Original Article

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Pathology Section

Primary Small Cell Carcinoma of The Esophagus – An Eight Year Retrospective Study

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ABSTRACT

Introduction: Primary small cell carcinoma of the esophagus is a rare and aggressive tumor. Patients present with metastatic disease and have a poor clinical outcome. The objective of the study was to correlate clinical and histopathological features of primary small cell carcinoma of the esophagus diagnosed and treated at our hospital.

Materials and Methods: A retrospective study of 11 patients diagnosed with primary small cell carcinoma of the esophagus in Kasturba Hospital, Manipal between 2006 and 2014 was done. The histopathological and immunohistochemical features were correlated with clinical and endoscopic findings.

Results: Eleven patients were diagnosed to have small cell carcinoma of esophagus with a male preponderance. Common presenting symptoms were dysphagia and weight loss. Majority of the patients showed mid esophageal ulceroproliferative growth. Biopsy findings were consistent with the characteristic morphology of small cell carcinoma and demonstrated immunoreactivity to neuroendocrine markers. In addition, few cases also showed adjacent squamous dysplasia/carcinoma. Most of the patients presented with metastatic disease, liver being the most common site. These patients were treated by chemotherapy and radiotherapy.

Conclusion: Esophageal small cell carcinomas are aggressive tumors with high rates of distant metastasis. Presence of squamous dysplasia /squamous cell carcinoma in the adjacent mucosa supports the hypothesis that this neoplasm arise from pleuripotent stem cells. Presence of the latter is also useful to rule out spread from lung primary.

Keywords: Neuroendocrine markers, Pleuripotent stem cell, Squamous dysplasia

INTRODUCTION

Primary esophageal small cell carcinoma (SCC) is extremely rare accounting for 0.4 to 2.8% of all esophageal malignancies [1]. It is a highly aggressive malignancy and often present with widespread metastasis at diagnosis resulting in poor clinical outcome [2]. The histogenesis of esophageal SCC remains unclear. Possible cell of origin proposed are argyrophilic cells or pluripotent basal epithelial cells [3,4]. Treatment options include surgical resection, radiotherapy and chemotherapy, alone or in combination. However, the prognosis remains grim. In the present study, we retrospectively analysed the clinicopathologic features of all cases diagnosed as primary esophageal SCC over a period of eight years.

MATERIALS AND METHODS

A retrospective study was conducted in Kasturba Hospital, Manipal during an eight year study period between January 2006 and December 2014. The medical records of 11 patients with diagnosis of primary esophageal SCC were reviewed for their clinical presentation, history of smoking or any comorbid disease, gastrointestinal and respiratory endoscopic findings, radiological investigations, type of treatment and clinical outcome. The histopathology slides and their confirmatory immunohistochemistry were reviewed with special reference to presence of associated changes in adjacent mucosa. Primary nature of SCC was defined by the presence of definite esophageal growth by endoscopy, confirmed by histopathological examination of the same along with absence of pulmonary lesion on radiology or bronchoscopy. The data obtained was thus tabulated and studied.

RESULTS

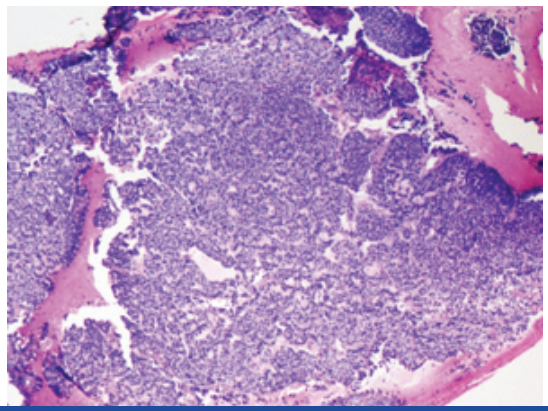
Between January 2006 and December 2014, 11 cases of primary small cell carcinoma of the esophagus were diagnosed on endoscopic biopsy specimens out of 935 patients with esophageal malignancies with incidence of 1.17%. The patient characteristics have been summarized in [Table/Fig-1]. The age range was between 40 and 76 years and included nine males and two females (male:female ratio-4.5:1). The most common presenting complaint was dysphagia. History of smoking was present in only one patient. Eight patients had ulceroproliferative growth detected in the esophagus on upper gastrointestinal endoscopy, predominantly affecting the mid esophagus (7 of 11 cases), followed by upper (3 cases) and lower (1 case) esophagus. One case also had multiple satellite nodules in the esophagus. Histopathological examination of these cases revealed small cell carcinoma with predominant nested pattern and irregular sheets [Table/Fig-2]. The neuroendocrine nature of tumour was confirmed by IHC markers like synaptophysin and/or chromogranin in nine of the eleven cases [Table/Fig-3]. Mucosa adjoining the tumour revealed squamous cell carcinoma, squamous cell carcinoma in situ and squamous dysplasia in three, one and two cases respectively [Table/Fig-4,5]. No glandular differentiation was noted. Eight patients had distant metastasis at presentation, with liver (6/11) being the common site; 3 with associated abdominal lymphnode involvement of whom one patient each also had pulmonary and bone metastasis. Abdominal lymphnodes involved included perigastric, para aortic, peripancreatic and periportal nodes. Six patients received chemotherapy, of which three also received radiotherapy. Five patients deferred treatment. Follow up data was available in two (cases 5 and 8) patients who were asymptomatic after one year. The esophageal, bone and pulmonary lesions in one of these patients (case 8) regressed following chemotherapy. Further follow up was not available.

