Basaloid Squamous Cell Carcinoma of Oesophagus: Definitely Rare but does it Differs Significantly from the Conventional Squamous Cell Carcinoma

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ABSTRACT

Introduction: Basaloid squamous cell carcinoma (BSCC) is a rare, poorly differentiated variant of squamous cell carcinoma (SCC). The diagnosis is made only after exclusion of conventional squamous cell carcinoma, adenoid cystic carcinoma and small cell carcinoma. Our aim is to present two cases of BSCCs identified in oesophagus with detailed clinicopathological, histological and immunohistochemical findings for better understanding of this rare entity which has limited literature available to avoid misdiagnosis.

Case Report: A detailed study of clinical and pathologic parameters in two cases of BSCC reported in our department who had underwent potentially curative surgical resection after a preliminary post biopsy diagnosis was made. Microscopically, both the cases showed a quite similar picture; they were composed of relatively small tumour cells, arranged in solid lobules with abundant comedo- necrosis. However, there were some minor variations as one of them was accompanied by large areas of typical conventional SCC, whereas the other one showed presence of bizarre cells. On immunohistochemical analysis, the tumour cells showed strong positivity for pan-CK with a high Ki67 index of 80-85%.

Conclusion: BSCC have a poorer prognosis than conventional oesophageal squamous cell carcinoma, but no definitive specific treatment protocol has been established till date. Still these cases were considered worthy of discussion due to the distinctness of this entity especially considering the site oesophagus where it is regarded to be quite rare, in addition to its aggressiveness and poor outcome.

Keywords: Basaloid Squamous Cell Carcinoma, Squamous Cell Carcinoma, Oesophagus, Pan-CK, Ki67

INTRODUCTION

Basaloid squamous cell carcinoma (BSCC) is a rare and distinct variant of squamous cell carcinoma (SCC) which is usually seen to be arising from a variety of anatomic sites, majorly in the upper aero digestive tract and is quite similar to BSCCs of the oesophagus.1-2 In 1986, Wain et al. coined this term and histopathologically described it as an invasive carcinoma with a basaloid pattern in close association with squamous cell carcinoma, carcinoma in situ, or focal squamous differentiation.2 Earlier most malignancies of the oesophagus with similar histopathological pattern of BSCC were diagnosed as adenoid cystic carcinoma (ACC). But scrutiny of the published reports showed that majority of these cases were histologically identical to BSCC and behaved more aggressively than ACC.4 WHO blue book has considered basaloid carcinoma as a rare but distinct variant of SCC in the oesophagus histologically composed of small crowded cells with hyperchromatic nuclei and scant basophilic cytoplasm showing a solid growth pattern, small cystic spaces as well as foci of comedo-type necrosis with evident prominent hyalinosis.5 The main differential diagnoses of BSCC to be kept in mind are adenoid cystic carcinoma and small cell carcinoma.

A very little data is available regarding its incidence and prognosis. Generally, it presented in older males and the reported incidence varies from 1 - 11% of all SCCs; true incidence likely to be 2%.6 The current study aimed to discuss in detail the histopathological and clinical features of BSCCs located in the oesophagus as well as to determine whether the management and prognosis of patients with BSCC of the oesophagus differ from that of patients with typical oesophageal SCC. Hereby, we present a detailed clinical, histopathological and IHC discussion on two cases of BSCC of the oesophagus reported in our department.

CASE REPORTS

Case report 1: A 37 year old female presented in the Department of GI Surgery with chief complaints of dysphagia only to solids since the last 2 months. There was no other significant history. Going further into the details, the surgeon found that the patient already had a barium swallow done which showed a short segment of mild luminal narrowing with mucosal irregularity involving mid thoracic oesophagus and a upper gastro endoscopy which showed a polypoidal ulcerated growth in the oesophagus at 25-28cm. (Fig 1a) Biopsy had been already taken from the affected site and histopathology of the same favoured squamous cell carcinoma (G2-Moderately differentiated) reported from outside. No previous surgery, preoperative radiotherapy or...
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International Journal of Contemporary Medical Research  
Volume 6 | Issue 10 | October 2019  | ICV: 98.46 | ISSN (Online): 2393-915X; (Print): 2454-7379

Basaloid cells arranged in solid or cribriform lobules with comedo necrosis. (Fig 2a-2b) These cells appeared monomorphic with moderate pleomorphism, oval to round hyperchromatic nuclei with open pale chromatin and scant basophilic cytoplasm. At places, the tumour showed peripheral palisading. Areas of conventional SCC were also noted in form of dysplastic keratin pearls and cells with intracytoplasmic keratinisation. (Fig 2c) Mitotic activity was increased. Foci of lymphovascular invasion noted. Multiple lymph nodes were dissected from the main specimen, out of which two showed metastatic tumour deposits.

