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【 CASE REPORT 】

Multiple Carcinomas and Intraepithelial Neoplasms in a Case of Familial Pancreatic Cancer: Rapid Morphological Changes in the Pancreatic Cyst and Pathological Lesions Undetected by Clinical Images

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Abstract:

A 69-year-old woman with a family history of pancreatic cancer was referred because of imaging changes of a pancreas cyst. Magnetic resonance cholangiopancreatography showed a faintly dilated main pancreatic duct and a pancreas body cyst that had changed rapidly over the past year. Computed tomography demonstrated an emerging enhancing lesion in the pancreatic cyst. Endoscopic ultrasonography revealed an irregular-margined, heterogeneous-echoic pancreatic mass, without findings of early chronic pancreatitis. She underwent distal pancreatectomy. A histologic examination of the resected specimen revealed invasive adenocarcinoma with numerous multicentric foci of pancreatic intraepithelial neoplasia (PanIN), including high-grade PanIN, apparently separate from the main cancer.

Key words: familial, pancreatic cancer, PanIN, diagnosis, cyst

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Introduction

Patients with a family history of pancreatic cancer (PC) have an increased risk of developing the disease themselves (1, 2). Familial PC (FPC) is defined by the presence of two PC patients among first-degree relatives. The concept of FPC is gradually being appreciated by clinicians, but the imaging features of FPC remain unclear.

We herein report a case of FPC with concomitant multiple atypical flat lesions (AFLs) (3) and various levels of pancreatic intraepithelial neoplasia (PanIN), including high-grade PanIN (3-6). These small precursor lesions were not visualized by preoperative clinical imaging.

Case Report

A 69-year-old woman was referred to our hospital for the further investigation of a cystic lesion of the pancreas body that had changed in morphology and size during the past 3 years of screening and especially in the last year (Fig. 1a-c). Three years earlier (2008), the patient had undergone cholecystectomy for a gallbladder polyp, and endoscopic ultrasonography (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) had revealed a pancreatic cystic lesion. EUS had demonstrated a unilocular cyst at the pancreas body (1 cm), and ERCP had shown a faintly dilated main pancreatic duct (MPD) and internal mucinous plaques. These findings were suggestive of a branch duct-type intraductal papillary mucinous neoplasm (IPMN).

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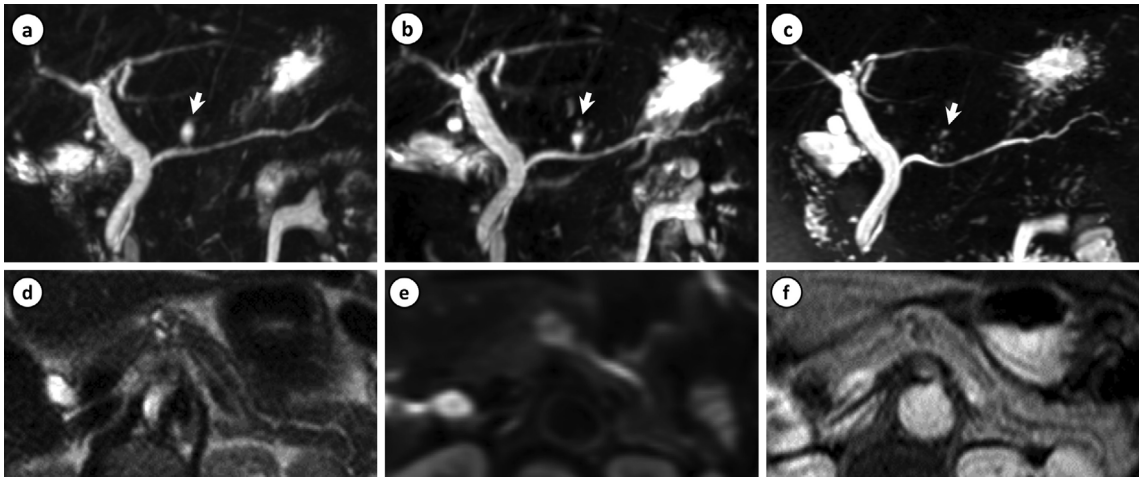

