Slide seminar 2

DIGESTIVE DISEASES PATHOLOGY [SS-02]

Tumors and tumor-like lesions of the esophagus

Case No 3: Carcinosarcoma of the upper esophagus

Presented by Gabriel BECHEANU

gbecheanu@yahoo.com

Clinical history

A 79 years old female patient was admitted in the hospital for episodes of dysphagia to solids and a pharyngeal discomfort debuted one month before. She also remarked a five kilos weight loss during this time. Upper endoscopy revealed a large tumor mass in the upper esophagus started from first part of the esophagus (cervical esophagus).

Macroscopically: large ulcerated tumor (size 7/4/1 cm) with infiltration in left pharyngo-laryngeal muscles.

Histology examination revealed a malignant proliferation with spindle cells immunoreactive for vimentin, but negative for cytokeratins, actin, desmin, p63, CD31 and CD 117, with an overexpression of p53.

The histopathological diagnosis was esophageal carcinosarcoma, stage pT4NxMx.

Surgery: total eso-pharyngo-laryngectomy was performed.

Follow-up: death with disseminated disease 18 months after surgery.

Description of the slide

The slide submitted for the seminar – section on a fragment sampled from the surgical specimen (Figure 1), presents an area of tumoral lesion with round or fusiform tumoral cells (Figure 4), disposed in dense fascicules with storiform pattern, with cellular pleomorfism and frequent mitoses (11 mitoses per 10 HPF); the marginal zone (Figure 2) is composed of squamous epitelium with high-grade dysplasia lesions (Figure 3).

The tumor infiltrates the chorion with extension to left lateral pharyngo-laryngeal muscles, but with preservation of cartilaginous structures and hyoid bone. In the peripheral

area of the tumor there are zones of moderate to high-grade dysplasia and some koilocytes in the surperficial epithelium.

Immunohistochemistry examination showed positive tumoral cells for vimentin, with an overexpression of p53 in 80% of nucleus (Figure 5) and also in squamous cells form the dysplastic area. The expression for cytokeratins (AE1/AE3, MNF 116, 34BE12, CK5/6), p63, desmin, actin, CD 117 and CD31 were negative in tumor cells.

The presence of high-grade dysplastic lesions in the peripheral part of the tumor and the overexpresion of p53 protein in this area and in tumor cells, even in the absence of cytokeratin expression, are in the favor of a carcinoma with spindle cells (esophageal carcinosarcoma).

