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ORIGINAL ARTICLE

Endoscopic Ultrasound and Fine Needle Aspiration in Chronic Pancreatitis: Differential Diagnosis between Pseudotumoral Masses and Pancreatic Cancer

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ABSTRACT

Context Pseudotumoral chronic pancreatitis can be difficult to differentiate from pancreatic carcinoma.

Objective To evaluate the role of endoscopic ultrasound and fine needle aspiration in differentiating between inflammatory masses and malignancies in chronic pancreatitis.

Design Retrospective study.

Setting Tertiary care endoscopy unit.

Patients and interventions Between February 1997 and December 2006, 69 pancreatic head masses from patients with alcoholic chronic pancreatitis underwent EUS-FNA using a linear echoendoscope and 22-gauge needles. Final diagnoses were obtained from surgery or clinical follow-up. The patients were subdivided into two groups: pseudotumoral chronic pancreatitis and pancreatic cancer.

Results Pseudotumoral masses and adenocarcinoma were found in 58 and 11 patients, respectively. The size of the lesions and the clinical presentation were similar in both groups, but the cancer patients were older than the patients with pseudotumoral masses (P=0.020). Fourteen of the 58 (24.1%) pseudotumoral masses were misdiagnosed as cancers, and 4 of the 11 (36.4%) cancers were erroneously diagnosed as pseudotumoral masses when evaluated by EUS alone. EUS-FNA confirmed the final diagnosis in 66 of the 69 (95.7%) cases. Cytopathology correctly classified 8 of the 11 (72.7%) malignancies and all benign cases. Three of the 11 (27.3%) cancers were misdiagnosed as pseudotumoral masses, and no pseudotumoral mass was diagnosed as a cancer. In two cases, the specimens were inadequate for cyto-pathological assessment. The sensitivity, specificity, positive and negative predictive values, and the diagnostic accuracy of EUS-FNA were 72.7%, 100%, 100%, 95.1% and 95.7%, respectively.

Conclusions The diagnostic accuracy of endoscopic ultrasound alone for differentiating between pseudotumoral masses and pancreatic cancer arising from chronic pancreatitis is unsatisfactory. Fine needle aspiration of these tumors significantly improves diagnostic capability.

INTRODUCTION

Pseudotumoral masses can be a consequence of chronic pancreatitis [1]. A differential diagnosis between pseudotumoral masses and pancreatic carcinoma can be challenging in clinical practice because of very similar imaging features [1, 2, 3, 4] and clinical

presentation [2, 5]. To date, there is no ideal diagnostic approach for differentiating between pancreatic cancer and pseudotumoral chronic pancreatitis [3, 6, 7]. Up to 6% of the cases suspected to be malignant were found to be benign at surgery; this is associated with a post-surgical complication rate of up to 21% of these cases [2].

Endoscopic ultrasound (EUS) has become the most accurate modality for the characterization, locoregional staging and sampling of pancreatic lesions [1, 8, 9, 10]. However, there is no consensus about the value of this method in the diagnosis of chronic pancreatitis or in the differential diagnosis between inflammatory masses and carcinomas in chronic pancreatitis [11, 12]. At this point, EUS-guided fine needle aspiration (EUS-FNA) of the pancreatic masses might confirm the nature of the lesion and, as a consequence, establish the best therapeutic approach for these patients [13].

The aim of this study was to evaluate the value of EUS and EUS-FNA as tools for the differential diagnosis between pancreatic cancer and pseudotumoral masses in alcoholic chronic pancreatitis based on morphologic features and cytopathological assessment.

PATIENTS AND METHODS

Demographic Features

Between February 1997 and December 2006, 69 patients (54 men, 15 women; mean age: 58.1 years, range: 34-84 years) with alcoholic chronic pancreatitis and pancreatic head masses underwent EUS-FNA because of suspected pancreatic cancer. The diagnosis of chronic pancreatitis was based on imaging tests (CT and/or ERCP) and clinical history: chronic excessive alcohol use (mean consumption: 176 g/day for no less than 5 years), abdominal pain (68 cases, 98.6%), weight loss (34 cases, 49.3%), jaundice (31 cases, 44.9%), and relapsing acute pancreatitis (10 cases, 14.5%). A CT scan was performed in all patients prior to EUS, and ERCP was done in the 31 cases with jaundice. ERCP detected morphological changes in 28 (90.3%) patients: 18 had ductal changes suggestive of chronic pancreatitis and 10 had a double stenosis (common bile and main pancreatic ducts).