Figure 1. **Magnetic resonance imaging (MRI). Magnetic resonance cholangiopancreatography (MRCP) conducted one year previously demonstrated a faintly dilated main pancreatic duct and a dilated branch duct (arrows), 1 cm in size (a). Six months later, the cyst had changed in shape, appearing as multiple locules (b), and showed further diminished cystic areas at referral one year later (c). T2-weighted imaging showed the separated locules (d). Diffusion-weighted imaging showed a diminished diffusion capacity at the pancreas body lesion (e). Enhanced MRI showed marginal enhancement around the lesion (f).**

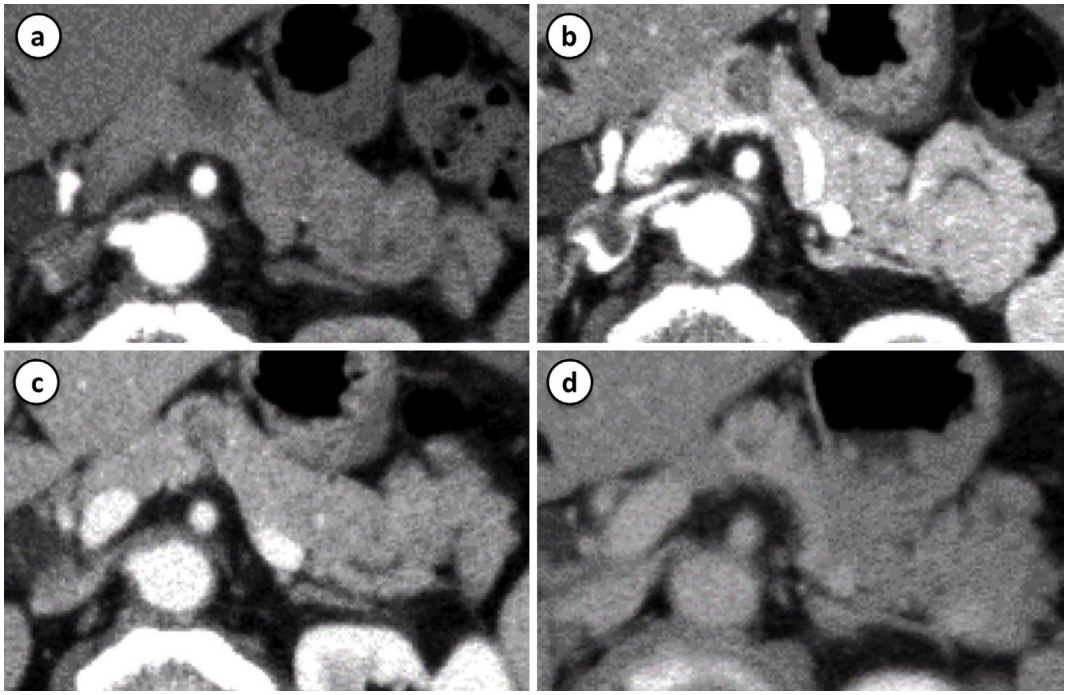

Figure 2. **Computed tomography (CT). Dynamic CT images showed a low-density lesion at the pancreas body (a) and a gradually enhanced internal area (b: 40 seconds after contrast injection, c: 70 seconds, d: 180 seconds).**

On referral to our department, the patient showed unremarkable blood test results, including serum carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), amylase, and hemoglobin A1c (HbA1c) in the normal range. She was negative for serum hepatitis-B surface antigen and hepatitis C virus antibody. Her younger brother had died of PC, but her family history was otherwise unremarkable. She did not consume alcohol, and she did not smoke.

Computed tomography (CT) demonstrated a relatively enhanced mass area in a well-demarcated, ill-enhanced lesion at the pancreas body where the cyst had existed (Fig. 2). Magnetic resonance cholangiopancreatography (MRCP) and T2-weighted magnetic resonance imaging (MRI) showed the faintly dilated MPD, with a maximum diameter of 2.5 mm at the pancreatic body, but the images also revealed an change in the pancreas body cyst, which had devolved into

