Squamous Differentiation in High Grade Large Cell Neuroendocrine Carcinoma of Ampulla of Vater

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Citation

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Abstract

Neuroendocrine tumors constitute a spectrum of lesions with varied morphology and clinical behavior. High grade neuroendocrine carcinoma includes both small cell and large cell neuroendocrine carcinoma (LCNEC). LCNEC in ampullary region is rare with only few cases reported in literature. Squamous differentiation in neuroendocrinal tumors is even rarer and has been reported in tumors arising from lung, salivary gland and only two ampullary neuroendocrinal tumors have been reported in literature showing areas of squamous differentiation, both of which were high grade in nature. Morphologically, one was small cell type and the other one was large cell neuroendocrine carcinoma. We report a rare case of High Grade Large Cell Neuroendocrine Carcinoma (LCNEC) arising from the ampulla of Vater with large areas of squamous differentiation. Squamous areas were easily identifiable on light microscopy with formation of keratin pearls and were confirmed by immunohistochemical expression of pan-cytokeratin. This tumor is distinctive because it showed an abrupt transition from large cell neuroendocrine differentiation to well differentiated squamous areas. The present case with bidirectional neuroendocrine and squamous differentiation favors the current hypothesis that neuroendocrine cells with APUD (Amine precursor uptake and decarboxylation) phenotype arise from endodermic stem cells instead of arising from neural crest. The significance of pure squamous differentiation in neuroendocrinal tumors is unknown, however, majority of these cases reported in literature are seen in association with poorly differentiated neuroendocrine carcinoma, having a grave prognosis.

INTRODUCTION

Most common ampullary tumor is adenocarcinoma, constituting more than 90% of ampullary malignancies. Neuroendocrine neoplasms are rare in this location. [1] High grade neuroendocrine carcinoma is even rarer and includes small cell and large cell neuroendocrine carcinoma. Large cell neuroendocrine carcinoma (LCNEC) is the recently described member of this family, originally reported in lung by Travis et al. [2] Since then, LCNEC has been described in many extrapulmonary sites including stomach, gall bladder, urinary bladder, uterine cervix, and kidney. [3,4,5,6,7] LCNEC is rare in ampullary region with only few cases reported in the literature. [8,9,10,11,12] It is an aggressive tumor type and shares with the small cell carcinoma its poor prognosis. Areas of squamous differentiation have been described in neuroendocrine tumors arising from salivary gland and lung. [13,14,15] Only two neuroendocrine tumors with squamous differentiation occurring in the ampullary region have been reported in literature and both were of high grade malignancy. [10,16] We report a rare case of LCNEC arising from ampulla of Vater with large areas of squamous differentiation.

CASE REPORT

A 60-year-old woman presented with recurrent epigastric pain for one year and vomiting off and on for 2 months. Epigastric pain was diffuse, progressive and non-radiating in nature. Vomiting was non-projectile, foul smelling and occurred after intake of food. Low grade fever was also present at the time of admission. There was no history of jaundice, constipation, diarrhea or itching. On examination, there was only mild hepatomegaly with no palpable mass. Six months earlier, when she was investigated for epigastric pain she was found to have raised serum amylase. However, CT abdomen done at that time did not reveal any mass lesion. A diagnosis of acute pancreatitis was then made.

Investigations done at the time of admission revealed raised levels of serum amylase (490-600 IU/L), abnormal liver function tests (Gamma-glutamyl transpeptidase 372 IU/L; Alkaline phosphatase 1309 IU/L) and total bilirubin 1.90 mg/dl. With a clinical diagnosis of obstructive jaundice, the patient underwent imaging studies. Abdominal ultrasound demonstrated enlarged liver, and mild increase in echogenicity of pancreas without evidence of stones. Side

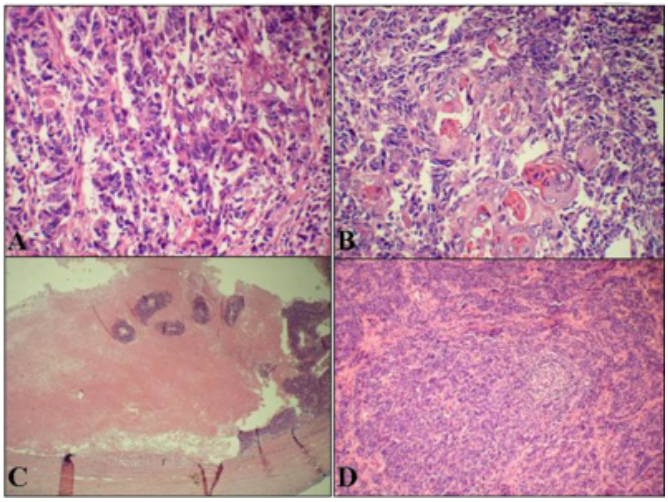
view endoscopy showed a large ulcer at the periampullary region. The patient underwent duodenopancreatectomy. Peroperative findings included a 2x2 cms ulcer in periampullary region with no significant lymphadenopathy; CBD was grossly dilated measuring 1.5 cms. There was no ascites and liver was grossly normal. The patient was discharged two weeks after operation with uneventful postoperative period.