EUS Examination and Fine Needle Aspiration

EUS was carried out by the same endosonographer (JCA) using a linear echoendoscope (FG 38-UX; Pentax Precision Instruments Corp., Orangeburg, NY, USA) connected to an ultrasound plataform (Hitachi EUB 515A, Mitsubishi, Conshockon, Philadelphia, PA, USA). EUS-FNA was performed by using a 22-gauge, 8 cm shot gun aspiration needle (NA-10J-1KB, Olympus Optical Co., Tokyo, Japan) under conscious sedation with propofol and cardiorespiratory monitoring. EUS-FNA was performed via a transduodenal approach for all lesions. For each puncture, the lesion was aspirated with 6 to-and-fro movements of the needle using continuous aspiration applied through a 20 mL syringe. A cytopathologist was not present during the procedures. The following EUS features were assessed: topography and size of the mass, texture, echogenicity, borders (well-defined or not), lobularity, hyperechogenic septa, calcifications, pseudocysts and intraductal stones. Pseudotumoral chronic pancreatitis was suspected in the presence of a homogenous hypoechoic/isoechoic lobular area with well-defined borders and positive

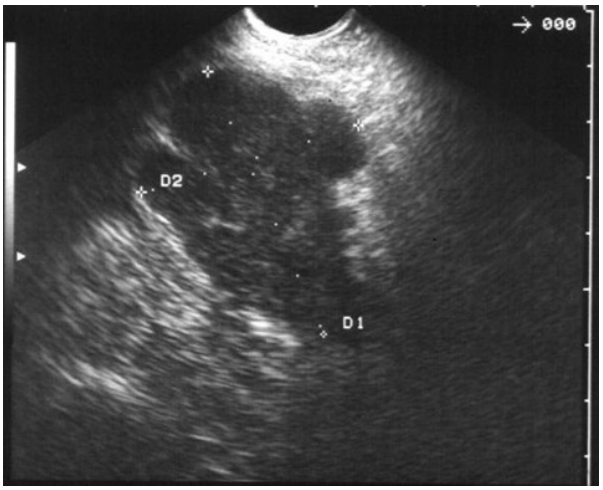

Figure 1. A 71-year-old woman with abdominal pain and jaundice. CT and EUS detected a mass in the pancreatic head. Note the lobularity. Cytopathology diagnosed chronic pancreatitis, confirmed by surgery.

power Doppler signals (Figure 1) [13]. Pancreatic cancer was defined as a hypoechoic heterogeneous mass with imprecise borders and the absence of power Doppler signals inside the mass (Figure 2) [14].

Cytopathological Assessment

All cytological samples were processed as cell blocks and were interpreted by the same experienced cytopathologist (FV). The specimens were considered satisfactory in the presence of several non-hemorrhagic small tissue filaments or even tissue core samples. The number of passes of the needle until satisfactory specimens were obtained was documented in each case. Briefly, once aspirated, the material was fixed in buffered formalin, underwent centrifugation, and was immersed in liquid agarose. Once solidified, the agar cone with the cells in the top was embedded in paraffin to be handled as a routine tissue block. On reviewing the slides, cellularity, presence of loosely cohesive aggregates or single tumor cells, quality and quantity of cytoplasm, nuclear pleomorphism, chromatin patterns, nucleus to cytoplasm ratio and necrosis were systematically analysed.

Follow-up

EUS images and cytopathological findings from EUS-FNA specimens were compared to the final diagnoses obtained either from surgical resection for diagnostic or palliative reasons in 25 patients (36.2%), or after a mean clinical follow-up of 35 months (range: 2 to 52 months) in 44 patients (63.8%). For the latter group, the data were obtained by means of telephone calls to the general practitioners, the patients or their close relatives as well as from medical records. A computed tomography was scheduled every 6 months to assess the stability or progression of the lesions. During follow-up, the clinical criteria used when pseudotumoral masses were suspected were: a) the improvement of the general clinical condition after medical treatment, together with weight gain and decrease of lesion size on CT; b) ultrasonographic findings suggestive of a pseudotumoral mass, such as isoechoic mass, lobulated, with well-defined borders, and positive power Doppler signals; c) a decrease of CA 19-9 serum levels. A malignancy was suspected in the absence of these criteria.