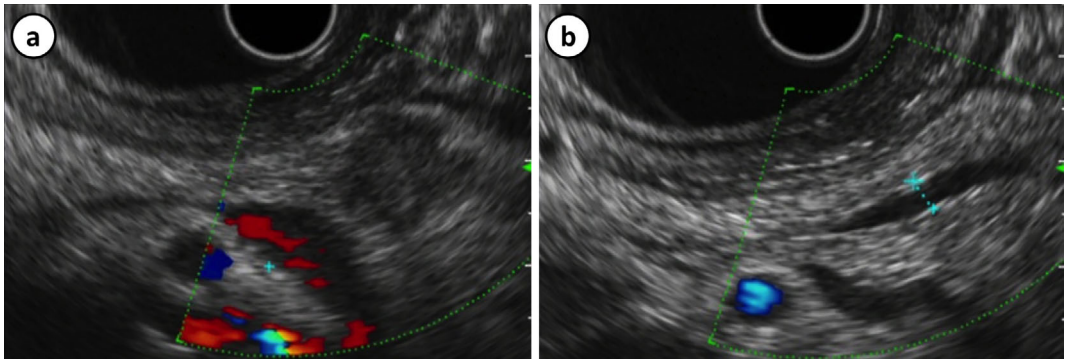

Figure 3. **Endoscopic ultrasonography (EUS). EUS showed an irregular-margined, low-echoic mass (a) and a faintly dilated main pancreatic duct nearby (b). These EUS findings did not meeting the criteria for early chronic pancreatitis.**

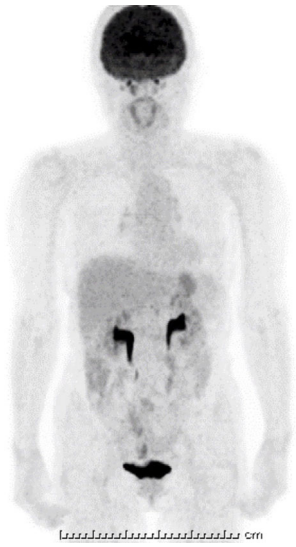

Figure 4. **Fluorodeoxyglucose-positron emission tomography (FDG-PET). FDG-PET showed no abnormal uptake of FDG at the pancreas.**

multiple small locules (Fig. 1c, d). Diffusion-weighted imaging demonstrated a slightly diminished diffusion capacity in the area of the cyst (Fig. 1e), while enhanced MRI showed only faint marginal enhancement around the cyst (Fig. 1f). EUS demonstrated an irregular-margined, low-echoic mass suggestive of PC, accompanied by small internal echo-lucent areas, in the pancreas body. No ultrasonographic findings meeting the criteria of early chronic pancreatitis (7) were visualized within the pancreas parenchyma (Fig. 3). ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) demonstrated no abnormal uptake at the pancreatic lesion (Fig. 4). Endoscopic retrograde pancreatography (ERP) with full contrast injection demonstrated a faintly dilated MPD and multiple equivocal levels of dilation of the branch ducts at the pancreas head and tail (Fig. 5a). Intraductal ultrasonography via the MPD revealed a low-echoic mass at the pancreas body (Fig. 5b). Cytology of aspirated pancreatic juice (5 mL) showed epithelial cells with a mild level of atypia. The CT images of the enhanced demarcated mass and the negative findings on diffusion-weighted MRI and FDG-PET were atypical for ordinary PC; however, the EUS finding of an irregular-margined, low-echoic mass suggested PC.

While the patient had a family history of PC, given that no marked findings were recognized in the pancreas head and no germline DNA information had been obtained, our institutional cancer board decided to treat the pancreatic lesion by distal pancreatectomy (DP). DP was performed in July 2011 but without EUS-guided fine-needle aspiration, due to concerns of tumor seeding.

