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【 ORIGINAL ARTICLE 】

Esophageal Granular Cell Tumors Can Be Differentiated from Leiomyomas Using Endoscopic Ultrasonography

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Abstract:

Objective Although esophageal granular cell tumors have been reported to present as hypoechoic tumors, we noticed that their echogenicity is similar to that of the submucosal layer. We investigated the sonographic features of esophageal granular cell tumors and the diagnostic accuracy of the features.

Methods Seven patients with esophageal granular cell tumors who underwent endoscopic ultrasonography were retrospectively reviewed. Thirteen patients with esophageal leiomyoma were selected as historical control subjects. The brightness of the tumor on ultrasonography images was measured and the echogenicity was standardized according to the echogenicity of the proper muscle and submucosal layers. Ten board-certified endoscopists then independently evaluated the endoscopic pictures of the 20 patients (Test 1), as well as the endoscopic ultrasonography images together with endoscopic pictures of the same patient set (Test 2).

Results The standardized echogenicity in granular cell tumors was significantly higher than that in leiomyomas. The diagnostic accuracy of the 10 evaluators using endoscopic pictures alone (Test 1) was 72.0%. The addition of endoscopic ultrasonography images (Test 2) significantly improved the accuracy to 93.0%.

Conclusion The echogenicity of granular cell tumors was similar to that of the submucosal layer, and it was significantly higher than that of leiomyomas. Endoscopic ultrasonography images facilitate the accurate identification of esophageal granular cell tumors.

Key words: granular cell tumor, esophageal neoplasms, leiomyoma, endoscopic ultrasonography, subepithelial tumor

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Introduction

Leiomyomas are the most common subepithelial tumors in the esophagus (1). These benign soft tissue neoplasms arise from smooth muscle. Thus, esophageal leiomyomas generally remain untreated and are often simply followed up. The prevalence of granular cell tumors (soft tissue neoplasms that originate in the Schwann cells of the nerve sheath) in the esophagus is lower than that of leiomyomas (2). Although most esophageal granular cell tumors are benign, 1.5-2.7% are considered to be malignant (3). Thus, some gastroenterologists suggest the resection of all esophageal granular cell tumors (4). Consequently, distinguishing esophageal granular cell tumors from leiomyomas is essential for establishing appropriate follow-up and treatment strategies for esophageal subepithelial tumors.

Endoscopic ultrasonography is a key procedure in the diagnosis of subepithelial tumors in the alimentary tract. It visualizes the location within the gastrointestinal wall and the exact size of the tumor. Information on the internal echogenicity of the lesion (*i.e.,* whether it is hyperechoic or hypoechoic, or homogeneous or heterogeneous) facilitates the characterization of subepithelial tumors. Typical esophageal granular cell tumors have been known to be hypoechoic and homogeneous on endoscopic ultrasonography (5). Thus, many authors have reported that granular cell tumors and leiomyomas cannot be differentiated using endoscopic ultra-

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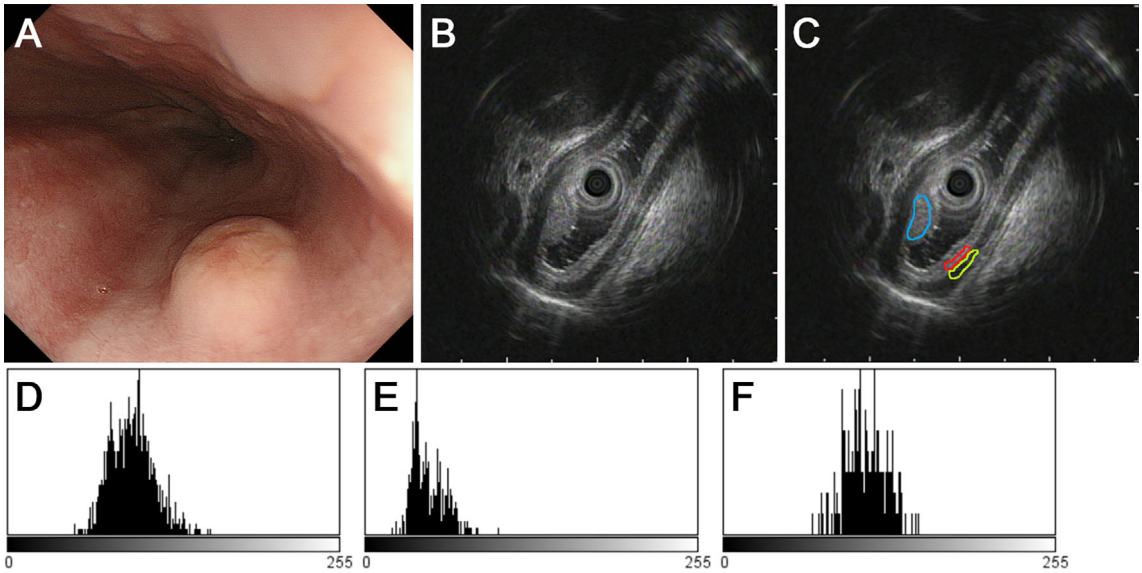