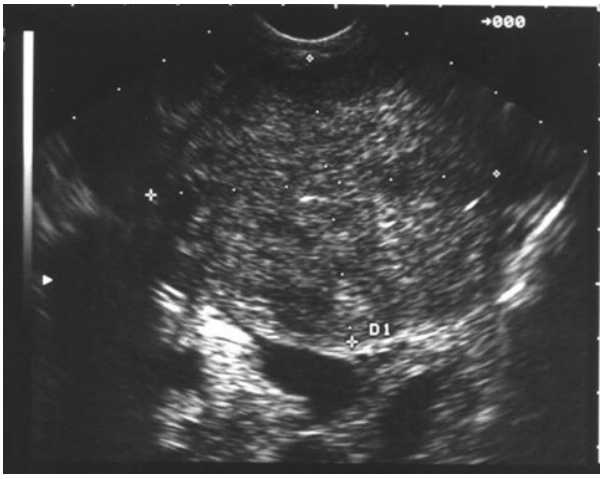

Figure 2. A 53-year-old man with chronic pancreatitis. CT detected a mass in the pancreatic head. EUS showed a 6.5 cm hypoechogenic and heterogeneous mass, with imprecise borders. FNA confirmed adenocarcinoma.

ETHICS

This study was approved by the Institutional Review Committee of the '9 de Julho Hospital' in accordance with the ethical guidelines of the World Medical Association Declaration of Helsinki. Written informed consent was obtained from each patient.

STATISTICS

Continuous variables were expressed as mean values and ranges, and comparative analysis between them were performed by Mann-Whitney test. Categorical data were expressed using absolute frequencies and percentages (together with the 95% CI [15]) and were analyzed by the Fischer's exact and the McNemar tests. Sensitivity, specificity, positive and negative predictive values, and cases correctly classified were calculated. Data were analyzed by means of the SPSS 10.0 (SPSS Inc., Chicago, IL, USA). The significance level was two-tailed P value less than 0.05 for all statistical procedures.

RESULTS

Final Diagnosis

The final diagnosis was a pseudotumoral mass in 58 patients (84.1%) and an adenocarcinoma in the remaining 11 cases (15.9%).

Surgery *vs*. Clinical Follow-up

Of the 58 benign cases at final diagnosis, surgery was carried out in 20 cases (34.5%) which were highly suspicious (clinical, imaging and laboratorial findings) for adenocarcinoma, including two patients without adequate cytopathological specimens. However, no cancer was confirmed by surgery. Five of these cases (25.0%) died within four weeks after the surgical intervention. The remaining 38 benign cases (65.5%) were followed up until the conclusion of the study, and five cases (13.2%) died from reasons not related to pancreatic disease.

Specifically, for the 11 malignancies, five of these cases (45.5%) underwent surgical resection, with adenocarcinoma and pseudotumoral masses were diagnosed prior to surgery in three and two cases, respectively. These latter two cases underwent surgery due to the pronounced clinical suspicion of neoplasia, which was confirmed by surgical findings. In the remaining six cases which were followed up (54.5%), EUS detected advanced malignancy in five cases (83.3%), all of them confirmed by EUS-FNA (vascular invasion, n=4; liver metastases, n=3; retroperitoneal involvement, n=2; inter-aortico-cava lymphadenopathies, n=1). In a single case, EUS-FNA revealed chronic pancreatitis but, eight months later, the patient showed several liver metastases on CT, although EUS had not detected any new pancreatic morphological changes in relation to the previous procedure. A new EUS-FNA of the left lobe of the liver detected an adenocarcinoma. All cases with an adenocarcinoma died before the end of this study.

EUS Findings

EUS detected pancreatic morphological changes in 68 (98.6%) patients. Only one case (1.4%) had no morphological evidence of pancreatic disease. The mean size of the lesions was 3 cm (range: 0.6-6.5 cm). EUS imaging alone found 48 (69.5%) pseudotumoral masses and 21 (30.4%) pancreatic cancers. Fourteen (24.1%) of the 58 pseudotumoral masses were misdiagnosed as cancers, and 4 of the 11 (36.3%) cancers were erroneously diagnosed as pseudotumoral masses.