The cut surface of the resected pancreas macroscopically showed a whitish solid mass at the pancreas body and a few small cysts (Fig. 6a). Histologically, the solid mass lesion showed invasive ductal carcinoma and markedly dilated branch ducts containing a large number of high-grade PanIN lesions (Fig. 6b). The cystically dilated branch ducts harbored papillary projections (1.0 mm in height) consistent with high-grade PanINs (Fig. 6c, d; section D in Fig. 6a) as well as focal low-grade PanINs (Fig. 6e; section E). Numerous foci of low-grade PanIN and AFL replacing acinar lobules were also recognized within the resected pancreas (Fig. 6f). At the pancreas tail and obviously apart from the invasive cancer lesion, a large amount of high-grade dysplasia was seen extending from the MPD to the peripheral pancreatic duct and ranging approximately 10 mm in length (section K in Fig. 6b, g, h). The invasive cancer in the pancreas body (17×15×14 mm in size) was positive for venous and perineural invasion but negative for invasion to the MPD and negative for lymph node metastasis (0/8). The cancer had minimally invaded outside the pancreas toward the retroperitoneal side; however, the surgical margins were all negative for cancer. Adjuvant gemcitabine chemotherapy was given for 6 months (days 1, 8, and 15; 1,000 mg/m^2).

One year and nine months after the surgery, a follow-up serum test revealed an elevated level of CA19-9 (399.5 U/mL). An ill-enhanced mass, 17 mm in size, was apparent in the remnant pancreas head, and a second surgery was attempted. However, laparotomy was canceled because of a finding of metastasis in multiple periaortic lymph nodes.

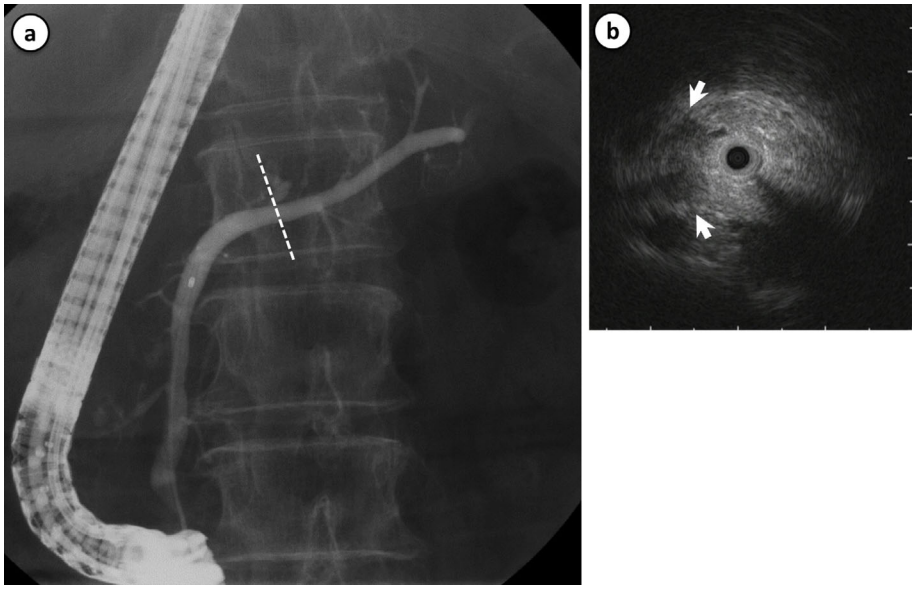

Figure 5. Endoscopic retrograde pancreatography. Full injection of ERP demonstrated slight dilation of the main pancreatic duct and mild dilation of the branch ducts in the pancreas head and tail. A contrast pool was recognized at the entrance of the pancreas body lesion (dotted line) (a), where the low-echoic mass was captured by intraductal ultrasonography (b).

Systematic chemotherapy with gemcitabine was restarted, but the patient died of cancer progression and peritonitis carcinomatosis two years and nine months after DP.

Discussion

The current case showed a rapid morphological change in a pancreatic cyst that had been clinically diagnosed as a branch duct-type (BD-type) IPMN (<10 mm in size) and been followed up by annual MRI/MRCP for 3 years. This surveillance approach was in compliance with the international consensus guidelines for IPMN (8). Several studies that have analyzed a large number of BD-IPMN cases have reported a remarkably low incidence of PC development, either as PC derived from IPMN (2-3% per year) (9, 10) or concomitant with IPMN (0.7-1.0% per year) (11, 12); these numbers are currently even lower, at 0.2-0.6% per year and 0-0.4% per year, respectively (13, 14). Kobayashi et al. (15), who conducted a clinical observation study, reported cyst enlargement in only 2% of their BD-type IPMN cases patients during an average of 41 months of follow-up. A Japanese multicenter study, which analyzed 53 cases of nodule-positive BD-type IPMN, reported cyst enlargement in 7.5% and nodule enlargement in 23%, over a mean follow-up period of 42 months. However, the current case showed dramatic imaging changes in the cyst over a three-year period, particularly within the third year. These changes were evident in the cyst morphology, as the cyst changed from unilocular to multilocular and finally to a dominant solid component. This rapid image change is quite atypical for a BD-type IPMN (8).

