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Letter to the Editor

ESOPHAGEAL GRANULAR CELL TUMOR ASSOCIATED TO SQUAMOUS CELL CARCINOMA: A CASE REPORT

Tumor esofágico de células granulares associado à carcinoma epidermoide: relato de caso

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INTRODUCTION

Primary tumors of the esophagus can be classified on the basis of cell origin into epithelial and nonepithelial tumors. Each category may be further subdivided into benign and malignant types. The nonepithelial tumors arise from the mesenchymal or supporting stromal tissue, most of them are benign. Nearly all esophageal cancers are carcinomas. Sarcomas rarely arise in the esophagus. The collision tumors are composed of tumors arising in adjacent but separate loci. As they grow, they merge and invade each other at the interface [1,2]. The esophagus is one of the most common sites for granular cell tumors (Abrikossof tumor) in the gastrointestinal tract. Esophageal granular cell tumor is a rare, usually solitary, small incidental lesion. Multiple tumors are found in about 10% of cases, and they may present with obstruction when large. The tumors arise more frequently in the lower third of the esophagus, producing a poorly circumscribed, firm, pale-yellow submucosal nodule[1,3,4].

Esophageal carcinoma is the sixth most common cancer among men and ninth among women, and it affects more than 450.000 people each year in the world. Survival is uniformly low, with 5-year survival rates usually less than 10%. Squamous cell carcinoma is the commonest malignant tumor of the esophagus, affecting males more often than females, with a median age of 60 years. Squamous cell carcinoma can occur in any portion of the esophagus, but the middle and lower third are the most common locations[2,5,6,7].

Herein, the authors report a case of esophageal granular cell tumor associated with squamous cell carcinoma, and describe the morphological, immunohistochemical and diagnostic criteria of these two distinct neoplasms.

CASE REPORT

A female white patient, 52 years, was admitted in the oncology service with clinical complaint of progressive dysphagia and weight loss during the last four months. Upper gastrointestinal endoscopy revealed a vegetating tumor in the lower third of the esophagus. The lesion prevented the duodenoscope progression. Thoracic computed tomography revealed an area of irregular thickening of the esophageal wall. A biopsy of the lesion was performed, and the histopathological diagnosis of squamous cell carcinoma was determined. On the basis of the clinical and pathological findings, a transhiatal esophagectomy was performed. The surgical specimen consisted of the distal esophagus and proximal stomach. The esophagus measured 11.0 cm length. At 6.5 cm from the top, a gray, vegetating tumor, with indistinct borders, was identified. The process measured 3.0 cm in length and invaded esophageal adventitia. Continuing to the injury described, on the muscular layer, it was identified a firm, ill defined, whitish lump, which measured 1.0 cm in diameter. On microscopic evaluation, two distinct neoplasms in collision have been identified. The largest one corresponded to a well-differentiated squamous cell carcinoma. The smaller lesion corresponded to a poorly demarcated neoplasia arising in the submucosal and muscular layers. It was composed by polyhedral or spindle cells, with finely eosinophilic granular cytoplasm and small rounded nuclei, arranged in nests or solid pattern, with low mitotic index, and no evidence of necrosis (Figure 1). The immunohistochemical study of the surgical specimen showed, in the smaller lesion, diffuse and strong immunoreactivity for vimentin (Vim3B4) and S100 protein (polyclonal), and negative immunostaining for alpha smooth muscle actin (1A4), desmin (D33), CD117 (polyclonal) and CD34 (endothelial cell, QB-END/10). The area corresponding to squamous cell carcinoma

showed positive imunostaining only for pancytokeratin (AE1/AE3). The morphology of the lesions associated with the findings of the immunohistochemical study was consistent with esophageal granular cell tumor associated with squamous cell carcinoma. No metastases have been identified on the isolated lymph nodes from the specimen. The portion of the stomach showed moderate chronic gastritis with formation of lymphoid follicles and intestinal metaplasia. The search for *Helicobacter pylory* (Giemsa method) was negative. After 14 months of clinical follow-up, the patient had no evidence of disease progression.