The specimen was fixed in 10% neutral buffered formalin and paraffin embedded sections were prepared. Sections were processed for conventional histopathological examination as well as for Immunohistochemistry using a standard avidin-biotin-peroxidase complex technique. Primary antibodies used included pan-cytokeratin, NSE (neuron specific enolase), Synaptophysin and Chromogranin. Negative and positive controls were included for each batch of slides tested.

Grossly, a large ulcer was present in the ampullary region measuring 2x2 cms. The cut surface of tumor was fleshy and creamish white. It was grossly infiltrating full thickness of duodenal wall at site. Microscopically the tumor was highly cellular with large areas of necrosis and ulceration of the overlying mucosa. The neoplastic cells were composed of cohesive islands; at places arranged in organoid and trabecular pattern. The tumor cells were large and demonstrated a varied morphological appearance ranging from oval, polyhedral to spindle cells with moderate pleomorphism. They were large with moderate amount of eosinophilic cytoplasm, round to spindle nuclei with open chromatin and nucleoli. Prominent squamous differentiation with formation of keratin pearls was present amongst the tumor cells, showing a transition from one to the other. Mitoses were numerous (>15 mitotic figures per 10 high power fields). Tumor showed extensive infiltration into the wall of duodenum extending up to the serosa and adjacent soft tissues. One of the lymph nodes was largely replaced by the tumor (Figure 1A-1D). Pancreatic tissue and resected margins were free from tumor and unremarkable.

Figure 1

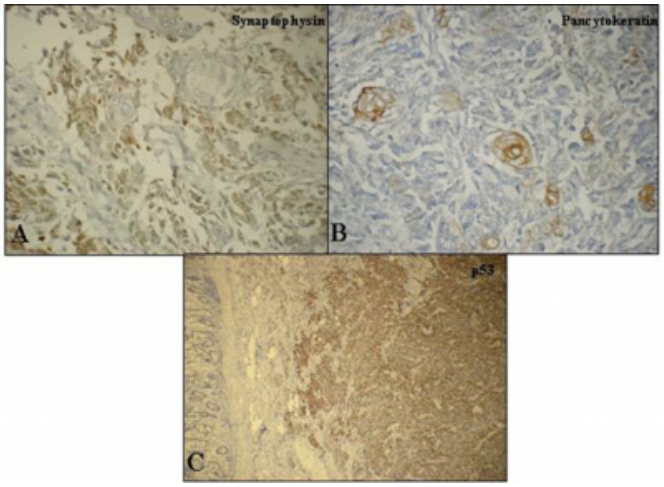
Figure 1: 1A Highly cellular tumor with polyhedral to spindle shaped cells with moderate pleomorphism and numerous mitoses (marked with arrows). 1B Areas of squamous differentiation scattered in between the tumor cells. 1C Large areas of necrosis were present within tumor. 1D Lymph node in vicinity of tumor is almost entirely replaced by tumor; a remnant lymphoid follicle can be seen near the centre.



Immunohistochemically, the tumor cells stained positive for NSE, Synaptophysin and Chromogranin. The areas with squamous differentiation were positive for pan-cytokeratin and negative for neuroendocrine markers (Figure 2A-2C). The tumor cells were strongly positive with p53 and cell proliferation marker Ki-67. Thus a diagnosis of large cell neuroendocrine carcinoma arising from the ampulla of Vater with squamous differentiation was made. The patient underwent a curative surgical resection, was alive and disease free at the time of writing (six months after the surgery).

