REVIEW

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Primary neuroendocrine neoplasm of the esophagus – Report of 14 cases from a single institute and review of the literature

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ABSTRACT – Background – Most prevalent esophageal neoplasm is squamous cell carcinoma and adenocarcinoma. Other tumors are uncommon and poorly studied. Primary neuroendocrine esophageal neoplasm is a rare carcinoma and most of its therapy management is based on lung neuroendocrine studies. Neuroendocrine tumors can be clustered in the following subtypes: high grade (small cell carcinoma or large cell carcinoma) and low grade (carcinoids). **Objective** – The present study aims to assess clinical and pathological neuroendocrine esophageal tumors in a single oncologic center. **Methods** – A retrospective analysis of patients and review of the literatures was performed. **Results** – Fourteen patients were identified as neuroendocrine tumors, 11 male and 3 female patients. Mean age was 67.3 years old. Ten patients were classified as small cell, 3 as large cell and 1 as carcinoid. Four patients presented squamous cell carcinoma simultaneously and 1 also presented adenocarcinoma. Main sites of metastasis were liver, peritoneum, lung and bones. Most patients died before 2 years of follow-up. Patient with longer survival died at 35 months after diagnosis. **Conclusion** – Neuroendocrine esophageal tumors are rare; affect mainly men in their sixties or seventies. High grade tumors can be mixed to other subtypes neoplasms, such as adenocarcinoma and squamous cell carcinoma. Most of these patients have poor overall survival rates.

HEADINGS – Esophageal neoplasms. Carcinoid tumor. Neuroendocrine carcinoma.

INTRODUCTION

Esophageal cancer is a rapidly progressive disease with poor survival rates. Most of these tumors are either adenocarcinoma or squamous cell carcinoma histologic types. Less frequent cancer subtypes, such as melanoma, lymphomas or neuroendocrine tumors are uncommon and poorly explored[34].

Neuroendocrine esophageal neoplasms are rare and most of studies are case reports. The classification and nomenclature are not well established and knowledge acquired in neuroendocrine neoplasms of lungs and certain gastrointestinal sites, such as pancreas, usually guide esophageal neuroendocrine management.

Neuroendocrine neoplasm subtypes are grouped based upon shared neuroendocrine features. The subtypes comprise small cell carcinoma, large cell neuroendocrine carcinoma, typical carcinoid, and atypical carcinoid[140].

This article is a descriptive report of clinical and pathological features of cases of neuroendocrine esophageal tumors in our institute, along 8 years of experience, and a review of the literature.

METHODS

All esophageal cancer patients' charts of our institution were reviewed, between 2008 and 2016. Cases of neuroendocrine neoplasm were identified and clinical and pathological features of these patients were assessed.

For review of the literature, database search was performed in MEDLINE, with search algorithm: ("neuroendocrine" [All Fields] OR "carcinoid tumor" [MeSH Terms] OR "carcinoid" [All Fields] OR "small cell carcinoma" [MeSH Terms] OR "large cell carcinoma") AND ("oesophagus" [All Fields] OR "esophagus" [All Fields] OR esophageal [All Fields]). Period searched up to 2016, with no idiom restriction. Review studies and no full-text studies were excluded. When more than one publication of a single trial existed, only the publication with the most complete data was included.

RESULTS

A total of 1,574 of esophageal cancers were reviewed. Fourteen (0.89%) cases of neuroendocrine neoplasm were selected, 3 female and 11 male patients (Table 1). Mean age was 67.3 (range 47 to 80) years old. Table 2 shows immunohistochemical panel of neuroendocrine neoplasm.

Three were classified as large cell esophageal carcinoma (LCEC), 10 as small cell carcinoma (SCEC), and 1 as carcinoid. Distal and middle esophagus were more often affected.

Endoscopic appearance was usually a vegetating and infiltrative tumor, except carcinoid subtype. (Figure 1).