Figure 1. An example of the calculation of the standardized echogenicity index of a granular cell tumor (A). In a representative ultrasonography image (B), the tumor was manually encircled (C, blue circle). The mean brightness value of the tumor (bT) was automatically calculated using the Image J software program (D). The mean brightness values of the proper muscle layer (bPM) (C, yellow circle and E) and submucosal layer (bSM) (C, red circle and F) were obtained as well. The standardized echogenicity index was calculated by dividing (bT-bPM) by (bSM-bPM).

sonography (3). However, we noticed that the echogenicity of esophageal granular cell tumors is similar to that of the submucosal layer and are observed as hyperechoic-rather than hypoechoic-lesions. Based on this feature, we hypothesized that esophageal granular cell tumors can be differentiated from leiomyomas using endoscopic ultrasonography. We investigated the endoscopic and sonographic features of esophageal granular cell tumors as well as the diagnostic accuracy of endoscopic ultrasonography.

Materials and Methods

A database search performed at our hospital's Department of Pathology identified nine patients with granular cell tumors in the esophagus who were diagnosed at our hospital between January 2006 and December 2016. The histological diagnosis was established based on morphologic and immunophenotypic analyses of endoscopically or surgically biopsied specimens or resected specimens. Two of the nine patients were excluded from this study because they had not undergone endoscopic ultrasonography. Thus, seven cases were analyzed in the present study. We used the patients' clinical records to analyze the data from their endoscopic, radiological, biological, and pathological examinations.

Historical control subjects for the leiomyoma group were selected from the database of the Department of Endoscopy. The principal investigator of this study (M. I.) randomly selected patients who were diagnosed with esophageal leiomyoma based on the pathological analysis of endoscopically or surgically biopsied specimens or resected specimens and who had undergone endoscopic ultrasonography. Finally, the leiomyoma group was formed by sampling 13 cases. Because the cases enrolled in this study were diagnosed over a 10-year period, the type of endoscopic ultrasonography equipment that was used and the settings of the equipment (*i.e.,* gain and contrast) varied among the patients. To overcome this issue, we used a standardized echogenicity index to judge whether the echogenicity of the tumor in question was similar to that of the proper muscle layer or the submucosal layer. The brightness of the tumor on ultrasonography images was measured using the Image J software program (National Institutes of Health, Bethesda, USA). First, the principal investigator (M. I.) selected a representative ultrasonography image (Fig. 1A and B) and manually encircled the tumor in the Image J software program (Fig. 1C). The mean brightness value of the tumor (bT) was calculated automatically (Fig. 1D). Second, the mean brightness values of the proper muscle layer (bPM) and the submucosal layer (bSM) were determined on the same ultrasonography image (Fig. 1E and F). The principal investigator attempted to select areas of the proper muscle and submucosal layers, in order that the distance between the probe and the selected areas was equal to the distance between the ultrasound probe and the tumor. The widths of the selected areas of the proper muscle and submucosal layers were as close (in length) to those of the tumor as possible. The standardized echogenicity index was calculated by dividing (bT - bPM) by (bSM - bPM). For this index, a value around 1 indicates an echogenicity similar to that of the submucosal layer and a value around 0 indicates an echogenicity similar to that of the proper muscle layer.

Ten board-certified endoscopists independently evaluated

Table. The Characteristics of the Patients with Esophageal Granular Cell Tumors and Patients with Leiomyomas (Control Subjects).

	Granular cell tumor	Leiomyoma	p value
Sex			
Male	4	6	1.000
Female	3	7	
Age (years, mean±SD)	46.3±5.5	55.2±13.4	0.115
Number of tumors			
Solitary	7	11	0.521
Multiple	0	2	
Location			
Upper esophagus	0	3	0.005*
Middle esophagus	0	6	
Lower esophagus	7	4	
Color			
Whitish	6	9	0.249†
Partly whitish	1	0	
Similar to that of the intact mucosa	0	4	
Size (mm, mean±SD)	6.6±2.1	9.5±4.4	0.120
Echogenicity			
Similar to that of the submucosal layer	7	0	<0.001
Similar to that of the proper muscle layer	0	13	

*Upper and middle esophagus vs. lower esophagus.

