Basaloid squamous carcinoma of esophagus: a clinicopathological, immunohistochemical and electron microscopic study of sixteen cases

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Subject headings esophageal neoplasms/pathology; esophageal neoplasms/ultrastructure; carcinoma, squamous cell/pathology; carcinoma, squamous cell/ultrastructure

Abstract

AIM To further clarify the clinicopathological, immunohistochemical and electron microscopic features, and prognostic aspect of basaloid squamous carcinoma (BSC), a rare esophageal carcinoma.

METHODS We reviewed 763 documented cases of esophageal malignancies (1977-1996) from our hospital, and discovered 16 (2.1%) cases of BSC. The clinicopathological features of these cases were evaluated. Immunohistochemistry (S-P method), histochemical stains, and electron microscopy were used to further characterize the neoplasm.

RESULTS The tumors were classified into stages I (n = 1), IIA (n = 6), IIB (n = 2), III (n = 5), and IV (n = 2) according to the criteria of the UICC TNM classification system of malignant tumors (1987). Most neoplasms were located in the mid third of the esophagus. Grossly, they had a similar appearance of conventional esophageal carcinoma, but showed a typical cytoarchitectural pattern of BSC histologically. The most important histologic feature of this tumor is carcinoma with a basaloid pattern, intimately associated with squamous cell carcinoma, dysplasia, or focal squamous differentiation. The basaloid cells were round to oval in shape with scant cytoplasm, arranged mainly in the form of solid, smooth-contoured lobules with peripheral palisading. A panel of immunostains were used for the basaloid component of the tumor with the following results: CK (Pan) 14/16 (+); EMA 16/16 (+); Vimentin 4/16 (+); S-100 protein 7/16 (+). CEA and smooth muscle actin were negative. Electron microscopy (EM) revealed that the basaloid cells were poorly differentiated, with a few desmosomes and fibrils, and numerous free and polyribosome. Of the 11 patients with adequate follow-up 8 died within 2 years, with an average survival time of 16.2 months. No stage II, III or IV cases survived beyond 5 years. The one-year survival rate was 60% and two-year 20%.

CONCLUSION The BSC of esophagus is a distinct clinicopathological entity with poor prognosis. The cellular differentiation and biologic behavior of esophageal BSC were assumed to occupy a station intermediate between that of conventional squamous cell carcinoma and small undifferentiated cell carcinoma.

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INTRODUCTION

The term basaloid squamous carcinoma (BSC) was first proposed by Wain *et al* in 1986 to describe a rare, aggressive neoplasm with a predilection occuring in the hypopharynx, base of tongue, larynx[1], and late in the esophagus[2], nasal and oral cavity[3,4], tonsil[5], nasopharynx[6], trachea, bronchus and lung[7-9], and other sites including external ear[10], anal canal, vulva and penile[11-13]. It is characterized by basaloid carcinoma intimately associated with squamous cell carcinoma, dysplasia, carcinoma *in situ*, or focal squamous differentiation. Approximatelly 400 cases of BSC have been reported in the world literature by the end of 1996, including 69 cases of BSC of esophagus. In a recent review of esophageal neoplasms at the Department of Pathology of our hospital, sixteen such tumors were identified. In this paper, we report about the clinicopathological and immunohistochemical features of these 16 cases of BSC of esophagus to further categorize this lesion. Electron microscopic features of seven cases, and their prognosis were also described.

MATERIAL AND METHODS

All resected esophageal tumor slices examined over the last 20 years (1977-1996) at the Department of

Pathology of our hospital were reviewed. Of 763 cases of esophageal malignancies, 16 showed the histopathologic pattern of basaloid squamous carcinoma[1]. Clinical data, including age and sex, location and size, and gross appearance were obtained from the medical records. Follow-up information was available in 11 cases. All surgical specimens were fixed in 10% formalin and processed in the usual way for paraffin embedding. In addition to routine hematoxylin and eosin -(H&E) staining, periodic acid-Schiff (PAS) with or without diastase, and Alcian blue (pH 2.5) staining was performed.