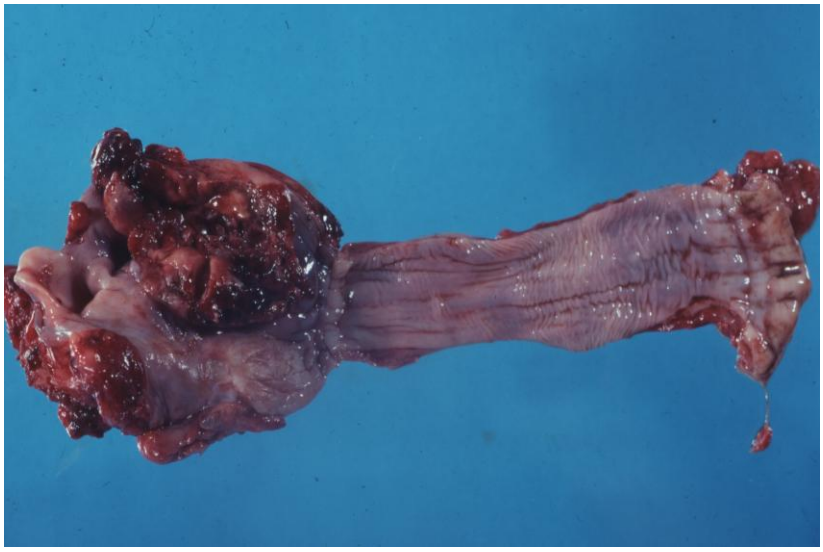

Figure 1. Macroscopic view of the tumor in the upper esophagus

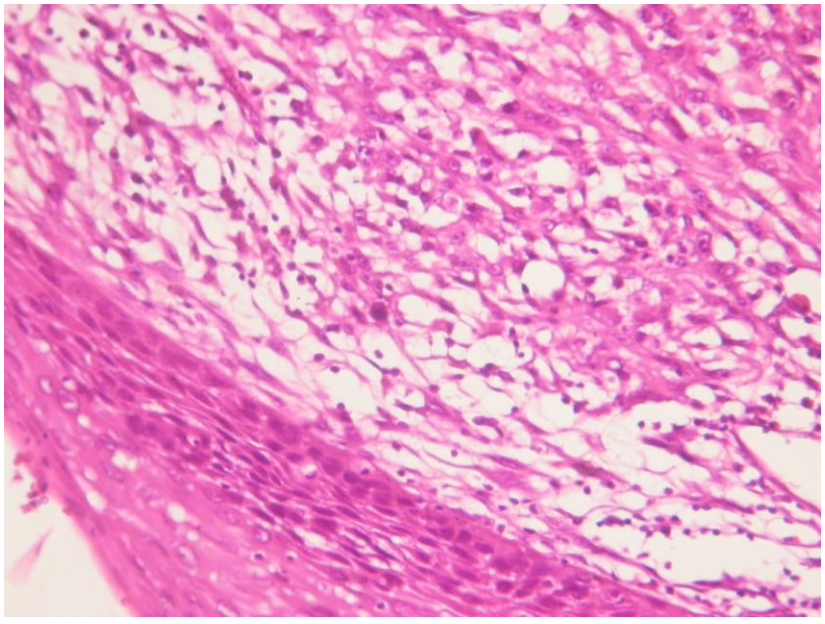

Figure 2 – Tumor spindle cells under the squamous dysplastic epithelium, HE stain,100x