DISCUSSION

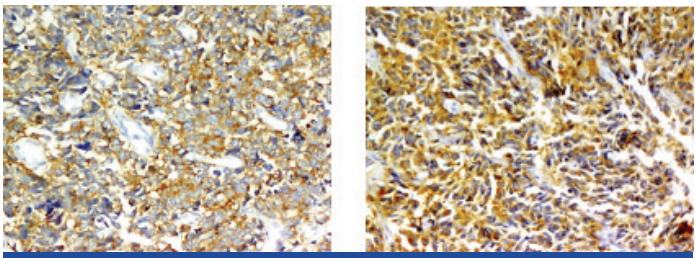
Small cell carcinoma is primarily described as a pulmonary malignancy accounting for 16% of all lung cancers [5]. Extrapulmonary sites of occurrence include nasal cavity and paranasal sinuses, gastrointestinal tract, salivary glands, uterus, prostate and urinary bladder [5-7]. Esophagus is reported as the most frequent digestive

Case	Age (years)	Sex	Symptoms	Endoscopy	Location in the esophagus	Secondaries	Immuno-histochemistry positivity	Associated lesion	Treatment	Follow up
1	60	M	Dysphagia + weight loss	Ulcero-proliferative growth	Mid third			Squamous cell carcinoma	-	-
2	50	M	Dysphagia	Ulcerated growth	Mid third	None	Synaptophysin	None	CT+RT	
3	76	F	Abdominal pain	Ulcero-proliferative growth	Mid third	Liver+ abdominal lymph Nodes		Squamous cell carcinoma in situ		
4	70	M	Vomiting	Ulcerated growth	Upper third	Liver	Synaptophysin, CK			
5	40	M	Dysphagia + weight loss	Ulceroproliferative growth	Mid third	Abdominal lymph Node	Synaptophysin		CT	Alive after 1 year
6	60	M	Dysphagia	Ulceroproliferative growth	Mid third		Synaptophysin	Squamous dysplasia		
7	58	M	Dysphagia	Ulceroproliferative growth	Upper third	Liver+ Bone	Chromgranin, Synaptophysin	Squamous dysplasia	CT+RT	
8	55	M	Dysphagia	Ulceroproliferative growth	Upper third	Paraesophageal lymph Node + Bone + lungs	Chromgranin, Synaptophysin	Squamous cell carcinoma	CT+RT	Alive after 1 year
9	68	M	Dysphagia + abdominal pain	Ulcer	Lower third	Liver +abdominal lymphnodes + lungs	Chromgranin, Synaptophysin		CT	
10	62	F	Dysphagia + abdominal pain	Ulceroproliferative growth	Mid third	Liver	Chromogranin, Synaptophysin		CT	
11	67	M	Abdominal pain	Ulceroproliferative growth	Mid third	Liver+bone+ abdominal lymph nodes	Synaptophysin			

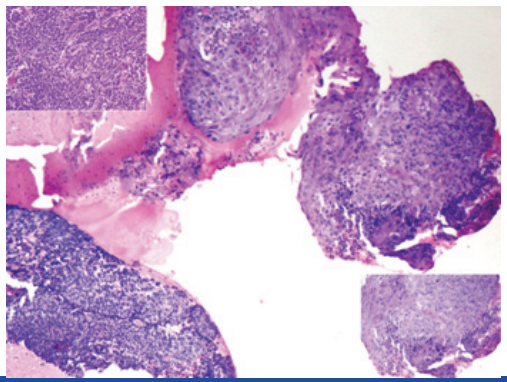
[Table/Fig-1]: Clinicopathological data on patients diagnosed with small cell carcinoma of the esophagus
M = male; F = female; CT = chemotherapy; RT = radiotherapy; CK = cytokeratin