Figure 2

Figure 2: 2A The neuroendocrinal tumor cells are positive for synaptophysin. 2B Squamoid areas stain positive with pancytokeratin. 2CThe tumor cells show overexpression of p53



DISCUSSION

Primary neuroendocrine tumors of the ampulla of Vater are rare with only a few more than 100 cases being reported in literature.[17] High grade neuroendocrine carcinoma in ampullary region is rare and may be of small and large cell type. The present case is a large cell neuroendocrine carcinoma. To the best of our knowledge LCNEC is extremely rare and has been documented in four case reports and one small series with 8 cases. [8,9,10,11,12] Squamous differentiation in ampullary LCNEC has been described in only one of the cases, making our case the second in literature of its kind. This case is morphologically consistent with the diagnostic criteria proposed by Travis et al [2] in 1991 report of an LCNEC of pulmonary origin.

Duodenal endocrine tumors have been classified recently by WHO (2000) as A) Well differentiated endocrine tumor (benign behavior) confined to mucosa and submucosa <=1 cm with no vascular invasion. B) Well differentiated endocrine tumor (uncertain behavior) confined to mucosa, submucosa, > 1 cm or vascular invasion. C) Well to moderately differentiated (Low grade malignant) invasion to muscularis propria or beyond or metastases. D) Poorly differentiated endocrine carcinoma (high grade malignant). The present case falls under the category D of WHO with features of high grade malignancy.

Morphologically, LCNEC is characterized by tumor cells arranged in classical organoid pattern, in trabeculae and rosettes. It also shows features of high grade malignancy with >10 mitoses per 10 high power fields and large areas of necrosis. The distinction between LCNEC and small cell carcinoma can be difficult and is based on cytologic details. In comparison with small cell carcinoma, the cells of LCNEC are larger, have a lower nuclear to cytoplasmic ratio, a more irregular chromatin pattern, and more frequent nucleoli. [18] In the present case the tumor cells were large, many having coarse chromatin and prominent nucleoli. Mitotic count was high with >15 mitoses per 10 hpf. The differential diagnosis of LCNEC in ampullary region is broad and includes well differentiated carcinoid, small cell neuroendocrine carcinoma, lymphoma, poorly differentiated carcinoma, sarcoma, and metastatic tumor. [1] The correct diagnosis can be done by identifying the characteristic morphology and confirming it by Immunohistochemistry as was done in the present case.

Gastroenteropancreatic neuroendocrine tumors are usually slow growing, however, survival of the patient depends on various factors including histological type, degree of differentiation, mitotic rate (Ki-67 or MIB-1 index), tumor size (> 3 cms), depth of invasion, location, presence of liver and lymph node metastases and age. [19] Although, the tumor size in present case was only 2 cms but because of its high grade the tumor infiltrated the entire wall thickness as well as the adjacent soft tissues. One of the lymph nodes also had tumor metastasis thus worsening the prognosis of patient.

In contrast to the earlier belief, gut and pancreatic neuroendocrine cells arise from endoderm, and not the neural crest, neuroectoderm or neuroendocrine programmed epiblast. [20] Neuroendocrine tumors have the capability to show multidirectional differentiation and this was stressed long ago in lung tumors. Evidence of both epithelial (non-neuroendocrine) differentiation in classical neuroendocrine tumors and of neuroendocrine differentiation in non-neuroendocrine tumors has been provided. [15]Divergent non-neuroendocrinal areas including both adenocarcinomatous and squamous have been demonstrated in neuroendocrine tumors at morphological, ultrastructural and immunohistochemical level. This present case with bidirectional neuroendocrine and squamous differentiation supports the new hypothesis that neuroendocrine cells that have acquired APUD (Amine precursor uptake and decarboxylation) phenotype arise from endodermic stem cells instead of being derived from neural crest. Several differentiation pathways are potentially available during clonal expansion of endodermic stem cells and thus explain the presence of large squamous areas in the present case.

The significance of pure squamous differentiation in neuroendocrinal tumors is unknown, however, majority of such cases reported in literature are seen in association with poorly differentiated neuroendocrine carcinoma, both small cell and large cell neuroendocrine carcinoma. Thus it can be proposed that neuroendocrine tumors that are associated with large areas of squamous differentiation tend to be poorly differentiated with a grave prognosis.

In summary, the present case of large cell neuroendocrine carcinoma with squamous differentiation, favors the current hypothesis that neuroendocrine cells arise from endodermic stem cells rather than neural crest. Neuroendocrine tumors with pure squamous differentiation tend to be more poorly differentiated with an aggressive behavior. More such cases should be reported and the comparison of pure neuroendocrine tumors with combined squamous-neuroendocrine tumors should be done to study the difference in clinical implications.

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