Case report 2: A 46-year-old female presented in the Department of GI Surgery with chief complaints of dysphagia to solids and significant loss of weight since the last 3 months. She was already diagnosed with carcinoma of oesophagus however had no history of any surgery, chemotherapy or radiotherapy in the past. Previously done gastroesophageal endoscopy revealed an ulceroproliferative growth in the oesophagus (Fig 3b) and biopsy of the same was reported as squamous cell carcinoma (G2: Moderately differentiated) from outside. A PET-CT was done for evaluation of whole body metastatic survey which revealed metabolically active asymmetric enhancing mural thickening of 8 mm at the mid thoracic region, however GE junction was unremarkable. (Fig 3b) Finally a VATS esophagectomy with cervical gastroesophageal anastomosis was performed. Per operatively, it was found that the oesophageal wall was thickened with enlarged sub carinal and right laryngeal lymph nodes. Gross examination of the resected specimen showed a greyish white to greyish brown nodular growth measuring 2 x 1.8 x 0.8 cm in size located in the mid oesophagus. (Fig 1c-1d) Microscopically, the sections examined showed an ulcerated thickened dysplastic squamous epithelium with an invasive tumour in the underlying connective tissue composed of masses, solid nests and strands of basolaid cells as well as cribriform lobules with comedo-necrosis. (Fig 2a-2b) These cells appeared monomorphic with moderate pleomorphism, oval to round hyperchromatic nuclei with open pale chromatin and scant basophilic cytoplasm. At places, the tumour showed peripheral palisading. Areas of conventional SCC were also noted in form of dysplastic keratin pearls and cells with intracytoplasmic keratinisation. (Fig 2c) Mitotic activity was increased. Foci of lymphovascular invasion noted. Multiple lymph nodes were dissected from the main specimen, out of which two showed metastatic tumour deposits.
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International Journal of Contemporary Medical Research ISSN (Online): 2393-915X; (Print): 2454-7379 | ICV: 98.46 | Volume 6 | Issue 10 | October 2019

Figure-1: 1a-1d: Fig 1a: Gastroesophageal endoscopy with a polypoidal ulcerated growth in the oesophagus. Fig 1b: PET-CT showing metabolically active asymmetric enhancing mural thickening at middle oesophagus. Fig 1c and 1d: Gross image revealing a greyish brown nodular growth in the mid oesophagus.

Figure-2a-c: Microscopic findings Fig 2a. An invasive tumour in the connective tissue with close approximation to the dysplastic squamous epithelium. (100X) Fig 2b. Tumour arranged in cribriform lobules with comedonecrosis. (100X) Fig 2c. Areas of conventional SCC present in form of fair number of dysplastic keratin pearls. (100X)

Figure-3a-c: Fig 3a: PET-CT showing metabolically active asymmetric enhancing mural thickening at lower oesophagus. Fig 3b: Gastroesophageal endoscopy with an ulceroproliferative growth in the oesophagus. Fig 3c: Gross image revealing a greyish white ulceroinfiltrative growth in the distal oesophagus involving the GE junction.

Figure-4a-c: Microscopic findings Fig 4a Tumour arranged in cribriform lobules with comedonecrosis as well as in solid nests (100X) Fig 4b. Tumour shows peripheral palisading and individual cell keratinization. (100X) Fig 4c. High power view shows tumour cells with moderate to marked pleomorphism, oval to round hyperchromatic nuclei with open pale chromatin and scant basophilic cytoplasm. (Fig 4a) Many bizarre cells were seen. (Fig 4b) At places, the tumour cells showed peripheral palisading. Few tumour cells showed individual cell keratinisation. (Fig 4c) Mitotic activity was increased. The gastro-oesophageal junction was involved by the tumour. No foci of lymphovascular invasion noted. All the lymph nodes dissected from the specimen were free of tumour.

the underlying connective tissue composed of masses, solid nests and large cribriform lobules with comedo-necrosis surrounded by small dark basaloid cells showing moderate to marked pleomorphism, oval to round hyperchromatic nuclei with open pale chromatin and scant basophilic cytoplasm. (Fig 4a) Many bizarre cells were seen. (Fig 4b) At places, the tumour cells showed peripheral palisading. Few tumour cells showed individual cell keratinisation. (Fig 4c) Mitotic activity was increased. The gastro-oesophageal junction was involved by the tumour. No foci of lymphovascular invasion noted. All the lymph nodes dissected from the specimen were free of tumour.