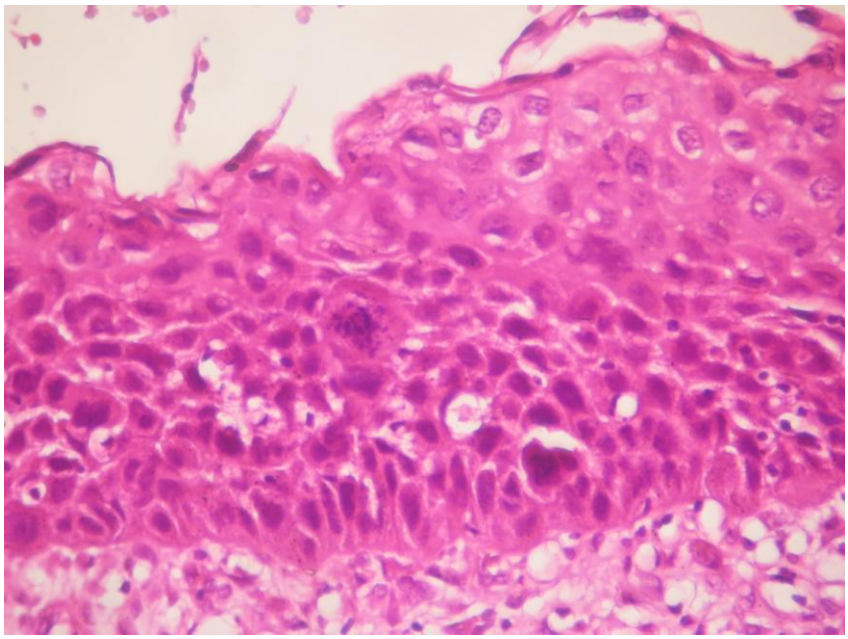

Figure 3 – Squamous epithelium with high-grade dysplasia, HE stain, 400x

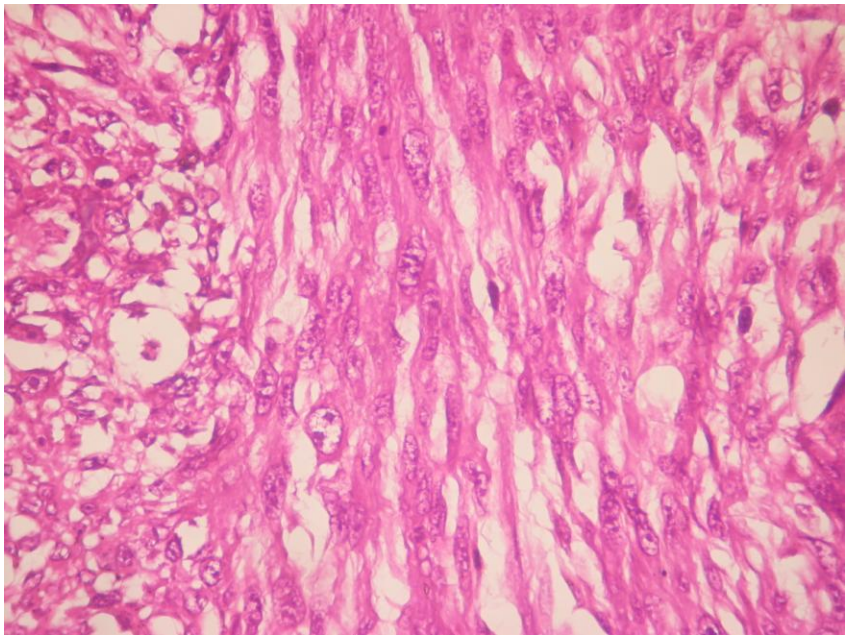

Figure 4 – Fascicules of spindle cells, HE stain, 400x

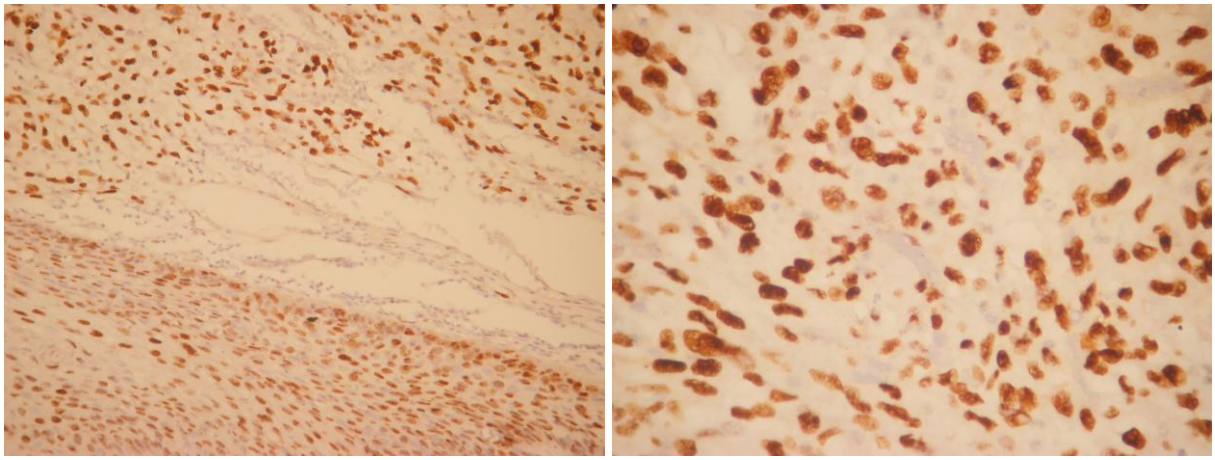

Figure 5 – Immunohistochemistry - strong overexpression of p53 protein in squamous epithelium (bottom left) and in tumor contingent (upper left and right image, in detail)

Comments

Esophageal carcinosarcomas are rare malignant lesions that represent 0.5-3 % from all esophageal tumors (Iyomasa et al, 1990; Hatch et al, 2000). The oncogenesis of this tumor remains unclear.