†Whitish and partly whitish lesions vs. lesions with a color similar to that of the intact mucosa.

the endoscopic pictures of the 20 patients with esophageal granular cell tumors or leiomyomas (Test 1). All of the evaluators were blinded to the patient information, including the age, sex, chief complaint, and the CT results. Furthermore, the numbers of patients with esophageal granular cell tumors and leiomyomas were not disclosed. Discussions were not permitted individually or in groups. Pictures were distributed to each evaluator in a randomized order. The evaluators judged whether the esophageal lesion was a granular cell tumor or leiomyoma. Subsequently, the 10 board-certified endoscopists evaluated the endoscopic ultrasonography images together with endoscopic pictures of the same patient set (Test 2). The evaluators determined whether the esophageal lesion was a granular cell tumor or leiomyoma again. During Test 2, the standardized echogenicity index of the tumor was not disclosed to the evaluators. Prior to Test 2, the principal investigator (M. I.) advised the evaluators to simply judge tumors according to the grayscale values of the tumor: specifically, a tumor with an echogenicity similar to that of the submucosal layer was judged to be a granular cell tumor, and a tumor with an echogenicity similar to that of the proper muscle layer was judged to be a leiomyoma. The usefulness of endoscopic ultrasonography in the clinical diagnosis of esophageal granular cell tumors was analyzed by comparing the diagnostic accuracy of Tests 1 and 2.

The results were analyzed using *t*-tests, chi-squared tests, and F-tests. These statistical analyses were performed using the JMP software program (version 12.0.1, SAS Institute, Cary, USA). p values of <0.05 were considered to indicate statistical significance. We used Fleiss' kappa to test inter-rater reliability in Tests 1 and 2. The Fleiss' kappa values were determined using the R software program (version 3.4.1, R Foundation for Statistical Computing, Vienna, Austria). The study design was approved by the ethics committee of our institution (No. 1703-045) and was in accordance with the Declaration of Helsinki.

Results

The backgrounds of the patients with esophageal granular cell tumors are summarized in Table. There were four men and three women. The mean age ± standard deviation (SD) at the time of the diagnosis of esophageal granular cell tumor was 46.3±5.5 years. Granular cell tumors presented as a single lesion and were located in the lower esophagus in all cases. The tumor size ranged from 5 to 11 mm (mean ± SD: 6.6±2.1 mm). The color of the lesion was whitish in six cases. In the remaining patients, the color was mostly similar to the surrounding esophageal mucosa, but was partly whitish (Fig. 2). On endoscopic ultrasonography, the echogenicity of the tumor was closer to that of the submucosal layer, rather than that of the proper muscle layer.

Scatterplot graphs of the standardized echogenicity index of the granular cell tumor and leiomyoma groups are shown in Fig. 3. The mean value ± SD of the standardized echogenicity index was 0.95±0.23 for granular cell tumors, and -0.17±0.26 for leiomyomas. The difference between the two groups was statistically significant.

The results of the assessment of endoscopic pictures with

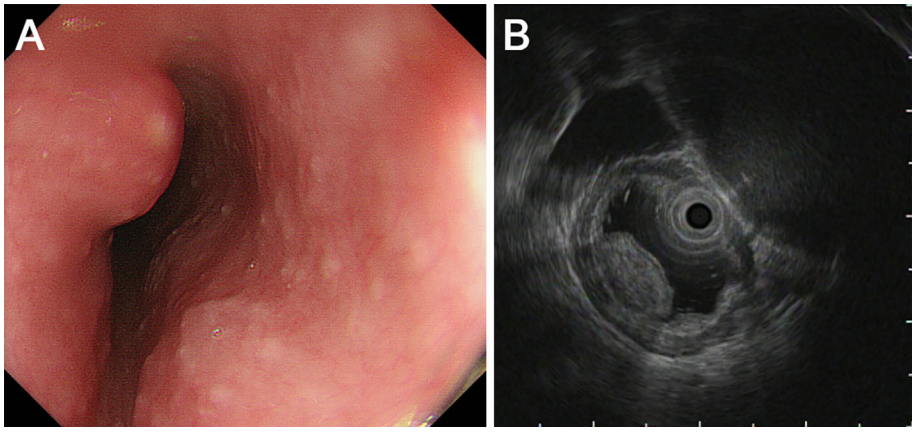

Figure 2. **A granular cell tumor. The color was mostly similar to the surrounding esophageal mucosa, but was partly whitish (A). The echogenicity of the tumor was similar to that of the submucosal layer (B).**