On immunohistochemistry, the tumour cells in both the cases were strongly positive of pan-CK (Fig 5a) with high Ki67 index of 80-85%. (Fig 5b). The final report released was Basaloid SCC, G3: Poorly differentiated (TNM stage: pT3N0M0). Both the patients were discharged 15 days after the surgery and regular periodic follow up has been
unremarkable with no evidence of recurrence or metastasis till date.

**DISCUSSION**

BSCC is a distinct malignant tumour which is most commonly encountered in the upper aero digestive tract. However, it is uncommon in the oesophagus. (7) It accounts for only 0.068–4.0% of oesophageal cancers. Only two cases (2%) of BSCCs are identified in our department out of 96 cases of oesophageal carcinomas reported till date which include both the biopsy as well as radical specimens. The findings were quite similar to studies done by Xin-Hua et al which documented just 16 cases (2.1%) of BSCC out of 763 cases and Abe et al who reviewed and listed only 07 cases (1.9%) of BSCC among 371 total cases of esophageal carcinomas.\(^8\)\(^9\)

However, Jung Li et al and Sarbia et al reported surprisingly high incidence.\(^10\)\(^11\) This may be due to the difference in region and selection of cases. Tsang et al stated that many tumours formerly reported as adenoid cystic carcinomas are better to be classified as BSCC,\(^12\) hence considering the delayed recognition and the confusion regarding this entity, the true incidence of BSCC in the oesophagus is still uncertain. Regarding clinical and radiological parameters, most of the cases are seen in older males with a mean age around 55-60 years and chief complaints of dysphagia, odynophagia and weight loss. Majority of these are located in the middle one third to lower one third of the oesophagus. Though in our scenario, both the cases were diagnosed in middle aged females with chief complaints of dysphagia and weight loss. Radiologically, one presented in the lower one third and the other one in the middle one third of the oesophagus. Grossly BSCC presents as a large ulcerated fungating invasive masses; hence it is very difficult to distinguish BSCC from conventional SCC. Therefore, its diagnosis depends predominantly on characteristic histopathological features. Tadashi tereda et al mentioned in their study that diagnosing BSCC on small biopsies are very difficult and we believe the statement is true.\(^13\) Both the cases in our study were falsely diagnosed as moderately differentiated squamous cell carcinoma on small biopsies which were reported in other institutes. Most important reason is the size of the biopsy which affects the assessment of the characteristic cytoarchitectural pattern and hence could lead a pathologist to pen down an inappropriate diagnosis. We have also noted that the cases discussed in various other literature were all based on resected specimens of oesophagus, hence it can be concluded that the diagnosis is made with accuracy most of the time on resected specimen of oesophagus.