Sensitivity, specificity, positive and negative predictive values, and the diagnostic accuracy of the EUS images in the differential diagnosis between pancreatic cancer and pseudotumoral chronic pancreatitis are depicted in Table 1.

EUS-FNA Findings

Aspiration samples were successfully collected in 68 (98.6%) patients after an average of 2.4 passes (range: 1-4). EUS-FNA was unsuccessful in one patient (1.4%) due to the very hard consistency of the lesion. In this particular case, EUS suggested chronic pancreatitis, which was confirmed by surgery. Pseudotumoral chronic pancreatitis and

Table 1. Sensitivity, specificity, positive and negative predictive values, and cases correctly classified by EUS and EUS-FNA in the diagnosis of pancreatic tumors in chronic pancreatitis (No.=69).

	EUS	EUS-FNA	P value
Sensitivity	7/11 (63.6%; 95% CI: 35.2-92.1%)	8/11 (72.7%; 95% CI: 46.4-99%)	1.000 [a]
Specificity	44/58 (75.9%; 95% CI: 64.8-86.9%)	58/58 (100%; 95% CI: 100-100%)	<0.001 [a]
Positive predictive value	7/21 (33.3%; 95% CI: 13.2-53.5%)	8/8 (100%; 95% CI: 100-100%)	0.002 [b]
Negative predictive value	44/48 (91.7%; 95% CI: 83.8-99.5%)	58/61 (95.1%; 95% CI: 89.7-100%)	0.697 [b]
Cases correctly classified	51/69 (73.9%; 95% CI: 63.6-84.3%)	66/69 (95.7%; 95% CI: 90.8-100%)	<0.001 [a]

[a] McNemar test
[b] Fischer's exact test

Table 2. Demographic data and clinical presentation of pancreatic lesions in patients with final diagnoses of pseudotumoral masses and pancreatic cancer in chronic pancreatitis.

	Pseudotumoral mass (No.=58)	Pancreatic cancer (No.=11)	P value
Mean age (range); years	56.9 (34-84)	67.3 (50-83)	0.020 [a]
Male gender:			0.434 [b]
- Male	44 (75.9%)	10 (90.9%)	
- Female	14 (24.1%)	1 (9.1%)	
Mean lesion size (range); mm	29.0 (6-60)	37.2 (21-65)	0.163 [a]
Clinical presentation:			
- Abdominal pain	57 (98.3%)	11 (100%)	1.000 [b]
- Weight loss	26 (44.8%)	8 (72.7%)	0.110 [b]
- Jaundice	24 (41.4%)	7 (63.6%)	0.202 [b]
- Acute pancreatitis	9 (15.5%)	1 (9.1%)	1.000 [b]

[a] Mann-Whitney test
[b] Fischer's exact test

adenocarcinoma were diagnosed in 58 and 8 cases, respectively. In the remaining 2 cases, the specimens were not adequate for cytopathological assessment, i.e. acellular material. In both cases, EUS suspected chronic pancreatitis which was also confirmed by surgery. In a single case, EUS detected only morphological evidence of chronic pancreatitis, but not pancreatic neoplasia. In this case, EUS-FNA was performed because of jaundice, abdominal pain, weight loss, a pancreatic head-mass in the setting of calcifying chronic pancreatitis on CT, ERCP with a double duct sign, and high serum levels of CA 19-9. FNA detected chronic pancreatitis, the patient underwent surgical intervention which confirmed a pseudo-tumoral mass.

There was only one procedure-related complication (non-significant bleeding). Neither transfusion nor treatment was needed for this case.

There was agreement between the cytological diagnoses of malignancy and the final diagnosis in 8 of the 11 (72.7%) patients. On the other hand, cytopathology correctly classified all non-neoplastic cases as a benign condition. Three of the 11 (27.3%) cancers were misdiagnosed as pseudotumoral masses by cytopathology, and none of the pseudotumoral masses was diagnosed as a cancer.

In an intention-to-treat analysis, EUS-FNA confirmed the final diagnosis in 66 of the 69 (95.7%) cases. Sensitivity, specificity, positive and negative predictive values, and the diagnostic accuracy of EUS-FNA in the differential diagnosis between pancreatic cancer and pseudotumoral masses were 72.7%, 100%, 100%, 95.1% and 95.7%, respectively (Table 1).