Seven cases was also reviewed electron microscopically. Immunohistochemistry was performed on paraffin sections of representative portions of the tumors using the streptavidin peroxidase method (S-P method)[14]. The S-P Kit was obtained from Zymed Laboratories Inc, USA. The prediluted antibodies against cytokeratin (Pan) (CK), carcinoembryonic antigen (CEA), epithelial membrane antigen (EMA), vimentin, smooth muscle specific actin (SMA), and S-100 protein were products of Maxim Biotech, Inc, USA. The results of immunohistochemical stains were recorded as negative (-), weakly positive (less than 10% positive cells), positive (10% - 15% positive cells) and strongly positive (more than 50% positive cells).

RESULTS

Demographic and clinical data

The clinicopathologic, TNM staging, therapeutic, and follow-up data are summariszed in Table 1. The patients ranged in age from 42 to 72, with a mean age of 58 years (median 57 years). There were 9 males and 7 females, all were Chinese. The patients presented with progressive dysphagia. The duration of symptoms ranged from 1 to 8 months. All cases were treated with either curative or palliative esophagectomy. Eleven patients were further treated by chemotherapy. Eleven of the 16 esophageal tumors were located at the middle third of the esophagus, 4 at the lower third, and 1 at the upper third. Their size ranged from 1.3 cm to 7.0 cm in greatest diameter. The gross appearance of the tumors in this series were infiltrative lesions in 4 cases, protuberant lesion in 6, ulcerative lesion in 5, and a polypoid mass in 1. The staging of the lesions followed the criteria of the UICC TNM classification system of malignant tumors, 1987[15]. The tumors were then classified as stage I (n = 1), stage II A (n = 6), stage II B (n = 2), stage III (n = 5), and stage IV (n = 2).

Table 1 Clinicopathological, Staging, Therapeutic and Follow-up Data in 16 Patients with Esophageal BSC

Case No.	Age/ sex	Tumor location	Tumor size (cm)	Gross appearance	Stage	Therapy		Mitoses (per 10HPF)	Follow-up
						Surgery	Chemo-therapy		
1	42/F	Lower 1/3	2.5×1.5×0.6	Polypoid	IIA(T2N0M0)	Curative esophagectomy		198	Not available
2	56/M	Middle 1/3	2.5×2.0×0.8	Protuberant	IIA(T3N0M0)	Curative esophagectomy		51	Not available
3	50/F	Lower 1/3	4.0×2.0×1.0	Ulcerative	III(T3N1M0)	Curative esophagectomy		74	Not available
4	62/M	Middle1/3	3.5×1.5	Protuberant	IIA(T2N0M0)	Curative esophagectomy	+	86	Died of tumor recurrence at 18 mos
5	56/M	Lower 1/3	4.3×2.8×1.8	Protuberant	I (T1N0M0)	Curative esophagectomy	+	60	Alive & well at 10
6	62/M	Upper 1/3	2.8×1.0×0.7	Ulcerative	III(T3N1M0)	Curative esophagectomy	+	45	Died of tumor, recurrence 14mo after operation
7	54/M	Middle 1/3	4.0×2.8	Infiltrative	IV(T2N0M1)	Palliative eso phagectomy	+	47	Metastases to lung and pleura, died 12mos after operation
8	60/F	Middle 1/3	2.5 (in diameter)	Infiltrative	III(T3N1M0)	Curative esophagectomy	+	98	Died of metastases and recurrence 8mo later
9	72/M	Middle 1/3	5.5×2.0	Ulcerative	IIA(T3N0M0)	Curative esophagectomy		136	Not available
10	62/F	Middle 1/3	3.5×2.0×3.0	Protuberant	IIA(T2N0M0)	Curative esophagectomy		49	Not available
11	49/M	Middle 1/3	3.5×3.0	Ulcerative	IV(T4N1M1)	Paliative esophagectomy	+	54	Metastases to lung and brain, Died 9mo after operation
12	70/M	Lower 1/3	5.0×2.0×1.5	Infiltrative	III(T3N1M0)	Curative esophagectomy	+	82	Died of tumor, recurrence 4 years after operation
13	67/M	Middle 1/3	5.0×4.8×2.0	Infiltrative	IIA(T3N0M0)	Curative esophagectomy	+	104	Died 16mo after operation
14	57/F	Middle 1/3 (with two lesions)	2.0×1.5 1.3(in diameter)	Ulcerative	IIB(T1N1M0)	Curative esophagectomy	+	60	Died 3mo after diagnosis
15	57/F	Middle 1/3	7.0×5.0×3.0	Protuberant	III(T4N1M0)	Palliative esophagectomy	+	85	Died 8mo after operation
16	52/F	Middle 1/3	4.0×2.5	Protuberant	II B(T2N1M0)	Curative esophagectomy	+	105	Alive 4mo after operation

The criteria of the UICC TNM classification system (1987) was used.