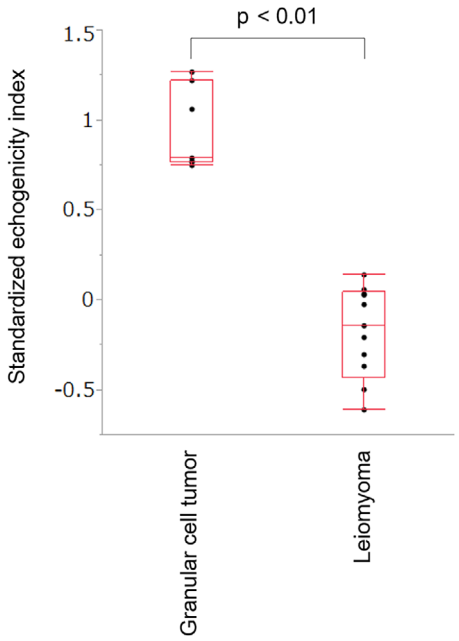

Figure 3. **Scatterplot graphs of the standardized echogenicity index. A value of around 1 indicates echogenicity similar to that of the submucosal layer and a value of around 0 indicates echogenicity similar to that of the proper muscle layer.**

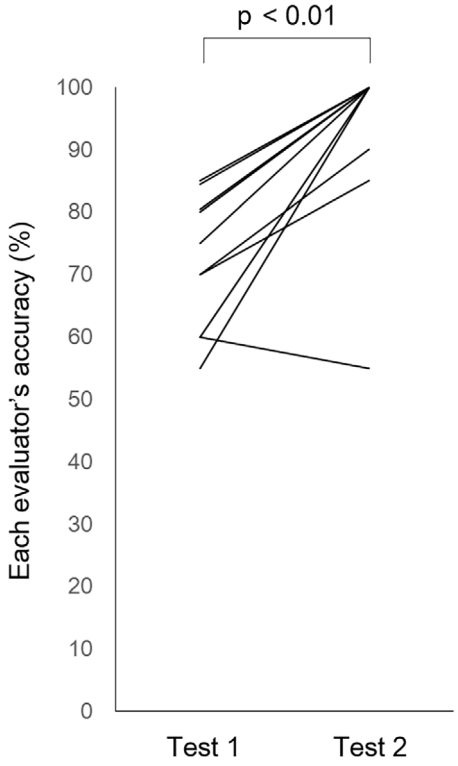

Figure 4. **The results of the assessments of the endoscopic images without ultrasonography images (Test 1), and the endoscopic ultrasonography images (Test 2). The assessments were made by 10 board-certified endoscopists.**

or without ultrasonography images by the 10 board-certified endoscopists are shown in Fig. 4. Each evaluator's accuracy ranged from 55% to 85% in Test 1, and from 55% to 100% in Test 2. The Fleiss' kappa values in Tests 1 and 2 were 0.458 and 0.740, respectively. The addition of the ultrasonography images improved the diagnostic accuracy in determining whether a tumor was a granular cell tumor or leiomyoma for 9 of the 10 evaluators. Notably, seven evaluators (70%) achieved 100% accuracy in Test 2. The difference in the diagnostic accuracy between Tests 1 (mean ± SD: 72.0±10.9%) and 2 (93.0±14.4%) was statistically significant. Figs. 2 and 5 show cases in which the percentage of correct answers was low. Fig. 2 shows a granular cell tumor that 9 evaluators misdiagnosed as a leiomyoma based on endoscopic pictures alone. Thus, the diagnostic accuracy was 10% in Test 1. In Test 2, in which endoscopic ultrasonography images were accompanied by endoscopic pictures, the same tumor was correctly diagnosed by all of the evaluators. Fig. 5A shows a small granular cell tumor, which was correctly diagnosed by three evaluators in Test 1, resulting in 30% accuracy. The addition of endoscopic ultrasonography images (Fig. 5B) improved the accuracy to 100%. Fig. 5C shows an esophageal leiomyoma with a mo-