Usually they are large polypoid lesion with smooth or ulcerated surface, localized in the middle or lower part of the esophagus and very rare in the upper esophagus. Frequently they are attached by a short pedicle but sometimes have only a wide base.

Because the tumor has a rapid growth, symptoms like dysphagia may occur earlier than in squamous tumors and the diagnosis is prompt.

Sarcoma-like elements are often observed in metastasis and this could be an argument in favor of malignant potential of this component.

Partial or total esophagectomy with regional node lymphadenectomy is usually performed for this tumor type. The prognosis is much better than for epidermoid carcinoma because of the early diagnosis and depends on invasive component. Despite their size, carcinosarcomas usually develop into the lumen and no deeper than mucosa. Some authors considered that prognosis is not as favorable as was initially expected because of hematogenous metastasis, and liver metastasis and peritoneal dissemination were described to accompanying sarcoma-like component (Sanada et al, 2006).

Radiation and chemotherapy could be considered after surgery for possible residual malignant cells and because of unpredictable evolution of this tumor.

Carcinosarcoma is a tumor with biphasic microscopic feature: an epithelial carcinomatous component and a pleomorphic sarcomatous component.

The epithelial component is usually squamous and could be minimal or invasive, and intermingle with sarcoma-like elements. Other components reported included squamous cell carcinoma, basaloid squamous carcinoma, adenocarcinoma, undifferentiated carcinoma and neuroendocrine carcinoma (Kanamoto et al, 2000).

The sarcomatous component often predominates and could contain foci of rhabdomiosarcoma, osteosarcoma, chondrosarcoma (Matsui et al. 1995). Usually is composed of pleomorphic spindle or stellate cells disposed in bundles or storiform pattern in an edematous matrix.

The surrounding mucosa may be normal or exhibit foci of epithelial dysplasia (Takubo et al, 1982) or squamous carcinoma.

Immunohistochemically spindle cells express strong positive reaction with vimentin and occasionally foci of weak expression with cytokeratin, usually in transitional areas; sometimes cells are focally positive for actin and desmin. Epithelial cells have a positive reaction for cytokeratin AE1/AE3. Ki-67 labeling index is usually high in both components.

Protein p53 usually was found to be positive in both tumor cells (Handra-Luca et al, 2001), as in our case, and both components had the same somatic mutation in the p53 gene (Kashiwabara et al, 2001), supporting the hypothesis of a monoclonal origin.

The strong reaction of two oncogens MDM2 and CDK4 in both carcinomatous and sarcomatous cells provides evidence of a role for these molecules in the pathogenesis of carcinosarcoma and support the idea of a single ancestor cell of origin (Nikitakis et al, 2002).

New features were revealed by discovering of two adhesion proteins - E-cadherin and beta-catenin - in the normal esophageal epithelium that shows strong expression of these markers at the cell membrane and the intercellular junctions. Disruption of the cadherin-catenin cell adhesion complex may play a role in the initial steps of cancer invasion and metastasis, and the expression on E-cadherin and beta-catenin was investigated in different tumors of the esophagus. Reduction of E-cadherin expression or loss of both proteins (E-cadherin and beta-catenin) was associated with post-operative recurrence and with poor prognosis in patients with esophageal carcinomas (Nakanishi et al, 1997). In squamous cell carcinomas the decrease of expression and loss of both proteins were always found in poorly differentiated tumors and

reduced of membranous expression on these markers was discovered in 66-70% of epidermoid carcinomas (Zhao et al, 2003).

Occasional high level expression of nuclear beta-catenin was found in carcinosarcomas and in a small group of mesenchimal tumors (Ng et al, 2005), serving as possible useful diagnostic tool.

The loss of E-cadherin expression was evident in most carcinosarcoma of the esophagus (Handra-Luca et al, 2001) and this change was suggested to reveal a possible epithelial-mesenchymal transition of tumoral cells.

