Immunostaining with synaptophysin and CD56 confirm neuroendocrine differentiation. Ki-67 was 70% suggesting neuroendocrine carcinoma (Grade3). The overlying dysplastic squamous epithelium was negative for p63, showed cytoplasmic positivity for CK20 and synaptophysin, and tumor nest positive for neuroendocrine markers. The IHC expression with CK20 by dysplastic squamous epithelium is a reliable marker for Merkel cell.

Paraneoplastic MG is a rare autoimmune disease affecting the neuromuscular junction and may be related to gastrointestinal NET's. It is immune response against the epitopes located on the tumor cells with cross reactivity against AchRs. It can complicate the patient's clinical course, response to treatment, impact prognosis and even be confused as metastatic spread. The main treatment is acetylcholinesterase inhibition by pyridostigmine.

The optimal treatment for esophageal SCNEC (small cell neuroendocrine carcinoma) is debatable. Few cases have been treated by esophago-gastrectomy. However, even following R0 resection there is high rate of disease recurrence with the median survival of 3-20 months. ^[8] Due to its rarity, limited experience is available in literature, along with lack of treatment algorithms for management of esophageal NEC.

TNM staging is an important independent prognostic factor for overall survival in esophageal NEC. Patients with early stage (I/II) have a longer survival than stage III. The best predictor for survival of NEC is Ki 67 index.

Conclusion

NEC esophagus with Merkel cell dysplasia is rare. Although small cell NECs can be distinguished from other epithelial tumors, in esophagus diagnosis is challenging due to its rarity and co-existence with other carcinomas. The immunohistochemical staining helps to confirm diagnosis.

Source(s) of support: Nil

Conflicting Interest (If present, give more details): There is no conflict of interest

Acknowledgment: Authors would like to thank technical and hospital staff for providing material for publication.

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