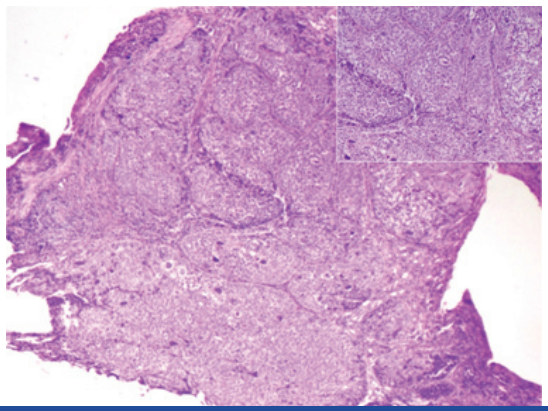
[Table/Fig-2]: Small cell carcinoma composed of uniform small round cells in irregular sheets and nested pattern (H&E X50)



[Table/Fig-3]: Esophageal SCC showing immunoreactivity for a) chromogranin and b) synaptophysin (X400)



[Table/Fig-4]: Esophageal SCC, adjacent mucosal squamous dysplasia (H&E X50) Inset: a) small cell carcinoma (top left) b) squamous dysplasia (bottom right) (H&E X200)



[Table/Fig-5]: Squamous cell carcinoma adjoining esophageal SCC (H&E X50) Inset (H&E X200)

tract site of extrapulmonary SCC with an incidence of less than 1.5% [6-8]. The incidence of esophageal SCC in our series was 1.17%.

Esophageal SCC usually affects individuals from sixth to eighth decade with male predominance [5-9] similar to the demographic profile in our study. Risk factors include smoking, alcohol consumption and Barrett esophagus [5,10]. In the present study, one patient was a chronic smoker. No other risk factors were observed.

Patients usually present with dysphagia, chest or abdominal pain, vomiting, weight loss and anorexia [5,6,10,11]. Associated paraneoplastic syndromes such as sensorimotor neuropathy and ectopic hormonal secretion have also been reported [10,12]. Eight of the 11 cases in the present study presented with dysphagia, two of them with associated abdominal pain. None had symptoms suggestive of paraneoplastic syndrome.

Endoscopically, esophageal SCC have been documented as ulcerated or ulceroproliferative lesions involving mainly middle and the lower third of the esophagus [5,6,10], with similar findings being noted in the present study. Histopathological examination of lesion biopsies revealed features similar to pulmonary SCC characterized by small round to spindle cells, scant cytoplasm, granular nuclear chromatin and inconspicuous nucleoli. The diagnosis is confirmed by demonstration of immunoreactivity to neuroendocrine markers (example: chromogranin, synaptophysin, CD56 and neuron specific

enolase). TTF-1 has also been shown to have high positivity in esophageal SCC [3,5,11]; hence is not useful to distinguish lung from esophageal origin. Recently, leucine-rich repeat containing G-protein coupled receptor 5 (Lgr 5) over expression have been reported to have significant correlation with tumour stage, response to therapy and prognosis [1].

Combined esophageal SCC and squamous cell carcinoma/ dysplasia or adenocarcinoma has been reported in literature [3-6,11]. In the study by Yun PJ et al., and Wu Z et al., 2/11 cases and 3/9 had associated squamous cell carcinoma [3,11]. A study at Tata Memorial hospital also reported three of 18 cases of combined small and squamous cell carcinoma [6]. Such co-existence of neoplasms with more than one cell type provides evidence to the common cell of origin. Amine precursor uptake and decarboxylation (APUD)/Kulchitsky cells present in the esophageal cardiac glands and pleuripotent esophageal basal reserve cells are proposed to be the cell of origin of esophageal SCC [3,4,6,11]. In our study, we had a relatively high occurrence of squamous neoplasm (6/11 cases) in the adjacent mucosa with three cases of squamous cell carcinoma, one case of carcinoma in situ and 2 cases of squamous dysplasia. Hence, our study supports the above hypothesis and also suggests that finding of such dual morphology could serve as a clue to the primary nature of the disease.

Patient characteristics such as clinical presentation and location of both esophageal small cell and squamous cell carcinoma are similar. Early dissemination, rapid growth, difference in treatment and poor prognosis emphasizes the importance of early and accurate diagnosis of SCC [3]. Majority of the patients of esophageal SCC have widespread metastasis at presentation, the most common site being liver. Other sites include lungs, peritoneum, thyroid, lymph nodes and bone [5,6,11]. Eight of the 11 patients in the present study had metastatic disease of which six involved the liver. Isolated liver involvement was seen in two patients while rest had associated lymph node, lung and bone involvement.

