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Granular cell tumor of the esophagus: Three case reports and review of the literature

Özofagusun granüler hücreli tümörü: Literatür eşliğinde üç olgu sunumu

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The esophagus is the most common site of origin of gastrointestinal tract granular cell tumors. Approximately 270 cases of esophageal granular cell tumors have been reported in the literature. Most esophageal granular cell tumors are found incidentally during endoscopy. Although granular cell tumor of the esophagus has become easily recognizable by its endoscopic features, it has to be differentiated from other benign and malignant mucosal and submucosal lesions. The majority of esophageal granular cell tumors are asymptomatic and benign; thus, close follow-up of the patients with endoscopy could be considered sufficient as a therapeutic management. New therapeutic options should be considered especially for larger lesions. Three cases of granular cell tumors with complaints of epigastric discomfort, regurgitation, nausea, and vomiting, which were detected in the lower part of the esophagus on upper gastrointestinal tract endoscopy, are discussed with the most recent literature review on this subject.

Key words: Esophagus, granular cell tumor, clinicopathological features, therapeutic options

Özofagus, gastrointestinal traktus granüler hücreli tümörlerinin en sık görüldüğü lokalizasyondur. Literatürde yaklaşık 270 özofajial granüler hücreli tümör olgusu bildirilmiştir. Birçok özofajial granüler hücreli tümör endoskopi sırasında tesadüfen bulunmaktadır. Özofagusun granüler hücreli tümörü endoskopik özellikleriyle kolayca tanınır olmasına karşın diğer benign ve malign mukozal ve submukozal lezyonlardan ayırt edilmelidir. Özofajial granüler hücreli tümörlerin büyük bir kısmının asemptomatik ve benign olması nedeniyle hastaların endoskopi ile yakından takibi tedavi yaklaşımı açısından yeterli sayılabilir. Yeni tedavi seçenekleri özellikle daha büyük lezyonlar için düşünülmelidir. Epigastrik rahatsızlık, regürjitasyon, bulantı ve kusma yakınmaları olan, üst gastrointestinal trakt endoskopisi ile alt özofagusta lokalize olduğu saptanan üç granüler hücreli tümör olgusunun, bu konu ile ilgili en son literatür taraması eşliğinde tartışılması amaçlanmıştır.

Anahtar kelimeler: Özofagus, granüler hücreli tümör, klinikopatolojik özellikler, tedavi seçenekleri

INTRODUCTION

Granular cell tumor (GCT), formerly known as "granular cell myoblastoma", was first described by Abrikossoff (1) in the tongue in 1926. Subsequently, he also reported the first GCT of the esophagus in 1931 (2). Since then, GCT has been reported in many different locations throughout the body, most commonly in the tongue, oral mucosa, skin, and subcutaneous tissue, but also in the breast, thyroid, respiratory tract, biliary tree, female genital tract, nervous system, and all segments of the gastrointestinal (GI) tract (3-7).

The widespread use of fiberoptic and video endoscopy has led to increased recognition of GCT of the esophagus, of which approximately 270 cases have been reported in the literature. Contrary to previous views that a female predilection is observed for all GCTs (3), esophageal cases are encountered more frequently in men (8). GCTs of the esophagus occur most commonly in the fourth, fifth, and sixth decades of life (8-10). Recently, the first GCT of the esophagus in a pediatric patient was reported (11).

The purpose of this paper was to discuss three GCTs of the esophagus, with an emphasis on the clinicopathological features and management of these tumors in light of the most recent literature review on this subject.

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CASE REPORTS

Two male patients (36 and 40 years old) and a female patient (29 years old) were admitted to our hospital with complaints of epigastric discomfort, regurgitation, nausea, and vomiting. Physical examination and laboratory findings were unremarkable in all patients. On upper GI endoscopy, whitish-yellow, firm, well-circumscribed sessile polypoid lesions, covered by normal mucosa and ranging from 3 mm to 7 mm in diameter, were discovered in the lower part of the esophagus. The two male patients had solitary lesions while the female patient had two lesions in the esophagus that arose metachronously. While endoscopic diagnoses were GCTs for the lesions in both male patients and the second lesion in the female patient, the first lesion of the female patient was suspected to be a lipoma.

Biopsy specimens taken from all patients showed submucosal lesions with slightly acanthotic squamous epithelium overlying typical GCTs composed of nests of plump round or polygonal cells having small, round, pyknotic central uniform nuclei with abundant, fine granular eosinophilic cytoplasm (Figure 1). Neither pleomorphism nor mitotic activity was detected in the lesions. The cytoplasm of the cells showed diffuse strong reactivity for S-100 protein immunohistochemically in all lesions (Figure 2).

DISCUSSION

The GI tract is one of the more uncommon locations of GCTs. Nearly one-third of them occur in the esophagus (3,7), the most common site of origin of digestive tract GCTs. They are found in the lower esophagus in 65-75%, in the mid-esophagus in 18-20%, and in the upper esophagus in 5-15% of cases (3). Though usually solitary, esophageal GCTs can be multiple in approximately 10% of cases, either in the esophagus alone or in other sites (7-9, 12). It has been reported that even up to 16 lesions have arisen synchronously and metachronously in a single patient (13). The female patient in our case had two lesions in the esophagus, which arose metachronously. The first lesion, which was suspected to be a lipoma endoscopically, was a yellow polypoid lesion 5 mm in diameter. One month after the detection of the first lesion, the second lesion, 3 mm in diameter, was discovered by endoscopy with a preliminary diagnosis of GCT.