Clinical and EUS Features between Pseudotumoral Chronic Pancreatitis as Compared to Pancreatic Cancer

The size of the pancreatic lesions and clinical presentation were similar in patients with malignant and benign lesions. However, the patients with cancer were significantly older than the patients with pseudotumoral chronic pancreatitis (Table 2; P=0.020).

Endoscopic ultrasonographic findings are shown in Table 3. In patients with a final diagnosis of cancer, the echogenic pattern was mainly heterogeneous (P=0.001) and hypo-echoic (P=0.017). On the other hand, in patients with pseudotumoral masses, the echogenic pattern was mainly homogeneous, similar to the rest of the pancreas, frequently multilobular (P=0.020), with the presence of Doppler signals (P=0.003) and hyper-echogenic septa (P=0.002).

DISCUSSION

In our experience, EUS findings were not capable of precisely differentiating between a pseudotumoral mass and a carcinoma in the setting of chronic pancreatitis. Cancer was

suspected in 21/69 (30.4%) of the cases with masses at the pancreatic head, of which only 11 (15.9%) cases were revealed to be a real malignancy. These numbers point out the low diagnostic accuracy of ultrasound images for the differential diagnosis of pancreatic carcinoma and pseudotumoral masses with concurrent chronic pancreatitis, as has previously been reported by other authors [16, 17, 18, 19]. Moreover, although weight loss and jaundice were seen more commonly in patients with cancer, no significant difference was detected in relation to the clinical presentation of both diseases, which is in line with the literature [2, 5]. Even the classic double duct sign associated with malignancy revealed a benign diagnosis in 5 of 10 cases, which is in accordance with Van Gulik *et al*. [2] who demonstrated a double duct sign in 36% of the patients with chronic pancreatitis who underwent surgery for suspicion of pancreatic cancer. However, patients in the cancer group were older than those suffering from benign disease.

In patients with a final diagnosis of cancer, the echogenic pattern was mainly heterogeneous and hypoechoic, with generally no Doppler signals. On the other hand, the pseudotumoral masses presented an homogeneous echogenic pattern, usually multilobular, with the presence of Doppler signals, and hyperechogenic septa. Specifically for main pancreatic duct abnormalities, no difference was detected for either tumors regarding the presence of irregularities or for intra-ductal stones. When only the EUS findings were taken into account, the diagnostic accuracy was under 80%.

To overcome these limitations, contrast enhanced ultrasonography might be an auxiliary tool, allowing the investigation of the particular vascularization pattern of the tumors [16, 20, 21, 22]. Hocke *et al*. [16] evaluated the method of differentiating pseudotumoral masses from pancreatic carcinoma in patients with chronic pancreatitis. The method increased the sensitivity of EUS from 73 to 91%, and the specificity from 83 to 93%. Nevertheless, Saftoiu *et al*. [23], when evaluating the unenhanced EUS, found a similar sensitivity (93%) and an accuracy of 88% for diagnosing a carcinoma in the absence of power Doppler signals inside the pancreatic mass. In our experience, pseudotumoral masses presented positive Doppler signals in almost 70% of the cases and were found in less than 6% of the carcinomas (P=0.003). Indeed, some authors suggest that enhanced ultrasonography should be used as a complement to CT and MRI, and propose obtaining a diagnosis with a percutaneous fine needle biopsy of all suspicious masses [21], even with the

Table 3. Endoscopic ultrasonographic findings in patients with pseudotumoral masses and pancreatic cancer in chronic pancreatitis (n=69).

