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# EDITORIAL
## *Granular cell tumor: What's new in diagnosis and treatment?*

Granüler hücreli tümör: Tanı ve tedavide yenilikler

*See articles on page 188-191 and 208-209*

Since the first description of granular cell tumors (GCT) by Abrikossoff in 1926 in the tongue (1), and a few years later in the esophagus (2), it has become obvious that they may occur at many sites, although they affect most frequently skin or subcutaneous tissues of the chest and upper extremities, tongue, breast, female genital organs and only rarely the gastrointestinal tract (3-6). Approximately 8% of all granular cell tumors (GCTs) occur in the gastrointestinal tract, the most common site being the esophagus followed by the large intestine (7). Over the years, more than 200 cases of esophageal GCTs have been published in the literature (8-15). Stomach localization, first described by Yasuda et al. (16) in 1995, is rarely seen, with approximately 20 cases reported, while duodenal localization is extremely rare (7, 17).

In the two papers by Hülagü et al. (18) and Bayan et al. (19), two esophageal GCTs were reported, and treatment choices in such cases were discussed.

Contrary to the previous view that a female predilection is observed for all GCTs (3), esophageal cases are encountered more frequently in men (8) in the fourth, fifth, and sixth decades of life (8-10). 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, as are both cases presented by Hülagü and Bayan, esophageal GCTs can be multiple in approximately 10% of cases, either in the esophagus alone or in other sites (7-9, 12). The majority of esophageal GCTs are asymptomatic, hence incidental tumors, while those patients with clinical symptoms due to esophageal lesion usually present with dysphagia; a minority of patients complain of substernal pain or regurgitation of food (8, 12). Both cases reported in the above-mentioned articles were symptomatic with epigastric pain or mild dysphagia.

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 observed in both Hülagü's and Bayan's cases. It can range from a plaque-like thickening of the mucosa to a nodular or polypoid mass, the shape of which is reminiscent of a molar on the gingiva (7). Hülagü et al. stated that endoscopic differential diagnosis should include esophageal cysts, inflammatory polyps, squamous papilloma and other submucosal tumors such as leiomyoma, lipoma, and hamartoma, by which they probably meant hamartomatous polyps. In their list, however, gastrointestinal stromal tumors (GISTs) should also be included as submucosal lesions, since they have an unpredictable and potentially malignant behavior in comparison to GCTs. The overlying hyperplastic squamous epithelium, so-called "pseudoepitheliomatous hyperplasia", may lead to an erroneous diagnosis of a squamous cell papilloma, as in the second case by Bayan et al., or to a highly differentiated squamous cell carcinoma prompting esophagectomy (20), particularly when the biopsies are too superficial (8, 21). In this regard, a Lugol staining technique (22) could help to differentiate GCT from squamous cell carcinoma endoscopically. However, no such technique was used in the case of Bayan et al., who mentioned the significance of differential diagnosis of GCTs from squamous cell carcinomas in their paper without further discussing "how".

Recently, endoscopic ultrasonography (EUS) has proven to be the procedure of choice for evaluation of upper GI submucosal lesions. By EUS, the location and extension of the tumor as well as its suitability for endoscopic resection can be determined. Although limited information is available regarding endosonographic features of esophageal GCTs, they appear mostly as hypo- echoic solid lesions of less than 3 cm with a mildly nonhomogeneous echo-pattern and smooth margins, arising

from the inner layers (second echo-poor or third echo-rich layer) of the esophageal wall. When endoscopic resection is not possible or refused by the patient or in the case of a small lesion, follow-up with EUS could be considered (23). If EUS shows that the tumor is located in the submucosa, not attached to the muscularis propria, endoscopic polypectomy could be attempted to allow histological diagnosis and treatment at the same time (22, 23). Endosonography was also used in Hülagü's case and proved to be helpful in the diagnosis by clearly demonstrating the margins so that the tumor could be excised using endoscopic submucosal dissection (ESD) technique.

Histologically, GCT is composed of sheets or nests of plump round or polygonal cells having abundant slightly amphophilic granular cytoplasm with small, round, centrally located uniform pyknotic nuclei (6). While neoplastic cells are mainly round or polygonal, areas composed of spindle cells can be observed, especially in colonic GCTs (24). The most characteristic feature of these lesions is that the cytoplasm of the neoplastic cells demonstrates globular and diffuse periodic acid-Schiff positivity, which remains after diastase digestion. Granular change seen in the cytoplasm has been interpreted by some authors as a degenerative phenomenon that might occur in non-neoplastic or neoplastic cells (7). Mitoses are rare to absent and necrosis is not observed in these lesions. The growth pattern varies with the age of the lesion; while the cells tend to form large nests surrounded by thin fibrous septae in younger lesions, the pattern of older lesions is characterized by marked desmoplasia with few scattered small nests of granular cells embedded in a dense collagenous stroma (4). In Hülagü's paper, histological features of the tumor were not described at all. It is also not clear whether any ancillary histopathological technique was used in the diagnosis and differential diagnosis of the lesion. In Bayan's paper, on the other hand, histopathological features were defined as "sheets of enlarged polygonal cells with granular cytoplasm" in the lamina propria of the esophagus. They also mentioned fibroblastic cells in the tumor tissue, which I believe are the mesenchymal cells forming the fibrous septae that are located between the nests or sheets of "granular cells". These fibroblastic cells are not a component of the tumor tissue (4). The authors also described the immunohistochemical profile of their tumor, which positively stained with S-100 protein and neuron-specific enolase (NSE) while it was negative with c-kit, SMA, desmin and myoglobin.