Though most esophageal GCTs are found incidentally during endoscopy or upper GI contrast studies performed to investigate other problems or at autopsy, dysphagia, substernal pain, regurgitation of food (8, 12) or non-specific symptoms such as nausea, vomiting, epigastric pain, heartburn, or dyspepsia (8, 10, 14, 15) can be observed in patients who have clinical symptoms, as in our cases. It is noteworthy that the frequency of symptoms increases in parallel to the size of the lesion, as those lesions larger than 1 cm may produce dysphagia (8, 10).

While many kinds of cells, including myoblasts, Schwann cells, histiocytes, perineural fibroblasts, and undifferentiated mesenchymal cells, have be-

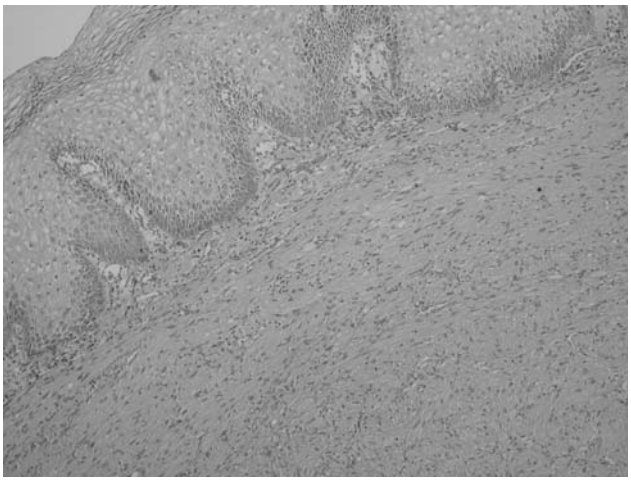

Figure 1. Submucosal granular cell tumor showing slightly acanthotic squamous epithelium, composed of nests of large polygonal cells with abundant eosinophilic granular cytoplasm (hematoxylin and eosin, x100).

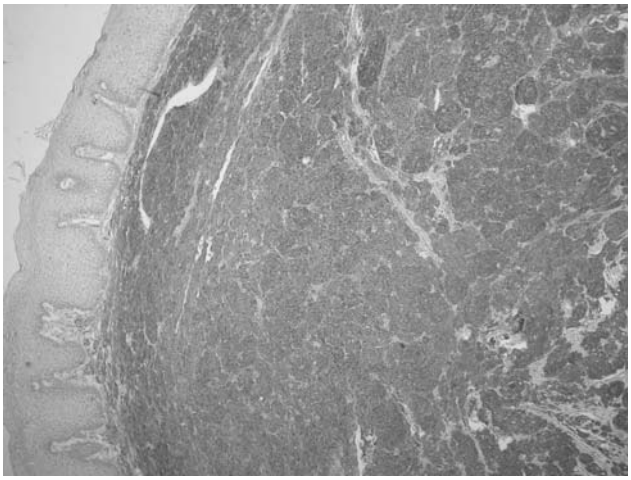

Figure 2. The cytoplasm of cells showing diffuse strong reactivity for S-100 (diaminobenzidine, x40).

en postulated as the origin of the tumor (6, 16, 17), theories of the non-neoplastic nature of the lesion, as in trauma and degenerative processes, as well as storage or metabolic disorders involving histiocytes have also been considered (4). However, recent studies support a peripheral nerve-related cell origin for the majority of these tumors based on the findings of cytoplasmic granules with numerous membrane-bound vacuoles containing myelin-like tubules, frequently reported "angulate bodies" found between granular cells having packets of microtubules also believed to be related to myelin, and close relation with pre-existent axons at the ultrastructural level (6, 16, 18-25). The expression of nestin in GCTs suggests that these tumors may arise from a common multipotential stem cell in the GI tract, which has the capability to differentiate along both interstitial cell of Cajal and peripheral nerve pathways (26).

The endoscopic appearance is often that of a small, usually less than 20 mm, yellowish-white, firm, sessile submucosal lesion covered by intact overlying mucosa, as in our cases. When the biopsies are taken too superficially, allowing only evaluation of the epithelium, the overlying hyperplastic squamous epithelium showing so-called "pseudoepitheliomatous hyperplasia" may lead to an erroneous diagnosis of a highly differentiated squamous cell carcinoma, prompting esophagectomy (8, 27, 28). In this regard, a Lugol staining technique, suggested for use by Tada et al. (29), could help to differentiate GCT from squamous cell carcinoma endoscopically.