The histology of the current PC was accompanied by a multilocular cystic lesion covered with papillary epithelial projections, 1.0 mm in height, with various levels of cytological atypia (mostly diagnosed as high-grade PanIN, partially with possible minimally invasion, and partially with low-grade PanIN; Fig. 6c-e). Although the current clinical images resembled BD-type IPMN, which appeared as a highly vascular area in the cystic lesion on the images (Fig. 1f, 2), the pathological diagnosis was ordinary-type PC derived from PanINs. Although the extension of the high-grade PanIN was large, like IPMN, the cancer invaded deeply (1.7 mm) relative to the small cyst size (1.0 cm). The current case progressed much more quickly than the classical BD-type IPMN and seemed to have a biological behavior similar to ordinary PC. Clinicians should bear in mind that small pancreatic cysts rarely grow rapidly or develop into invasive cancer within a short period.

The present PC patient had a first-degree relative with PC, meeting the criteria of FPC. Although not determined in this case, a familial predisposition gene may have contributed to her course. Multiple precancerous and cancer lesions were recognized and had spread throughout the resected pancreas (6). In particular, numerous foci of AFLs and PanINs with various levels of cytological atypia were recognized, involving several pancreatic acini. High-grade PanIN was seen in a large area and was apparently separate from the invasive ductal carcinoma of the pancreas body. This histological finding is characteristic of FPC (5, 6). Shi et al. reported that patients with familial PC have greater numbers of precursor lesions than do patients with sporadic PC (2.8 times higher for low-grade neoplasms and 5.5 times higher for high-grade neoplasms) (5). Similarly, Brune et al. (6) found multicentric precursors accompanied by atrophic pancreatic parenchyma in the resected pancreas of patients with a strong family history of PC. They also reported that ultra-