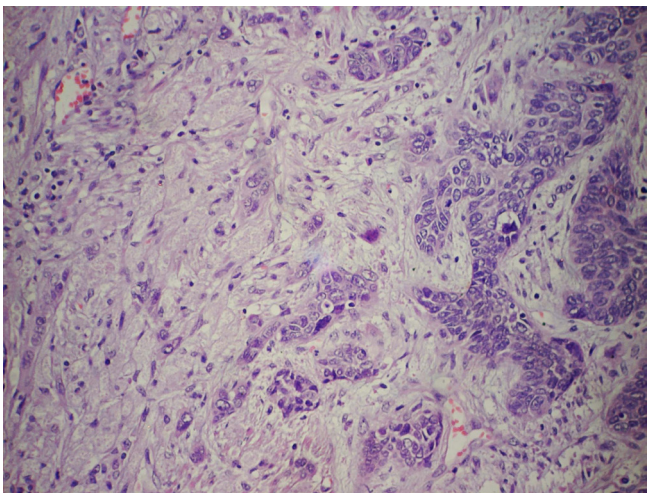

FIGURE 1 - The transition between the solid pattern of the granular cell tumor and the invasive pattern of the squamous cell carcinoma (Hematoxilin-eosin, 200X)

DISCUSSION

Granular cell tumors arise throughout the gastrointestinal tract, but they are more common in the esophagus, especially in the lower segment. Most esophageal cell tumors are slowly growing lesion. The tumors develop in individuals from ages 20 to 70, equally affecting men and women. The size of the tumor correlates with symptoms, which consist principally of dysphagia or pain. These intramural nodules produce sessile lumps when viewed from the mucosal aspect. The tumors usually appear as smooth, sessile, solitary, grayish-white lesions measuring 1 to 4 cm in diameter. They are located in the submucosa or muscularis propria in an infiltrating pattern, and are covered by a hyperplastic epithelium. On microscopic examination, the process exhibit nests and cords of polygonal to rounded bland cells with small rounded nuclei and abundant granular eosinophilic cytoplasm. In most cases granular cell tumors are benign process. The suspicious lesions for malignancy include tumors with large size (> 5cm), presence of necrosis, increased cellularity, high mitotic index (greater than two mitoses per 10 hpf), nuclear pleomorphism, large nucleoli, areas of necrosis, and invasion of adjacent organs. The red granules in the cytoplasm are PAS positive. On immunohistochemistry evaluation, the granular cell tumors are positive to antibodies to S100, vimentin, CD68, GFAP, NSE and Leu7. Some lesions are immunopositive to cytokeratin and CD117. The differential diagnosis includes malignant melanomas or the rare cases of metastatic carcinoma[1,4,8]. The ultrastructural findings of granular cell tumors include cells showing numerous cytoplasmic vacuoles containing myelin-like tubules[1,4,8,9,10,11,12].

Granular cell tumors may coexist with squamous cell carcinoma adenocarcinoma, gastrointestinal stromal tumors, and leiomyomatosis [1,3,4,9,11,13,14]. Squamous cell carcinoma is the commonest malignant tumor of the esophagus, affecting more males with a median age of 60 years. The possible etiologic factors include smoking, alcohol consumption, dietary deficiency, fungal contamination of foods, achalasia, esophageal diverticula, Plummer-Vinson syndrome, tylosis, history of previous irradiation, and celiac disease. In most cases of these conditions there is a chronic esophagitis[1,3,5,9].

Squamous cell carcinomas usually occur in the middle or lower third of the esophagus, and the overall prognosis is poor. Most advanced tumors are associated with progressive dysphagia, weight loss and anemia. Grossly, the lesions are usually circumferential, exophytic, partly ulcerated, with irregular margins. On cut sections, a gray or white tumor with indistinct borders is a commonly aspect, more often extending to the muscular wall or behind. Submucosal and intraepithelial spreading is also common, and blood vessel invasion is present in three fourths of cases. Histologically esophageal squamous cell carcinoma can range from well-differentiated tumors to poorly differentiated neoplasms. The tumors in surgical specimens usually invade the muscular coat with variable infiltration of the extraesophageal tissues. Multicentric lesions can be found in less than 30% of cases. Unfavorable prognostic indicators include vascular or lymphatic invasion, areas of tumoral necrosis, poorly-differentiated lesions and presence of nodal metastases. Others factors related to lower survival are tumors affecting males, and stage. The histological variants of squamous cell carcinoma of the esophagus include superficial spreading carcinoma, verrucous variant, and basal cell carcinomas. The differential diagnosis is made from hyperplastic or reactive epithelium, poorly-differentiated adenocarcinoma, and eventually malignant melanoma. On immunohistochemical technique, squamous cell carcinoma of the esophagus stain positive to antibodies to AE1/AE3, CAM5.2, 34betaE12, CK19, CK5 and p63 [2,5,6,7,9].

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