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TABLE 1. Main characteristics of the 14 patients diagnosed with neuroendocrine tumor

Patient	Age	Sex	KPS	ECOG	Stage	Histologic subtype	Associated neoplasm	Site	Survival (months)	Esophagectomy	Chemotherapy	Radiotherapy
1	79	M	50	4	Unstaged	SCCE	No	Lower	2	No	No	No
2	65	M	90	1	IIIA	SCCE	No	Middle	Alive at 26 months	Yes	No	No
3	60	M	80	1	IIIB	LCCE	No	Middle and lower	13	No	IP	30 cGy
4	65	M	30	4	IA	Carcinoid	No	Lower	7	No	No	No
5	75	F	90	1	IIA	LCCE	No	Lower	13	Yes	IP, PC	45 cGy
6	51	M	100	0	IIIC	SCCE	No	Upper and middle	Lost to follow-up at 4 months	No	EP	No
7	58	M	80	2	IV	SCCE	SCC	Middle	2	No	No	No
8	64	M	100	0	IIIA	SCCE	SCC	Middle and lower	35	Yes	IP, PT	45 cGy
9	47	M	100	0	IV	SCCE	No	Lower	10	No	IP, PT	50.4 cGy
10	78	F	70	1	IV	SCCE	SCC	Lower	13	No	IP, PT	45 cGy
11	75	M	80	1	IIIC	SCCE	No	Upper and middle	12	No	IP	45 cGy
12	80	F	50	3	IV	SCCE	SCC	Middle	6	No	No	No
13	76	M	60	3	IV	SCCE	No	Middle	5	No	IP	No
14	69	M	90	1	IIIB	LCCE	EA	Lower	18	Yes	XP (neoadjuvant), IP	No

SCEC: small cell esophageal cancer; LCEC: large cell esophageal cancer; KPS: Karnofsky Performance Status; ECOG: Eastern Coorporative Oncology Group; SCC: squamous cell carcinoma; EA: esophageal adenocarcinoma; PC: Paclitaxel and Carboplatin; PT: Cisplatin and Paclitaxel; IP: Irinotecan and Cisplatin; EP: Etoposide and Cisplatin; XP: Capecitabine and Cisplatin.

TABLE 2. Immunohistochemical panel of patients with esophageal neuroendocrine neoplasm

Patient	Grade of cellular differentiation	Syp	CgA	Ki-67(%)	Ber-EP4	Ck7	AE-1/AE-3	35BH11	P63	CD 56	TTF-1	Vimentin
1	Poorly	+	NP	>90	NP	NP	NP	NP	NP	+	NP	NP
2	Poorly	NP	-	80-90	NP	NP	NP	+	-	+	+	NP
3	Poorly	NP	+	90	+	NP	-	NP	-	NP	NP	NP
4	Well	+	+	<1	NP	NP	NP	NP	NP	NP	NP	NP
5	Poorly	+	+	>90	NP	+	NP	NP	-	NP	NP	NP
6	Poorly	+	+	90	NP	NP	NP	NP	NP	NP	+	NP
7	Poorly	+	+	NP	+	NP	NP	NP	+	NP	NP	NP
8	Poorly	-	+	50	NP	+	+	NP	+	+	+	+
9	Poorly	+	+	80-90	NP	NP	NP	+	-	+e	NP	NP
10	Poorly	+	+	NP	NP	-	+	+	-	+	+	NP
11	Poorly	NP	-	NP	-	NP	+	+	-	+	NP	NP
12	Poorly	+	+	90	NP	NP	+	NP	+	+	NP	NP
13	Poorly	NP	NP	NP	NP	NP	+	+	+	+	+	+
14	Poorly	+	+	70	-	+	NP	NP	-	NP	NP	NP

(+): positive; (-): negative; Syp: Synaptophysin; CgA: Chromogranine A; Ck: Cytokeratin; NP: not performed.