Follow-up information was obtained from 11 cases. Nine patients died 3 to 48 months after operation. The average survival of these nine patients was 16.2 months. One patient is alive disease free at 10 years, and another patient is still on chemotherapy 4 months after operation. The survival rate was 60% at 12 months, and 20% at 24 months.

Histopathologic findings

All 16 neoplasms fulfilled the basic histological features of BSC[1]. The basaloid cells arranged mainly in the form of solid, smooth-contoured lobules, some cases also in the form of solid sheets, anastomosing trabeculae, or microcystic structures (Figure 1). In fourteen cases, the basaloid component was found to represent between 60% to 95% of the tumor examined. In the remaining two cases (case 6 and case 7), it accounted for less than 20% and 30% respectively. In all 16 cases, the intertrabecular spaces and stroma of the tumors had eosinophilic hyaline materials. These hyaline materials, extending between and replacing the tumor cells, were PAS positive both before and after diastase treatment (Figure 2). In 8 cases, the microcystic spaces, some of which lined by PAS-positive lamina material, contained basophilic mucoid matrix which was Alcian blue positive but PAS negative. The basaloid cells were round to oval in shape, with scant, amphophilic cytoplasm, but sometimes it was abundant and clear. The nuclei showed either dark, hyperchromatin without nucleoli or dusty chromatin, vacuolated nucleoplasm with 1 to 3 small distinct nucleoli. The nuclear pleomorphism was frequently observed in all cases. The number of mitotic figures (including atypical ones) was extremely high, ranging from 45 to 198 mitoses per 10 high-power fields. The cells at the edges of the basaloid islands tended to show peripheral nuclear palisading. Comedo necrosis was found within the basaloid lobules in all cases (Figure 3).

An intimately associated squamous cell component was another major histopathologic feature of the tumor. In seven cases, invasive, keratinizing-squamous cell carcinoma covered 5%-80% and merged with the basaloid component. Two cases (cases 1 and 7) showed conventional squamous cell carcinoma as well as spindle cell component, the latter infiltrated between the basaloid lobules (Figure 4). In case 5 and 13 carcinomas *in situ* were found in the overlying epithelium. Four of the 16 (case 3, 11, 15 and 16) cases only had focal squamous differentiation and keratinization in the basaloid lobules (Figure 3). In one case (case 1 4), squamous cell dysplasia, squamous cell carcinoma *in situ* in the overlying epithelium as well as invasive squamous cell carcinoma and small cell carcionoma were the associated components of basaloid cell carcinoma with areas of ductular or glandular differentiation.

Table 2 Histochemical and immunohistochemical findings

Case	Component	CK	EMA	CEA	Vim	S-100	SMA	Stroma		
								ABP	AS	D-PAS
1	B	+	+	-	-	-	-	+	+	+
	S	++	++	-	-	-	-			
	SP	-	-	++	-	-				
2	B	+++	+	-	+	-	-	-	+	+
	S	+++	+++	-	-	-	-			
3	B	++	+	-	-	-	-	+	+	+
	S	+++	+	-	-	-	-			
4	B	++	+	-	-	-	-	-	+	+
	S	+++	+++	-	-	-	-			
5	B	+	+	-	-	-	-	+	+	+
	S	+	+++	+	-	-	-			
6	B	+++	+	-	++	-	-	-	+	+
	S	+++	+++	+	-	-	-			
7	B	+++	-	-	-	++	-	+	+	+
	S	+++	+++	-	-	-	-			
	SP	-	-	-	++	-	+			
8	B	++	+	-	-	-	-	+	+	+
	S	++	++	-	-	-	-			
9	B	+++	++	-	-	+	-	-	+	+
	S	+++	++	-	-	-	-			
10	B	+	+	-	-	+	-	-	+	+
	S	++	+++	-	-	-	-			
11	B	-	++	-	-	-	-	-	+	+
	S	+++	++	-	-	-	-			
12	B	++	++	-	-	+	-	+	+	+
	S	+++	++	-	-	-	-			
13	B	-	+	-	-	+	-	-	+	+
	S	++	++	-	-	-	-			
14	B	+++	++	-	-	-	-	+	+	+
	S	+++	++	-	-	-	-			
	SM	++	++	-	-	-	-			
15	B	++	+	-	+++	+++	-	+	+	+
	S	+++	+++	++	-	-	-			
16	B	+	+	-	++	+	-	-	+	+
	S	+++	++	-	-	-	-			