Differential diagnosis of the large esophageal polypoid mass involves a fibrovascular polyp, an esophageal lipoma, a squamous cell papilloma or carcinoma (especially verrucous variant) or a malignant melanoma. Esophageal carcinosarcomas must be histologically differentiated from sarcomas, melanomas and biphasic malignant mesotheliomas, mainly on immunohistochemical profile.

In conclusion, carcinosarcoma of the upper esophagus is an extremely rare polypoid malignant tumor with uncertain histogenesis, with a possible epithelial-mesenchymal transition of the tumor cells suggested by research studies.

References

1. Iyomasa S, Kato H, Tachimori Y, Watanabe H, Yamaguchi H, Itabashi M: Carcinosarcoma of the esophagus: A twenty-case study. Jpn J Clin Oncol 1990;20:99-106
2. Kanamoto A, Nakanishi Y, Ochiai A, Shimoda T, Yamaguchi H, Tachimori Y, Kato H, Watanabe H. A case of small polypoid esophageal carcinoma with multidirectional differentiation, including neuroendocrine, squamous, ciliated glandular, and sarcomatous components. Arch Pathol Lab Med. 2000 Nov;124(11):1685-7
3. Handra-Luca A, Terris B, Couvelard A, Molas G, Degott C, Flejou JF, Spindle cell squamous carcinoma of the esophagus: an analysis of 17 cases, with new immunohistochemical evidence for a clonal origin. Histopathology 2001 Aug;39(2): 125-32
4. Hatch GF 3rd, Wertheimer-Hatch L, Hatch KF, Davis GB, Blanchard DK, Foster RS Jr, Skandalakis JE: Tumors of the esophagus. World J Surg 2000;24:401-411
5. Kashiwabara K, Sano T, Oyama T, Najahima T, Makita F, Hashimoto N, Iwanami K, Kawashima O, Matsumoto T, Matsuzaki Y.A case of esophageal sarcomatoid carcinoma with molecular evidence of a monoclonal origin. Pathol Res Pract. 2001; 197(1):41-6.
6. Matsui K, Yukimasa A, Endou N, et al. A case report of esophageal carcinosarcoma showing bone and cartilage formation with gastric cancer. Tottori Med J 1995; 23:275-281
7. Nakanishi Y, Ochiai A, Akimoto S, Kato H, Watanabe H, Tachimori Y, Yamamoto S, Hirohashi S. Expression of E-cadherin, alpha-catenin, beta-catenin and plakoglobin in esophageal carcinomas and its prognostic significance: immunohistochemical analysis of 96 lesions. Oncology. 1997 Mar-Apr;54(2):158-65
8. Nikitakis NG, Drachenberg CB, Papadimitriou JC. MDM2 and CDK4 expression in carcinosarcoma of the esophagus: comparison with squamous cell carcinoma and review of the literature. Exp Mol Pathol. 2002 Dec;73(3):198-208.

9. Ng TL, Gown AM, Barry TS, Cheang MC, Chan AK, Turbin DA, Hsu FD, West RB, Nielsen TO. Nuclear beta-catenin in mesenchymal tumors. Mod Pathol. 2005 Jan;18(1):68-74
10. Sanada Y, Hihara J, Yoshida K, Yamaguchi Y. Esophageal carcinosarcoma with intramural metastasis. Dis Esophagus. 2006; 19:119-131
11. Takubo K, Tsuchiya S, Nakagawa H, Futatsuki K, Ishibashi I, Hirata F., Pseudosarcoma of the esophagus, Hum Pathol. 1982 May;13(5):503-5
12. Zhao XJ, Li H, Chen H, Liu YX, Zhang LH, Liu SX, Feng QL.Expression of e-cadherin and beta-catenin in human esophageal squamous cell carcinoma: relationships with prognosis. World J Gastroenterol. 2003 Feb;9(2):225-32.