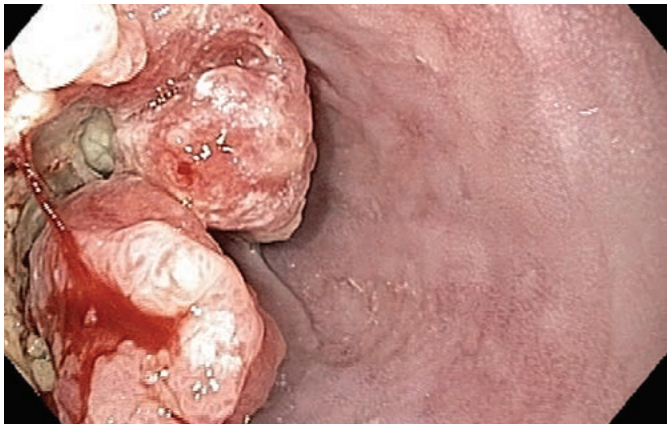

FIGURE 1. Endoscopic view of a high grade neuroendocrine neoplasm. It shows a circumferential infiltrative and ulcerating tumor.

Main symptoms were dysphagia (14/14) and weight loss (mean 11.7 ± Std Dev 6.3 kg). Duration of symptoms prior to diagnosis was 6.2 ± Std Dev 3.3 months.

Associated squamous cell carcinoma could be seen in 4/14 cases and associated adenocarcinoma (adenoneuroendocrine) in 1/14. Immunohistochemical panel can be seen in Table 2.

Of these patients, 10/14 had previous history of high amount of alcohol intake and 12/14 were tobacco smokers.

Most cases were diagnosed at late stages (III and IV), accordingly AJCC 7th Edition[122]. Metastasis sites were lungs, liver, adrenal, peritoneal and bones.

Cause of death was pneumonia in five cases, urinary tract infection in one case, and sepsis of unknown origin in one case. The five remaining patients, cause of death was not clearly established.

Curative intent surgery was performed in 4/14 patients, of which one is still alive at 26 months of follow-up.

Most cases had low survival rates (see Figure 2). Patient who lived longer died at 35 months of pneumonia. Patient "2" is still alive without disease up to this paper publication. Patients "6" lost to follow-up, with disease. The remaining patients died with disease.

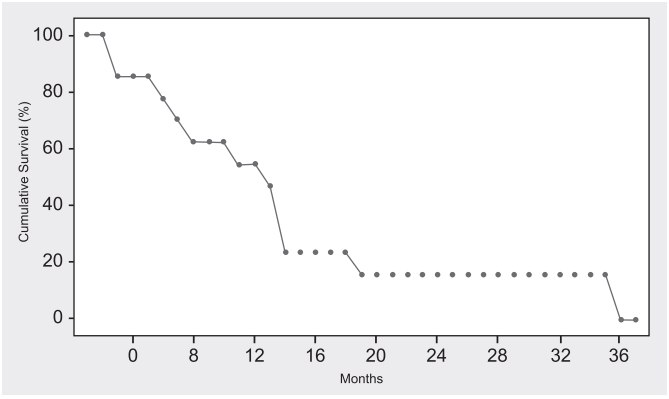

FIGURE 2. Kaplan-Meir curve for survival of patients with esophageal neuroendocrine neoplasm

Patient diagnosed with carcinoid tumor presented myelofibrosis during follow-up, leading to pancytopenia and early death.

Review of the literature

For review of the literature, a total number of articles by database search were 1007. After excluding duplicates and screening by title and abstract, 154 articles remained[1-33, 35-79, 81-115, 117-119, 121, 123-139, 141-162].

A cumulative sample size of 2,957 patients was evaluated, in 20 different countries. Of this patients, 2,899 were SCEC (77% in East countries; 23% in West countries); 35 were LCEC (6% in East countries; 94% in West countries); and 23 were carcinoid (54% in East countries; 43% in West countries).

Among all esophageal malignances, prevalence of SCEC was 1.05% in East countries and 0.72% in West countries. There are few studies data concerning carcinoid tumors and LCEC prevalence. Most of the studies approaching LCEC were performed in West countries.