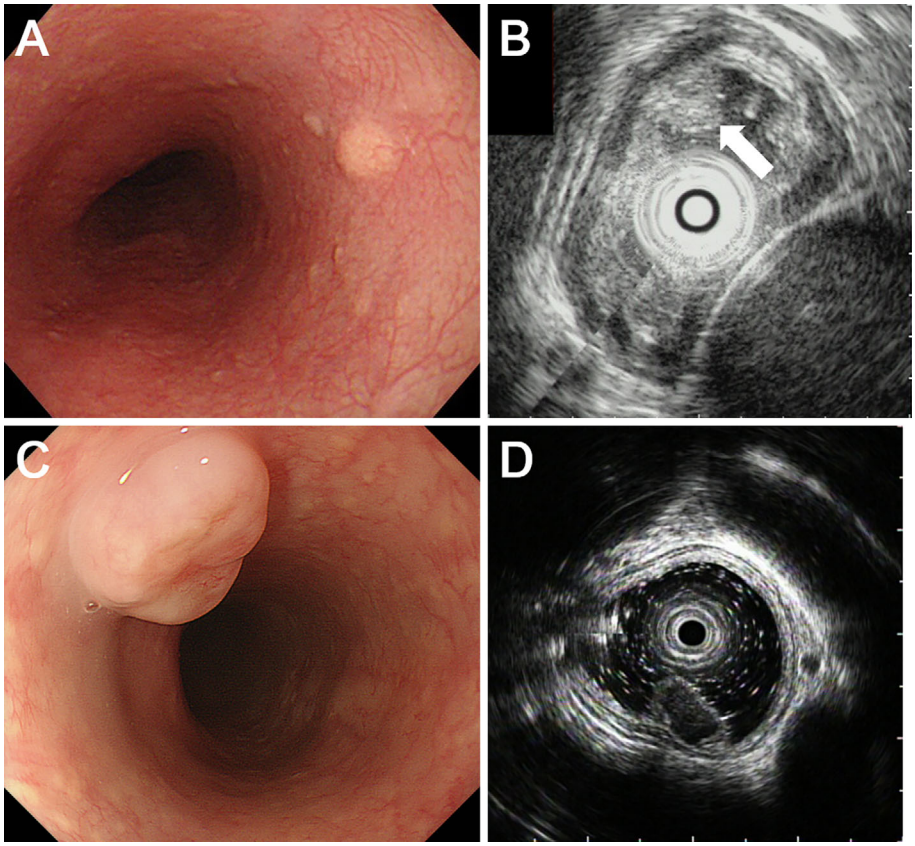

Figure 5. **Representative cases for which the percentage of correct answers on Test 1 was low. The diagnostic accuracy for a small granular cell tumor (A, B) was 30% on Test 1 and 100% on Test 2. The diagnostic accuracy for an esophageal leiomyoma with a molar tooth-like appearance (C, D) was 10% on Test 1 and 100% on Test 2.**

lar tooth-like appearance. In Test 1, the accuracy of the evaluators was 10%. Endoscopic ultrasonography images, which showed a hypoechoic tumor (Fig. 5D), improved the diagnostic accuracy to 100% in Test 2.

Discussion

In the present study, esophageal granular cell tumors presented as solitary lesions in the lower esophagus. The size of the tumors ranged from 5 mm to 11 mm in diameter. Generally, esophageal granular cell tumors are found as solitary lesions; up to 11% of cases have multiple esophageal lesions (2, 6). The tumor size is <2 cm in 95% of cases (7). These tumors are most frequently found in the lower esophagus (50 to 65%), followed by the proximal (15 to 40%) and middle esophagus (20%) (3). These characteristics are compatible with our results. Although the color of the lesion was whitish in all but one case in the present study, various colors have been reported, including white-gray, pink, and yellow (4). Morphologically, some granular cell tumors bear a resemblance to an erupting molar tooth (8-10). However, esophageal granular cell tumors cannot be diagnosed based on morphology alone since they are often identified as non-specific, hemispherical submucosal tumors. Moreover, leiomyomas, in rare instances, present with a molar tooth-like appearance (Fig. 5C).