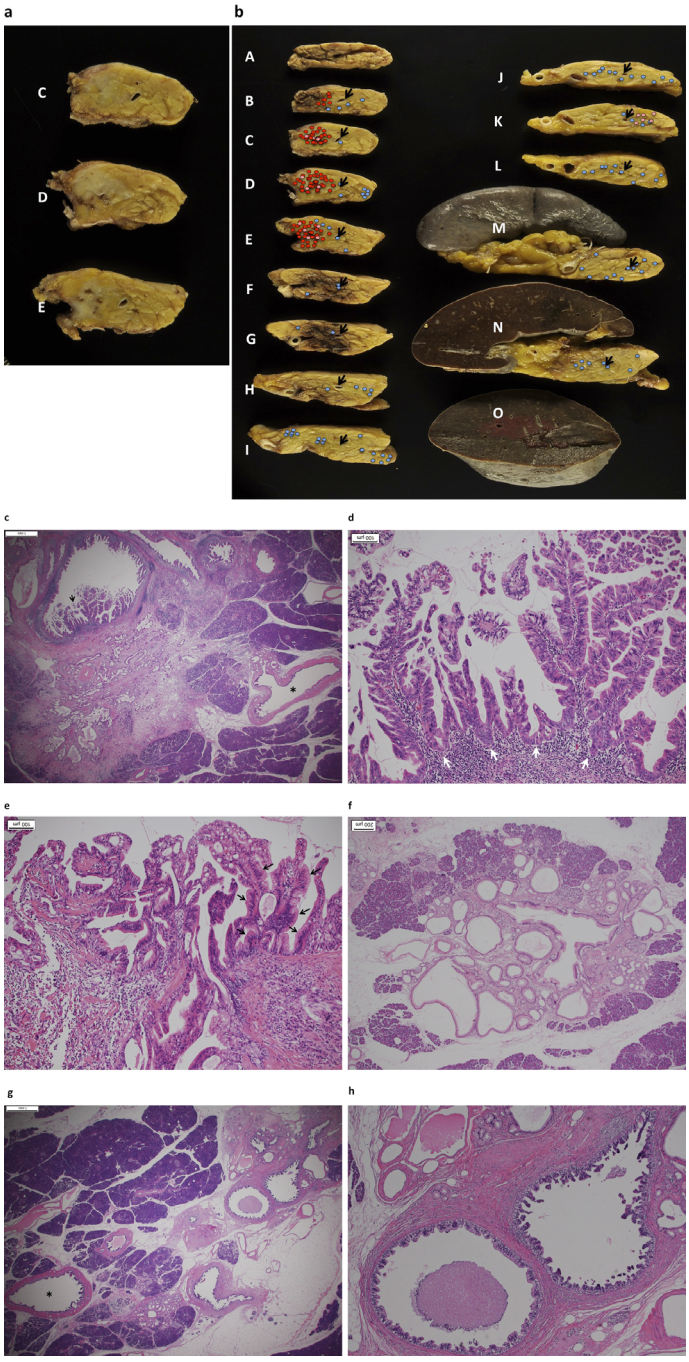

Figure 6. **Resected pancreas. A macroscopic view of the cut surface of the pancreas body showed a whitish mass and multiple cystic areas (a). Mapping of the neoplastic lesions revealed an invasive cancer at the pancreas body, high-grade pancreatic intraepithelial neoplasia (PanINs) at the pancreas tail, and multicentric pancreatic low-grade PanINs (b) [red dot: invasive cancer, pink dot: intraductal carcinoma, blue dot: low-grade PanIN, arrows: main pancreatic duct (MPD)]. A low-power view of section D showed an invasive cancer lesion, multiple dilated branches of high-grade PanIN (left-upper side), and the MPD (asterisk), separate from cancer invasion (c) [Hematoxylin and Eosin (H&E) staining, ×12.5]. A high-power view at the arrowhead in the cyst shown in C mostly showed a high-grade PanIN, approximately 1.2 mm in height. White arrows indicate possible minimal invasion (d) (H&E staining, ×100). A high papillary epithelial component (approximately 0.8 mm), diagnosed as mixed low- and high-grade PanINs, was seen in the part with the continuous cyst wall (e) (arrows indicating low-grade PanIN components, H&E staining, ×100). In the peripheral site of section I, multiple PanINs and atypical flat lesions (AFLs) had replaced the acinar lobule (f) (H&E staining, ×40). A low-power view of section K (g) (H&E staining, ×12.5) showed a lesion of high-grade PanIN extending from the MPD (asterisk) to the peripheral ducts (h) (H&E staining, ×40).**

sonographic findings of early chronic pancreatitis are characteristic in the pancreas in patients with a strong family history of PC (6, 16). In the present case, we were unable to detect these intraductal lesions by any of the attempted imaging modalities. Despite the widespread presence of AFLs, low-grade PanINs and high-grade PanINs, we did not recognize any ultrasonographic findings meeting the criteria for early chronic pancreatitis, except for mild dilation of the MPD. This shortcoming raises questions regarding pancreatic screening using the currently available imaging devices.

Substantial clinical surveillance has been conducted for the early detection of PC in individuals with an inherited risk (1, 16), such as the current case. The prognosis is reported to be significantly better for PC cases detected by surveillance than for those detected outside of surveillance (17); nevertheless, the outcome remains poorer than desired (1, 18). Recently, the Japanese Familial Pancreatic Cancer Registry (JFPCR) decided to recommend surveillance by imaging and blood examinations every six months for high-risk individuals with a familial risk of PC. This surveillance is especially recommended for those with pancreatic findings, such as cystic lesions and dilation of the MPD.

Significant advances are still needed for the diagnosis of microscopic PanIN lesions and minimally invasive cancer of the pancreas [stage 0 and Ia in the Union for International Cancer Control (UICC) classification] (1, 18). For instance, a molecular analysis of the duodenal fluid, which contains DNA shed from intraductal lesions in the pancreas (19), could be added to endoscopy performed at annual health checkups. Molecular imaging is also a promising and still-developing approach for the early detection of PC (20). Further efforts are expected to identify new methods for diagnosing curable PC.

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

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