Microscopically, BSCC consists of solid or cribriform lobules with comedo-necrosis surrounded by basaloid cells with oval to round nuclei, mitotically active hyperchromatic nuclei and scant basophilic cytoplasm.\(^14\) Some may show microcystic pattern with basophilic material, peripheral palisading, round globular lumina and stromal hyalinisation. Areas of conventional invasive, in-situ SCC or squamous dysplasia of adjacent mucosa are seen admixed with the tumour. Our cases were no different. Microscopically both of them presented with an invasive tumour arranged in solid nests, cribriform lobules with comedonecrosis as well as strands of mitotically active basaloid cells. These areas were intermingled with areas of conventional SCC and individual cell keratinization. On immunohistochemistry, BSCC displayed reactivity for antibodies against pan-CK and CK subtypes (CK14, AE1/AE3, CK 19), EMA and P53. SMA, Leu 7 and S100 may or may not be present. The most important differential diagnosis considered were conventional SCC, adenoid cystic carcinoma (ACC) and small cell carcinoma. The common presenting symptoms and histomorphological features along with immunohistochemical stains are enumerated in Table I. ACC occurs more commonly in females aged 40 to 60 years with a mean age of 52 years. Histologically, the tumour shows a cribriform growth pattern with prominent pseudocysts surrounded by bland looking basaloid cells having mild pleomorphism and infrequent mitosis.\(^15\) Perineural invasion is commonly encountered. However, focal continuity with the abnormal surface epithelium or carcinoma in situ or an associated invasive squamous cell carcinoma are not seen in ACC. The differential diagnosis between BSCC and ACC is of important prognostic value as BSCC is more aggressive and associated with poor outcome.\(^15\) IHC is of importance in distinguishing BSCC from ACC as expression of S100 protein or smooth muscle actin is poor or absent in most of the BSCC.\(^16\) Small cell carcinomas occur mainly in 6\(^{th}\)–7\(^{th}\) decade and twice common in males with a mean age of 56 years. They are typically located in lower third of oesophagus. Microscopically, there are solid sheets and nests of small cells with dark round to oval nuclei and scant cytoplasm as
well as areas of crushing artefact. The lobular and cribriform growth pattern that dominates in BSCC is not typical of small cell carcinoma.\textsuperscript{17} Immunohistochemically, expression of cytokeratin subtypes 13 and 14 and/or the absence of markers of neuroendocrine differentiation may help to rule out the possibility of small cell carcinoma. However, positive immunostaining with one neuroendocrine marker does not rule out the diagnosis of BSCC.\textsuperscript{23} Distinguishing between these two entities is important for therapeutic consequences as small cell carcinoma is highly responsive to chemotherapy and therefore it is generally the recommended primary treatment. In contrast, the role of chemotherapy in the treatment of BSCCs has not yet been determined.

Squamous cell carcinoma is the most common oesophageal malignancy, with median age around 65 years in both males and females. 90% of the risk of SCC can be attributed to tobacco and alcohol. Histologically the tumour shows masses as well as proliferation of rete like projections of dysplastic squamous epithelium. WHO grades SCC into well differentiated, moderately differentiated and poorly differentiated based on the parameters of mitotic activity, anisonucleosis and degree of differentiation. Basaloid SCC is also a distinct variant of SCC but histologically quite different from conventional SCC. IHC is of limited importance in distinguishing BSCC and conventional SCC as both of them are positive for CK and p53.\textsuperscript{10} This is true that SCC and BSCC resemble each other a lot and no different treatment protocol had been established yet, still we consider that BSCC should be given acknowledgement and needs to be reported as soon as possible since they are associated with wide spread metastasis at presentation hence showing a poor prognosis.\textsuperscript{20} Kumagai et al reported that the rate of lymphatic invasion, venous invasion and lymph node metastasis were 5.6, 89, and 67%, respectively.\textsuperscript{21} These tumours are characterized by a higher proliferative activity and apoptotic indices as compared with typical conventional SCC. Sarbia et al showed that BSCC proliferates more rapidly than typical SCC on the basis of quantitative assessment of several proliferation associated parameters however they could not find any differences in survival between patients with BSCC and conventional SCC of the oesophagus. A separate treatment protocol for BSCC has not been formulated yet considering postoperative radiation therapy and chemotherapy and thereby the sensitivity of these treatments is still dicey, therefore they are currently treated as typical SCC i.e., by surgery, radiotherapy, chemotherapy or a combination of both.\textsuperscript{22} Ho et al suggested that a totipotent primitive cell is the common precursor of all epithelial neoplasms of the oesophagus. When they are carcinogenically stimulated, the totipotent cells are activated and differentiate into neoplastic squamous cells, adenocarcinoma, basaloid 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 and mucous-producing cells.\textsuperscript{23} The intimate relationship of BSCC with the dysplastic surface epithelium and the squamous differentiation all support this hypothesis. Hence we believe that only those tumours bearing a biphasic cellular pattern of basaloid and squamous components should be considered true BSCC.

In Table no II, we have discussed the comparison between clinicopathological parameters, histology and IHC of BSCC in various studies with our cases.

**CONCLUSION**

Basaloid squamous cell carcinoma of the oesophagus indeed represents a specific, unique as well as an uncommon clinicopathological entity with a highly aggressive behaviour, increased rate of metastasis and a poor outcome. Identification of BSCC from other tumours having basaloid component is important because this lesion may be confused with less aggressive lesions, such as adenoid cystic carcinoma or a more aggressive lesion such as small cell carcinoma. However, the prognosis and treatment of patients with BSCC of the oesophagus does not differ from that of patients with typical SCC of the oesophagus. In the end, we would emphasize the need to report BSCC as a separate entity due to its poor prognosis as well as widespread metastatic rate.

**REFERENCES**

Section: Pathology

397–403.