Neoplasms were staged as limited disease (LD) or extend disease (ED). LD is defined as disease confined to the esophagus and adjacent organs with or without regional lymph node involvement while ED is defined for neoplasm with distant spread[59]. Main features and differences concerning neuroendocrine subtypes are presented in Table 3.

DISCUSSION

Neuroendocrine esophageal neoplasms are exceedingly rare, and hence there are few large sample clinical studies approaching this issue. Consequently, most of the knowledge is based on neuroendocrine lung neoplasms.

Neuroendocrine lung tumors are classified as low grade (carcinoids) or as high grade (SCEC and LCEC)[120].

SCEC have nuclear appearance, with finely granular chromatin; lack of predominant nucleoli; nuclear fragility; fusiform cells; scant cytoplasm and indistinct cells borders; high mitotic rate; and large area of necrosis[120]. (Figure 3).

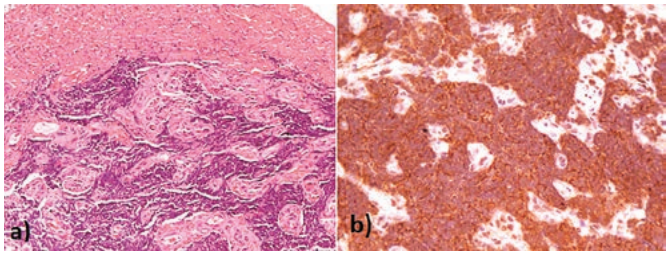

FIGURE 3. Small cell esophageal carcinoma (SCEC). High power view of infiltrative proliferation of round small cells with scanty cytoplasm and dark nuclei with intense crush artifacts lined by ulcerative epithelium (a) (HE, 200x). CD56 positive (b) (400x).

TABLE 3. Main features and differences concerning neuroendocrine subtypes

		SCEC	%	LCEC	%	Carcinoid	%
Prevalence	East countries	1,527 (145,717)	1.048	Unknown	-	Unknown	-
	West countries	533 (73,290)	0.727	5 (1,105)	0.452	Unknown	-
Age	Mean	63.8	-	62.1	-	58.3	-
	< 60 yr	542	48.26	0	0	12	57.1
	≥ 60 yr	581	51.74	4	100	9	42.9
Sex	M	1,517	69.5	32	88.9	14	70
	F	666	30.5	4	11.1	6	30
Mixed	SCC	82 (786)	10.4	2 (36)	5.6	0 (13)	0
	Adenocarcinoma	31 (786)	4	14 (36)	38.9	0 (13)	0
Tumor site	Upper	202	12.4	1	10	1	7.7
	Middle	904	55.5	5	50	2	15,4
	Lower/GEJ	523	32.1	4	40	10	76.9
Stage	LD	1,519	70.2	16	55.2	13	100
	ED	645	29.8	13	44.8	0	0
Tumor size	< 5 cm	423	42.2	2	66	9	64.3
	≥ 5 cm	580	578	1	33	5	35.7
OS	1 yr	803 (1,744)	46	1 (2)	50	9 (10)	90
	2 yr	275 (1,250)	22	0 (1)	0	6 (7)	86
	3 yr	234 (1,693)	13.8	0 (1)	0	6 (7)	86
	5 yr	144 (1,853)	7.7	0 (1)	0	6 (7)	86

OS: overall survival; GEJ: gastroesophageal junction; SCEC: small cell esophageal cancer; LCEC: large cell esophageal cancer.

LCEC presents non-small cell nuclear features (vesicular clumpy chromatin, predominant nucleoli), abundant cytoplasm, and large cell size[120]. (Figure 4).