B: basaloid cell; S: squamous cell; SP: spindle cell; SM: small cell; D-PAS: diastase treating PSA stain

Immunohistochemical findings

Table 2 gives the immunohistochemical staining pattern of the 16 neoplasms studied. All squamous cell component, and basaloid cell component of 14 cases showed variable intracytoplasmic staining for cytokeratin (Pan) (Figure 5). But the spindle cells in case 1 and case 7 had negative staining for CK. EMA-positivit y was also demonstrated in nearly all the cases, nevertheless, the reactivity was focal and faint in the basaloid component, and in some cases, CK and EMA staining highlighted the glandular spaces focally. CEA was weakly expressed in squamous area of three cases. Vimentin immunoreactivity was found focally in the basaloid component of three cases and in the spindle cells in case 1 and case 7. In six cases, S-100 protein positive reaction was focally found within the lobules of basaloid component. However, the basaloid component in case 15 had diffusely and strongly positive staining for vimentin and S-100 protein (Figure 6). SM-actin immunoreactivity was absent in all cases except the spindle cell component in case 7.

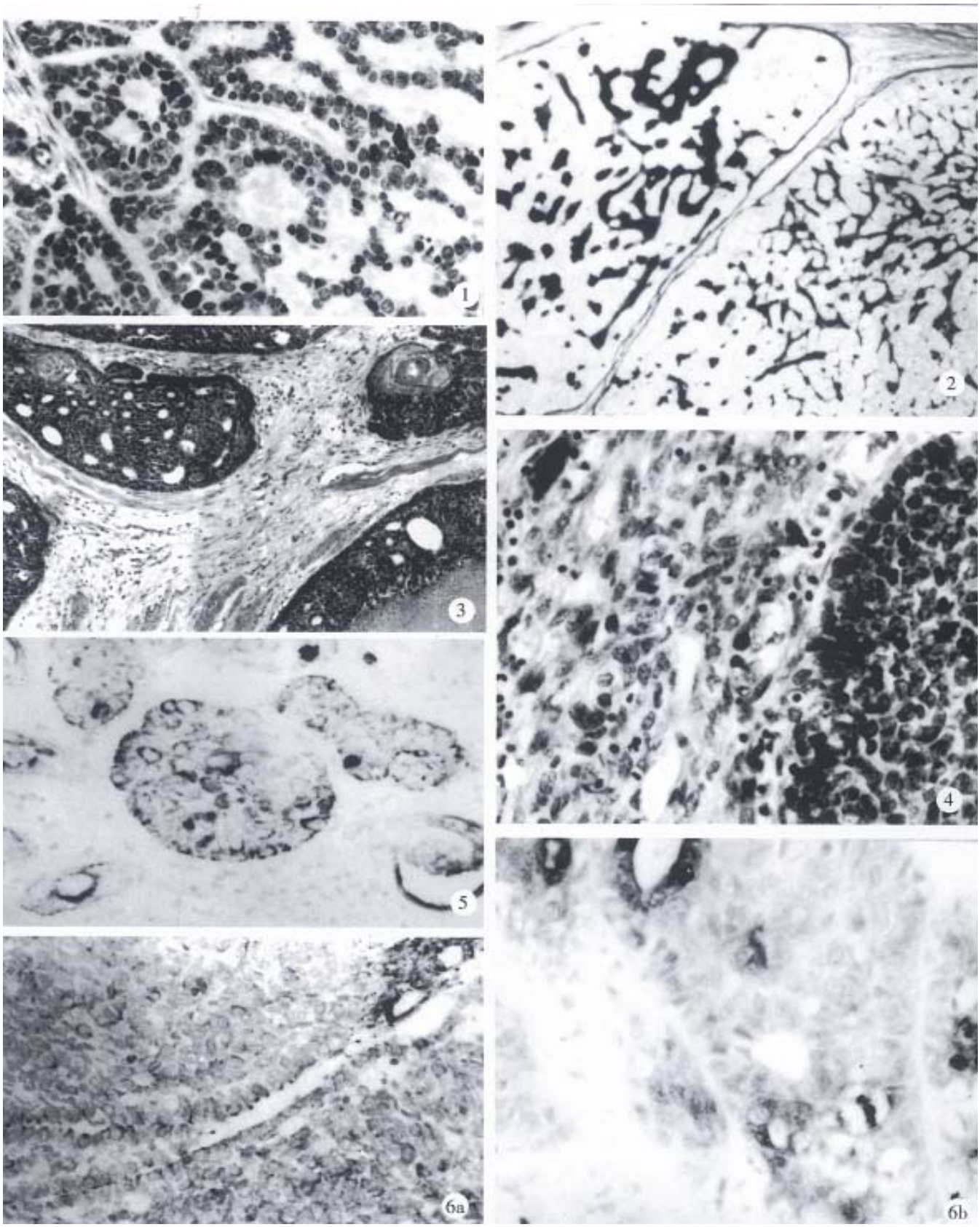

Figure 1 The basaloid cells arranged in the form of anastomosing trabeculae and microcystic structures. H&E, ×200
Figure 2 The intertrabecular and microcystic spaces filled with eosinophilic hyaline material which were PAS positive. ×100
Figure 3 Focal squamous differentiation and keratinization and comedo necrosis were found in the basaloid lobules. H&E, ×100
Figure 4 Basaloid cell carcinoma with spindle cell component. H&E, ×200
Figure 5 Immunohistochemical studies (S-P method) show positivity in the basaloid components for cytokeratin (Pan). ×200
Figure 6 The basaloid components in case 15 are diffusely and strongly positive staining for (a) vimentin and (b) S-100 protein. ×200

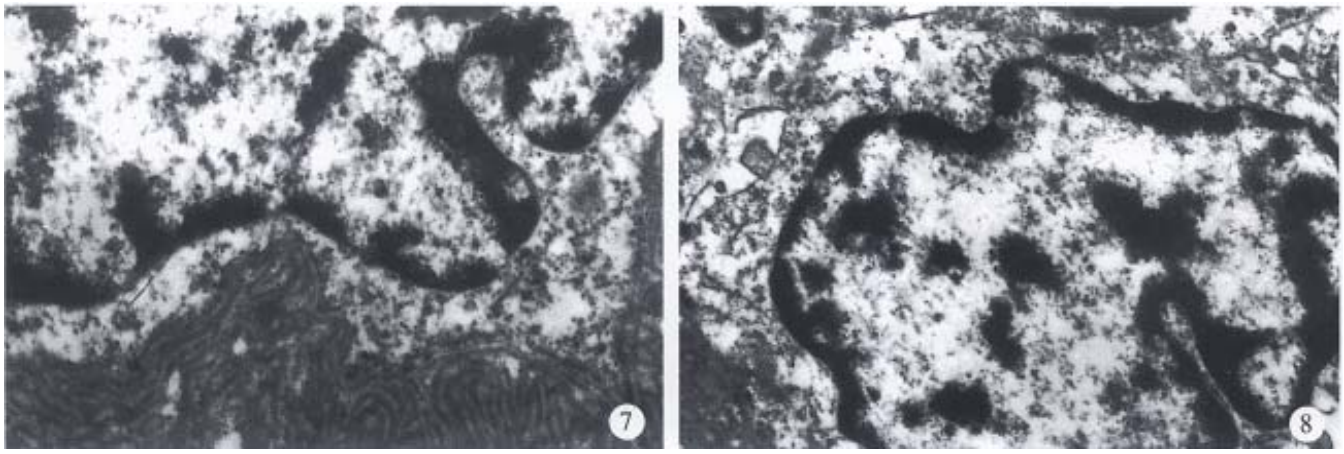

Figure 7 Electron microscopic photograph of esophage al BSC demontrating replicated basal lamina in fingerprint-like pattern filled in the intertrabecular and intercellular spaces. ×20000
Figure 8 Electron microscopicphotograph of esophageal BSC demonstrating well-formed intercellular desmosomes. ×16000