Treatment of esophageal SCC has been controversial, since most of these are detected at an advanced stage at presentation. Options include surgical resection, chemotherapy and radiotherapy. Like pulmonary SCC, esophageal SCC is also highly chemosensitive. Hence, systemic chemotherapy remains the mainstay of therapy. Chemotherapy with radiotherapy and surgical resection has shown to provide long term remission and increase survival rates among these patients [2,6,11,13,14]. Rare cases of complete response to chemo radiotherapy have also been reported [2]. Three of our patients received chemotherapy while three received additional radiotherapy. Inspite of aggressive treatment, the prognosis remains poor, the median overall survival ranging from 4.2 to 18.5 months [6].

CONCLUSION

Small cell carcinoma of the esophagus is a rare, aggressive and rapidly progressive disease with widespread metastasis at diagnosis. Possibility of metastasis from a lung primary needs to be ruled out. In such a scenario, the presence of squamous or glandular differentiation in the adjacent mucosa in addition to suggesting pleuripotent stem cell origin, also provides a histologic pointer to the tumor being a primary esophageal neoplasm.

REFERENCES

[1] Chen WW, Wang F, Zhang DS, Luo HY, Wang ZQ, Wang FH, et al. Primary small cell carcinoma of the esophagus: clinicopathological study of 44 cases. *BMC Cancer.* 2014;14:222. doi: 10.1186/1471-2407-14-222.

[2] Lv J, Liang J, Wang J, Wang L, He J, Xiao Z, et al. Primary small cell carcinoma of the esophagus. *J Thorac Oncol.* 2008;3(12):1460-65. doi: 10.1097/JTO.0b013e31818e1247.

[3] Wu Z, Ma JY, Yang JJ, Zhao YF, Zhang SF. Primary small cell carcinoma of esophagus: report of 9 cases and review of literature. *World J Gastroenterol.* 2004;10(24):3680-82.

[4] Briggs JC, Ibrahim NB. Oat cell carcinomas of the oesophagus: a clinico-pathological study of 23 cases. *Histopathology*. 1983;7(2):261-77.

[5] Nevárez A, Saftoiu A, Bhutani MS. Primary Small Cell Carcinoma of the Esophagus: Clinico- pathological Features and Therapeutic Options. *Curr Health Sci J*. 2011;37(1):31-34. Epub 2011 Mar 21.

[6] Pantvaidya GH, Pramesh CS, Deshpande MS, Jambhekar NA, Sharma S, Deshpande RK. Small cell carcinoma of the esophagus: the Tata Memorial Hospital experience. *Ann Thorac Surg*. 2002;74(6):1924-27.

[7] Madroszyk A, Egreteau J, Martin L, Queneau PE, Bosset JF, Merrouche Y. Small-cell carcinoma of the esophagus: report of three cases and review of the literature with emphasis on therapy. *Ann Oncol*. 2001;12(9):1321-25.

[8] Law SY, Fok M, Lam KY, Loke SL, Ma LT, Wong J. Small cell carcinoma of the esophagus. *Cancer*. 1994;73:2894–99.

[9] Casas F, Ferrer F, Farrús B, Casals J, Biete A. Primary small cell carcinoma of the esophagus: a review of the literature with emphasis on therapy and prognosis. *Cancer*. 1997;80(8):1366-72.

[10] Markogiannakis H, Theodorou D, Toutouzas KG, Larentzakis A, Pattas M, Bousiotou A, et al. Small cell carcinoma arising in Barrett's esophagus: a case report and review of the literature. *J Med Case Rep*. 2008;2:15. doi: 10.1186/1752-1947-2-15.

[11] Yun JP, Zhang MF, Hou JH, Tian QH, Fu J, Liang XM, et al. Primary small cell carcinoma of the esophagus: clinicopathological and immunohistochemical features of 21 cases. *BMC Cancer.* 2007;7:38.

[12] Shimoda T, Koizumi W, Tanabe S, Higuchi K, Sasaki T, Nakayama N, et al. Small-cell carcinoma of the esophagus associated with a paraneoplastic neurological syndrome: a case report documenting a complete response. *Jpn J Clin Oncol*. 2006;36(2):109-12.

[13] Eccles DM, Allan SG, Sang CT, Cornbleet MA. Small cell carcinoma of the oesophagus: report of three cases and review of published cases. *Thorax*. 1989;44(9):749-50.

[14] Medgyesy CD, Wolff RA, Putnam JB Jr, Ajani JA. Small cell carcinoma of the esophagus: the University of Texas M. D. Anderson Cancer Center experience and literature review. *Cancer*. 2000;88:262–67.

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