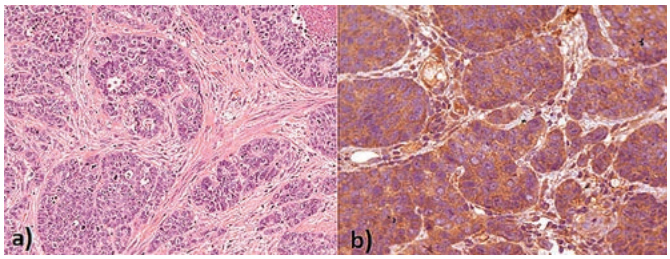

FIGURE 4. Large cell esophageal carcinoma (LCEC). Solid nests of large and intermediate cells, with eosinophilic cytoplasm, vesicular nuclei and prominent nucleoli, focal necrosis and high mitotic rate (a) (HE, 200x). Chromogranin positive (400x) (b).

Carcinoids typical morphology includes coarsely granular "salt and pepper" chromatin, overall uniformity, prominent vascularity, lack of prominent nucleoli, low mitosis rate. Usually no necrosis is seen[120].

Esophageal high grade tumors tend to be aggressive. Usually, patients are diagnosed lately, with widespread disease, and with poor prognosis. Currently, clinical treatment strategies of high grade cancers neuroendocrine neoplasms are very limited and full of contradiction. High grade neoplasms are often regarded as a systemic disease and, just like in lung cancer, chemotherapy is the mainstay of therapy[17]. Additional therapy (surgery or radiotherapy) should be considered, but randomized controlled trials still unavailable[80, 116].

Our data suggests a much good prognosis for low grade neuroendocrine tumors, with high overall survival rate. For limited disease (LD) carcinoid, surgical intervention is the treatment of choice[18].

Although low incidence of esophageal neuroendocrine tumors, our results give a better picture of the behavior of this rare condition. The present study shows this disease affects mainly men in sixties or seventies. Middle and lower esophageal thirds are most frequently affected. Nevertheless, future multicenter efforts are needed for randomized clinical trials evaluating therapeutic guidelines.

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Authors' contributions

Tustumi F: study elaboration and data collect. Takeda FR: study elaboration. Uema RH: data collect. Pereira GLS: oncologic review. Sallum RAA: orientation of the study. Cecconello I: orientation of the study.

Tustumi F, Takeda FR, Uema RH, Pereira GLS, Sallum RAA, Cecconello I. Neoplasia neuroendócrina primária de esôfago – Relato de 14 casos e revisão de literatura. Arq Gastroenterol. 2017,54(1):4-10.

RESUMO – Contexto – As neoplasias esofágicas mais prevalentes são o adenocarcinoma e o carcinoma espinocelular. Outros subtipos histológicos são incomuns e pouco estudados. Neoplasia neuroendócrina esofágica é uma patologia rara e seu manejo atualmente se baseia nos conhecimentos prévios de tumores neuroendócrinos de pulmão. Tumores neuroendócrinos podem ser divididos nas seguintes formas: alto grau (pequenas células ou grandes célula) e baixo grau (carcinoides). **Objetivo** – Avaliar clínica e patologicamente os tumores de esôfago em um centro oncológico referenciado. **Métodos –** Foi realizada análise retrospectiva e revisão da literatura de neoplasias neuroendócrinas de esôfago. **Resultados –** Foram identificados 14 pacientes com tumores neuroendócrino, sendo 11 homens, 3 mulheres. Idade média foi de 67,3 anos de idade. Desses pacientes, 10 foram classificados como pequenas células, 3 como grandes células e 1 como carcinoide. Foram encontrados quatro casos de tumor misto neuroendócrino e carcinoma espinocelular, e um caso de tumor misto adenoneuroendócrino. Principal sítio de metástases foi fígado, peritônio, pulmão e ossos. A maioria dos pacientes foi a óbito em até 2 anos de seguimento. Paciente com sobrevida mais longa foi a óbito após 35 meses do diagnóstico. **Conclusão** – Neoplasias neuroendócrinas de esôfago são raras, afetam principalmente o sexo masculino na 7ª ou 8ª década de vida. A maioria dos pacientes com tumores de alto grau tem sobrevida curta.

DESCRITORES – Neoplasias esofágicas. Tumor carcinoide. Carcinoma neuroendócrino.

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