Electron microscopic features

Seven cases were examined under electron microscopy (case 9, 10, 11, 12, 14, 15, 16). Lobules of basaloid cells were seperated from the stroma by an external lamina. The cells within the lobules had widened intercellular spaces. The microcystic and intertrabecular spaces identified by light microscopy were lined by basal membranes and filled with either loose reduplicated or compact globoid basal lamina, showing fingerprint-like pattern (Figure 7). The basaloid cells were polygonal. The nuclei had oval profiles and there were irregular identations, containing finely dispersed chromatin and small clumps of hetero-chromatin. One to three compact nucleoli were present in some nuclei. Within the cytoplasm were numerous free and polyribosomes, a few desmosomes, tonofilaments and mitochondria (Figure 8), but rare other organelles, and absence of neuro secretory granules.

DISCUSSION

Before the term basaloid squamous carcinoma was introduced by Wain[1] in 1986, most malignancies of the esophagus with similar histopathologic pattern to BSC were diagnosed as adenoid cystic carcinoma (ACC). But scrutiny of the published reports showed that most cases were histologically identical to BSC[16,17], and behaved more aggressively than ACC. Tumors with identical morphology and similar clinical behavior have also been noted in other areas such as the uterine cervix[18], anal canal[19] and lung[9]. Other terms had also been used to describe this tumor such as adenosquamous carcinoma, poorly-differentiated squamous cell carcinoma, and small undifferentiated cell carcinoma. In the recent World Health Organization classification of esopha geal tumors, there is no mention of this newly recognized type of basaloid squamous carcinoma[20]. But the presence of lobules or cords of small, closely packed basaloid cells with scant cytoplasm, with or without small cystic spaces and hyalinized stroma, as well as an associated abnormal squamous cell component makes this tumor different from other common esophageal carcinomas. They have identical clinical and histopathologic features to that of BSC occuring in the larynx, pharynx and base of tougue described first by Wain *et al*, and belong to the same entity of malignant carcinoma.

In this series, sixteen cases of BSC of esophagus were found, accounting for 2.1% of 763 esophgeal carcinomas reviewed. The incidence is higher than that previously reported[2,21], but similar to the incidence by Abe *et al*[22]. This may be due to the difference of case selection. In our series, all cases were confirmed by esophagectomy. Morover, the main portion of each tumor is composed of basaloid carcinoma in 14 of 16 BSC cases as described in the literature[1], but in the remaining two, the major portion of the tumor is composed of squamous cell carcinoma, the basaloid component accounting for less than 30%. The most common location of the tumor is the middle third of the esophagus (11/16). The gross appearance of BSC is similar to that of other squamous cell carcinoma, only the cut surface in the former is more delicate.

BSC of esophagus should be distinguished from adenoid cystic carcinoma (ACC). The latter occurs more commonly in females, usually in women aged 40 to 60 years, with a mean age of 52 years[23], and with a more protracted clinical course. Histologically, the focal continuity with the abnormal surface epithelium or carcinoma *in situ*, an associated invasive squamous cell carcinoma, and focal squamous differentiation in the islands of