	Pseudotumoral mass (No.=58)	**Pancreatic cancer (No.=11)**	**P value**
Ecotexture:			
- Heterogeneous	15 (25.9%)	9 (81.8%)	0.001
- Hypoechogenic	28 (48.3%)	10 (90.9%)	0.017
- Imprecise borders	45 (77.6%)	10 (90.9%)	0.440
Doppler present	48 (82.7%)	4 (36.4%)	0.003
Parenchima:			
- Lobularity	34 (58.6%)	2 (18.2%)	0.020
- Hyperechogenic septa	55 (94.8%)	6 (54.5%)	0.002
- Hypoechogenic areas	55 (94.8%)	11 (100%)	1.000
- Calcifications	20 (34.5%)	7 (63.6%)	0.095
- Pseudocysts	1 (1.7%)	1 (9.1%)	0.295
Main pancreatic duct:			
- Irregularity	45 (77.6%)	9 (81.8%)	1.000
- Intra-ductal stones	1 (1.7%)	1 (9.1%)	0.295

Fischer's exact test

potential risk of implanting neoplastic cells in the needle track [24, 25]. As can be seen, contrast enhanced ultrasonography seems to be a promising diagnostic procedure, but experience with it is still limited, and there is not an extensive body of literature about the results of this method when evaluated by EUS.

We did not consider CA 19-9 serum levels because they can be falsely elevated in both acute and chronic pancreatitis as well as in the presence of jaundice [26].

In the absence of a consensus about the best diagnostic procedure for pancreatic head masses in patients with chronic pancreatitis, EUS-FNA might be a good choice, the one procedure carries out the identification of the lesion, the locoregional staging and the sampling of the tumor and suspicious non-pancreatic lesions, such as lymph nodes or liver lesions [1, 8, 9, 10]. Moreover, there is a lower risk of neoplastic seeding in patients undergoing EUS-FNA when compared to percutaneous FNA [27].

As a consequence of the low sensitivity and positive predictive value obtained by EUS alone for the differential diagnosis between pseudotumoral masses and pancreatic carcinoma, we decided, as protocol, to perform fine needle aspiration biopsies in all pancreatic head masses, despite the EUS findings. Given the small number of confirmed cancers, a large number of biopsies were carried out in patients with benign conditions. Nonetheless, it is crucial to emphasize that there is no ideal method for diagnosing these lesions. Surgery could be a good option, although a benign diagnosis can be found in up to 6% of those cases suspected of being malignant, with complications occurring in up to 21% of these cases [2].

In our experience, malignant disease was confirmed by cytopathology in almost 73% of the cases, and the same was true for 97% of non-neoplastic cases correctly classified as a benign condition. No false-positive results were found, and the final diagnosis was confirmed in approximately 93% of the cases. Fine needle aspiration demonstrated a slightly higher sensitivity (63.6% *vs*. 72.7%; P=1.000) in differentiating between pancreatic carcinoma and pseudotumoral masses as compared to EUS images. However, the specificity and the frequency of cases correctly classified by EUS-FNA were much better, both higher than 95%, while the positive predictive value presented the most impressive improvement (100% *vs*. 33.3%; P=0.002).

In our series, 3 cases of pancreatic cancer were missed by EUS-FNA. This is consistent with the results of the data published, in which the reliability of EUS-FNA is lower in the presence of chronic pancreatitis. Varadarajulu *et al*. [28] evaluated the diagnostic reliability of EUS-FNA in the evaluation of pancreatic mass lesions in the presence or the absence of chronic pancreatitis in 282 patients. EUS-FNA also showed some limitations in the presence of chronic pancreatitis, in particular, a lower sensitivity (74% *vs*. 91%; P=0.020) in comparison to patients without chronic inflammation. This rate resembles our own experience. False-negative cytology was 8% for both groups. Fritscher-Ravens *et al*. [17] analyzed the diagnostic reliability of EUS-FNA in 207 patients with pancreatic lesions, 74 of them in the presence, and the remaining 133 in the absence of chronic pancreatitis. The sensitivity of EUS-FNA was 89% in the absence of chronic pancreatitis, but it was only 54% in the presence of chronic pancreatitis. In a multicenter study, Bhutani *et al*. [29] evaluated 20 cases of pancreatic neoplasms missed by experienced endosonographers. The most important factor increasing the likelihood of false-negative results was chronic pancreatitis, accounting for 60% of all cases.

In conclusion, the diagnostic accuracy of endoscopic ultrasound imaging alone is not adequate for differentiating between pseudotumoral masses and pancreatic cancer arising from chronic pancreatitis. EUS-FNA of these suspicious tumors significantly improves the diagnostic reliability of endoscopic ultrasound, and should be regarded as the first choice for the diagnostic approach of these lesions in this setting.

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Conflict of interest The authors have no potential conflicts of interest

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