Granular cell tumors show immunoreactivity for S-100 protein, vimentin, NSE, CD68, and CD57 (6, 25-29). Recently, Parfitt et al. (24) demonstrated expression of an intermediate filament protein called nestin (found normally in neuroectodermal stem cells and early skeletal muscle) in GCTs, some of which were located in the esophagus (30). Thus, nestin might be regarded as a useful marker for identifying GCTs. 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 (31). However, Parfitt et al. (24) 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.

There is controversy concerning the histogenesis of GCTs, thus several synonyms have been used to describe this entity (32). Myoblasts, Schwann cells, histiocytes, perineural fibroblasts, and undifferentiated mesenchymal cells have been postulated as the origin of the tumor (6, 33), while theories of the non-neoplastic nature of the lesion resulting from trauma, as a degenerative process, or as a storage disorder involving histiocytes have also been considered (4). However, recent studies support a peripheral nerve-related cell of origin for the majority of these tumors based on the findings of cytoplasmic granules with numerous membrane-bound vacuoles containing myelin-like tubules and "angulate bodies" that show close relation with pre-existent axons at the ultrastructural level, found between granular cells (6, 25, 26, 32, 34-36). 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 (24). Although Hülagü et al. discussed the histogenesis of GCTs in their paper, it is difficult to relate these to the case that was presented in the paper since no histopathological detail was given.

Granular cell tumors are generally benign neoplasms, and malignancy rate is estimated to be less than 2% of all lesions (6). There are reports of cases that have recurred or metastasized despite having a benign histological appearance (6, 37). 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, 37-39). Multifocality does not seem to carry an increased risk of malignant behavior (17). Recently, Fanburg-Smith et al. (40) proposed histological criteria to define malignant GCTs of the soft tissue, including necrosis, spindling of the tumor cells, vesicular nuclei with large nucleoli, increased mitotic activity (>2 mitoses/10 high power fields at x200 magnification), a high nuclear to cytoplasmic ratio, and pleomorphism. They classified GCTs that satisfied three or more of these criteria as histologically malignant, whereas a tumor demonstrating only focal pleomorphism was classified as benign. These authors also noted that a positivity rate of more than 50% for p53 and a Ki67 index of more than 10% significantly correlated with malignancy (40).

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, 41-43), whereas surgical or endoscopic excision should be restricted to the tumors producing symptoms of dysphagia, larger than 1 cm, demonstrating rapid growth, having transmural infiltration, or suspected of malignancy (8-11, 14, 15, 44). However, for larger tumors, the views concerning treatment have been changing over the years with the introduction of new therapeutic options including laser, diathermy loop (45), and endoscopic resection (16, 22, 45).

Endoscopic mucosal resection (EMR) and ESD have been introduced to the literature by the Japanese gastroenterologists (46) in the treatment of early gastric cancer. In the first case, Hülagü et al. performed ESD for their tumor, which was located in the submucosa. By means of chromoendoscopy using Lugol solution, the margins were depicted and the lesion was excised successfully, whereas the second case was a polypoid tumor and was easily resected by polypectomy during endoscopy. Hülagü et al. stated that ESD was the treatment of choice since their lesion was located in the submucosa with free margins as demonstrated by EUS. They also added that both EMR and ESD had some advantages over tissue-destroying therapies such as laser and diathermy loop, since they allowed histopathologic evaluation of the tissue.

Since most of the esophageal GCTs are asymptomatic and benign, the most cost effective approach in the management of these tumors seems to remain conservative with endoscopic follow-up after the initial diagnosis. Surgical or endoscopic excision should be restricted to symptomatic patients with larger tumors or to those with tumors demonstrating rapid growth, having transmural infiltration, or suspected of malignancy. When GCT of the esophagus is suspected, it should be kept in mind that EUS is valuable to assess the exact location and extent of the tumor and to determine the indication for endoscopic polypectomy, EMR or ESD. Though the majority of GCTs have a characteristic histology, a thorough differential diagnosis should be made using histochemistry as well as immunohistochemistry in order to differentiate these tumors from other more aggressive tumors of the esophagus.

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