Histologically, the tumor is composed of sheets or nests of plump, round or polygonal cells having abundant lightly amphophilic but strikingly granular cytoplasm with small, round, pyknotic central uniform nuclei (6). While neoplastic cells are mainly round or polygonal, areas of spindling can be observed, especially in colorectal GCTs (26). The most characteristic feature of these lesions is diffuse periodic acid-Schiff positivity even after diastase digestion of the cytoplasm. Mitoses are rare to absent and necrosis is not observed in these lesions. Since areas of spindling can be observed in a GCT, a pathologist can face difficulties in differentiating a spindle-cell lesion of the esophagus, especially on frozen section. In this regard, one of the most problematic entities that enters into the differential diagnosis of esophageal GCT is gastrointestinal stromal tumor (GIST), not only because it is composed of interlacing fascicles of spindle-shaped and plump epithelioid cells with abundant granular eosinophilic cytoplasm but also because GIST is one of the commonest esophageal mesenchymal tumors. The importance of differentiating GCT from GIST lies in the fact that GIST has an unpredictable behavior, whereas GCT is usually benign. Thus, pathologists should be aware that GIST might mimic GCT, particularly in frozen section (30).

Granular cell tumors show immunoreactivity for S-100 protein, vimentin, neuron-specific enolase, CD68, and CD57 (6, 22, 23, 31-33). Recently, Parfitt et al. (26) demonstrated expression of an intermediate filament protein called nestin (found normally in neuroectodermal stem cells and early skeletal muscle) in 100% of the seven GI tract GCTs, some of which were located in the esophagus. Inhibin-alpha was reported to be expressed consistently in GCTs of the gallbladder and extrahepatic biliary tree in a recent study conducted by Murakata and Ishak (34). However, Parfitt et al. (26) found this marker to be uniformly negative in their series consisting of esophageal, colorectal, and anal GCTs, explaining this discrepancy as a reflection of a site-specific phenomenon distinguishing GCTs of the biliary tree.

Granular cell tumors are generally benign neoplasms, with the malignancy rate estimated to be less than 2% of all lesions (6, 33). There are reports of cases that have recurred or metastasized despite having a benign histological appearance (6, 35). Although morphology can not reliably predict the biological behavior of GCTs, local recurrence, rapid growth to a size greater than 4 cm, and infiltrative pattern of growth should raise concerns about the possibility of malignancy (8, 35, 36). Multifocality does not seem to carry an increased risk of malignant behavior (25).

A general consensus about the management of esophageal GCTs has not yet been achieved. Surgical excision of the tumor has long been regarded as the treatment of choice (12, 14, 19, 37), and endoscopic biopsy of the tumor has not been advised by several authors because of the risk of bleeding, ulceration, fistula formation, secondary infection, subsequent interference with removal of the lesion without entering the mucosa at operation, and mistaken diagnosis of squamous cell carcinoma (37-40). The conclusion that most esophageal GCTs have a benign clinical course can be drawn from the relatively long-term follow-up of many cases. No evidence of recurrence has been obser-

ved in the patients who underwent surgical or endoscopic excision with a follow-up period ranging from 6 months to 5 years (4, 11, 15, 19, 25, 29, 41-47), and patients monitored without therapy for as long as 11 years have shown stable tumor size or even regression (8-10, 12, 14, 26, 48, 49). As a result, many authors recommend that small, asymptomatic lesions can be safely followed-up periodically with endoscopy, thus avoiding the potential complications of surgical procedures (8-10, 14, 15, 46, 47), whereas surgical or endoscopic excision should be restricted to those tumors producing symptoms of dysphagia, with size larger than 1 cm, rapid growth, transmural infiltration, or suspicion of malignancy (8-11, 14, 15, 47). However, for larger tumors, views concerning treatment have continued to evolve over the years with the introduction of new therapeutic options including laser (50), diathermy loop (51), and endoscopic resection (29,50,52). Despite the fact that laser treatment has been carried out successfully without adverse effects, it is an expensive technique that is not always available (50). Although diathermy loop is an effective procedure, it carries a high risk of perforation due to the submucosal localization of the tumors (51). Polidocanol injections into the tumors have been used for palliative treatment of GI tumors to achieve necrosis of the submucosal neoplastic cells (45). Excision by biopsy forceps or endoscopic polypectomy is a low-cost and more readily available procedure when compared with the laser technique, although it is not free of risk due to incomplete removal (29). Yasuda et al. (52) suggested that criteria for endoscopic removal of GCTs include small size (<20 mm) and non-attachment to the muscularis propria. When endoscopic resection is not possible or refused by the patient or in the case of a small lesion, follow-up with endoscopic ultrasonography could be considered (53).

In conclusion, GCT of the esophagus is being recognized with increasing frequency and, therefore, should be taken into consideration in the differential diagnosis of other more common esophageal lesions. These tumors can arise simultaneously and metachronously in various segments of the GI tract and can be associated with other neoplasms, particularly squamous cell carcinoma of the esophagus. Thus, non-excisable lesions should be closely followed-up, the entire GI tract should be examined even when only a solitary lesion is encountered, and the onset of new upper GI signs and symptoms in a patient with multiple GCTs should alert the physician for the presence of possible concomitant neoplasms. Lastly, nestin could be considered a useful immunohistochemical marker for identifying these tumors.

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