To our knowledge, this study is the first to reveal that esophageal granular cell tumors can be differentiated from leiomyomas using endoscopic ultrasonography. We investigated the diagnostic value of endoscopic ultrasonography in differentiating esophageal granular cell tumors from leiomyomas. As described previously, most researchers have described granular cell tumors as "hypoechoic lesions" (3, 5) and have reported that it is impossible to differentiate granular cell tumors from leiomyomas. Meanwhile, a few articles have mentioned that the brightness values of granular cell tumors are higher than those of esophageal leiomyoma (2, 5, 11, 12). We consider that such inconsistency regarding the echogenicity of esophageal granular cell tumors is a result of the vagueness surrounding the term "hypoechoic". This term is a relative expression that indicates an echogenicity that is weaker or lower than normal in the surrounding regions. Thus, the term "hypoechoic lesion" encompasses tumors that display echogenicity that is considered to be quite low, as well as those that display echogenicity that is only slightly low. Another concern is that brightness values of the lesion vary according to the gain settings of the ultrasound machine. To overcome these issues and objectively express the echogenicity of the lesion, we used a standardized echogenicity index. The analysis of the

indexes revealed that the brightness values of the granular cell tumors were similar to the brightness values of the submucosal layer, while leiomyomas showed similar brightness values to the proper muscle layer. As shown in Fig. 3, some granular cell tumors showed lower echogenicity than the submucosal layer; nevertheless, the brightness value was closer to that of the submucosal layer than to that of the proper muscle layer.

The diagnostic criteria, which were based on the echogenicity of the tumor, were useful for evaluators to differentiate esophageal granular cell tumors from leiomyomas. On Test 2, the evaluators simply judged tumors based on the grayscale values of the tumor: a tumor with echogenicity similar to the submucosal layer was diagnosed as a granular cell tumor, and a tumor with echogenicity similar to the proper muscle layer was diagnosed as a leiomyoma. We consider these simple criteria, which are based on a visual observation by an endoscopist, to be convenient and useful, since they significantly improved diagnostic accuracy. Although one evaluator showed worse accuracy on Test 2 than on Test 1, the evaluator confessed that he did not understand the criteria before taking the tests. The concordance rates of the standardized echogenicity index and the simple method of visual observation should be investigated in future studies. Another advantage of the diagnostic criteria is that they could reduce the influence of the type of equipment used to perform endoscopic ultrasonography and the settings of the equipment (*i.e.,* gain and contrast) because the tumor was diagnosed based on the similarity of the echogenicity to that of the proper muscle or submucosal layers, rather than the absolute value of the tumor echogenicity. We expect that the diagnostic criteria used in this study will be applicable in all institutions.

The management of esophageal granular cell tumors and indications for their treatment are controversial. Since malignant degeneration has been reported in 1-2% of the cases (12), some gastroenterologists recommend endoscopic resection for all esophageal granular cell tumors, as described previously (4). Others state that the management strategy should vary according to their size. For example, several authors have suggested conservative endoscopic follow-up for tumors of <1 cm in size in asymptomatic cases and endoscopic removal for tumors of >1 cm or symptomatic cases (2, 3). Although surgical excision has been performed for esophageal granular cell tumors of >20 mm in size, it has recently become possible to resect such large tumors by endoscopic submucosal dissection or submucosal tunnel endoscopic resection (2). Irrespective of the management strategy, it is essential to be able to make an accurate preoperative diagnosis of subepithelial tumors. In this context, we believe that endoscopic ultrasonography is useful for the prompt identification of granular cell tumors.

The present study is associated with several limitations. First, this was a retrospective study involving a small number of patients. Although all granular cell tumors had similar brightness values to those of the submucosal layer in this study, the echogenicity in other cases might vary, as granular cell tumors have been reported to appear as hypoechoic lesions in the majority of previous reports. Second, the endoscopic images and control cases with esophageal leiomyomas that were presented to evaluators were selected by a principal investigator. Thus, biases might have existed in the selection process. In particular, although the tumor sizes of the two groups did not differ to a statistically significant extent, the granular cell tumors were smaller than the leiomyomas. The smaller tumor size might have hampered the ability of the evaluators to make an accurate diagnosis based on the observation of endoscopic pictures alone. Nevertheless, the endoscopic ultrasonography images improved the diagnostic accuracy; thus, endoscopic ultrasonography may be useful in the identification of granular cell tumors, even those of a smaller size. Prospective studies are required in order to confirm the features of esophageal granular cell tumors on endoscopic ultrasonography images and to confirm the applicability of the use of the diagnostic criteria proposed in this paper.

In conclusion, the brightness of granular cell tumors on ultrasonography was similar to that of the submucosal layer, and it was significantly higher in comparison to leiomyomas. These endosonographic features helped the evaluators distinguish between esophageal granular cell tumors and leiomyomas, which led to an improvement of diagnostic accuracy. We consider endoscopic ultrasonography images to be a great aid in diagnosing esophageal granular cell tumors.

The authors state that they have no Conflict of Interest (COI).

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