basaloid cells are not features of ACC, while alone or in combination, they have been found in all cases in the present series. The cells in ACC seem bland with mild pleomorphic nuclei and infrequent mitosis, and often exhibits identifiable two-cell-type differen ciation (palar ductal epithelium and darker basaloid cells) and distinctive crib riform structures in nerve invaded areas[24]. Under electron microscopic examination, four cell types were revealed in ACC: the intercalated duct cells; the secretory cells; the myoepithelium; and the pluripotential reserve/stem cells. These cells, especially the secretory cells and myoepithelium, were not noted by either immunohistochemical staining or electron microscopic examination in current series. The correct differential diagnosis between BSC and ACC is of important prognostic value. Basaloid squamous carcinoma of the esophagus is associated with poor outcome. The overall 3-year survival rate of BSC has been estimated at 28.5%[25]. In our series, most patients had developed into advanced stages at their presentation. Of the 11 patients with adequate follow-up, 8 died within 2 years from diagnosis, the survival rate being 60% at 12 month and 20% at 24 month. While the cumulative survival rates for patients with grade I, II and III of ACC were 92%, 65% and 14% at 5 years[24]. Epstein and coworkers[17] have proposed labelling tumors in the esophagus with histological features of BSC as "carcinoma with adenoid cystic differentiation" instead of "adenoid cystic carcinoma". But we think this descriptive term is too long and inconvenient to use, and the prognosis is apt to be overestimated by clinicians. In contrast, the term basaloid squamous carcinoma is shorter and more convenient to use. Furthermore, the two tumor elements, basaloid and squamous, of the term make it unique and differ from other kinds of tumors.

Cytoplasmic staining of BSC for a variety of antibodies to cytokeratins of different molecular weight has demonstrated variable staining with these antibodies[2,8,26,27]. In this study, the faint immunoreactivity pattern for EMA in basaloid component, and focal positivity for CK in some cases, together with intercellular desmosomes and cytoplasmic organelles and fibrils revealed by electron microscope provides an evidence that the basaloid cells in BSC may be largely undifferentiated, sometimes exhibiting focal tubular or squamous differentiation. Although Klijanienko and associates[27] suggested that the immunophenotype of S-100 protein-positive and vimentin-positive cells would indicate adiagnosis of adenoid cystic carcinoma, our seven S-100 protein-positive cases and four vimentin-positive cases are typical BSC rather than ACC. The S-100 protein-positive cells are not dendritic Langerhan's cells as described by the same authors, but basaloid carcinoma cells.

The exact line of differentiation or pathogenesis of basaloid squamous carcinoma is still unknown. Some reported cases of BSC were associated with smoking and heavy alcohol consumption[4,16], with a second primary tumor[28], and rarely, with previous irradiation[3]. The relationship of this tumor with viral agents, i. e. , Epstein Barr viruses *vs* BSC of the nasopharynx[6], human papillomavirus *vs* BSC of the external genitalia, perineum, and anus[11-13], has also been suggested by some authors. Based on the evidence provided by the present series and those reported in the literature, weagree with the theory of Ho *et al*[29] that a totipotent primitive cell is the common precursor of all epithelium neoplasms of the esophagus. With certain carcinogenic stimulation, the totipotent cells are activated and transformed into malignant cells. These transformed cells may differentiate into neoplastic squamous cells, adenocarcinoma, basaloid cell carcinoma (reserve cell carcinoma) and small cell carcinoma. These basaloid and small cells are rather primitive and retain their potential for further differentiation into keratin-forming cells, spindle-cell carcinoma, mucous-producing cells, and so on. We believe that only those tumors bearing a biphasic cellular pattern of basaloid and squamous components in an intimate relationship should be considered true BSC, if not, as some cases reported by Brambilla *et al*[8], should be considered bas aloid (or reserve) cell carcinoma.

The cellular differentiation and biologic behavior of BSC were assumed to occupy a station intermediate between that of conventional squamous cell carcinoma and small cell carcinoma. This assumptive placement into an intermediate position was based on the following. First, the clinical behavior of the tumors, which was less aggressive than that of small cell carcinoma (most of the patients died within 6 months from the time of diagnosis)[30], but more aggressive than that of conventional squamous cell carcinoma. In their 170 radical resected esophageal squamous cell carcinoma, Zheng *et al*[31] reported that the 5-year survival rate was 47.3% for stage II A cases, 22.2% for stage II B, and 16.1% for stage III; while in our patients whose follow-up data were obtained, no stage II, III, or IV cases survived beyond 5 years. Second, the histopathologic feature of this tumor, i. e. , the combination of basaloid and squamous carcinom a in most cases in our series and differentiation pattern in some cases. And third, numerous mitotic figures which were observed throughout tumor tissues in all our cases.

In conclusion, the BSC of the esophagus represents a specific and unique clinico pathological entity with a highly aggressive behavior and a poor

outcome. Identification of BSC is important because this lesion may be confused with less aggressive lesions, such as adenoid cystic carcinoma.

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