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A Case of Duodenal Neuroendocrine Tumor Accompanied by Gastrointestinal Stromal Tumors in Type 1 Neurofibromatosis Complicated by Life-Threatening Vascular Lesions

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Female, 45-year-old
Final Diagnosis: Neuroendocrine tumor
Symptoms: Bleeding
Medication: —
Clinical Procedure: Pancreaticoduodenectomy
Specialty: General and Internal Medicine

Objective: Rare disease

Background: Type 1 neurofibromatosis (NF1) is known to be associated with not only neurogenic tumors but also gastrointestinal (GI) neoplasms. However, there are few reports on vascular lesions and the incidence is unknown.

Case Report: We report here the case of a 45-year-old woman with a history of NF1 referred to our hospital for the purpose of detailed examination for positive fecal occult blood test. On the basis of the investigation reports, she was diagnosed with a neuroendocrine tumor (NET)-G1. We planned a subtotal stomach-preserving pancreaticoduodenectomy. The abdominal structures, including the vascular system, were abnormally fragile, and it was very difficult to achieve satisfactory hemostasis. The total amount of intraoperative blood loss was 7580 mL. Fulminant intra-abdominal bleeding occurred on postoperative day (POD) 3. Urgent angiography showed a rupture of the gastroduodenal artery. Transarterial embolization was performed, but the patient died of multiorgan failure on POD5. On histological examination, neurofibroma cells proliferating into the surrounding blood vessels were seen; moreover, immunohistochemistry staining with S-100 antibody showed positive neurofibroma cells surrounding the vascular wall. The pathological diagnosis was duodenal NET-G1 with multinodal involvement.

Conclusions: This case is a rare presentation of a NET with multiple gastrointestinal stromal tumors associated with NF1, which led to a fatal outcome due to the extreme fragility of the vessel walls. Since patients with NF1 might have vulnerable vessel walls, adequate surgical preparation for major surgical treatment is necessary.

MeSH Keywords: Neuroendocrine Tumors • Neurofibromatosis 1 • Vascular System Injuries

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Background

Neurofibromatosis type 1 (NF1), known as von Recklinghausen's disease, is one of the most common autosomal dominant inherited disorders, with an incidence of approximately 1 in 3000 individuals [1]. NF1 is characterized by café-au-lait maculae, benign neurofibromas, axillary freckling, Lisch nodules on the iris, and bone lesions [2–4]. It is associated with an increased risk of neurologic and malignant gastrointestinal (GI) neoplasms. The rate of complications of GI disease in patients with NF is 10–25% [5–9]. It is also known that 1.0–3.6% of patients with NF1 have vasculopathies such as stenoses, aneurysms, and arteriovenous malformations [10,11]. The most common lesions of NF1 vasculopathy involve the aortic, mesenteric, and renal arteries [12]. These vasculopathies have few symptoms but can cause fatal outcomes. For any major surgery in NF1 patients, evaluation of risk factors – including vascular lesions – and preoperative preparation for transarterial embolization (TAE) are necessary to prevent a fatal outcome. We report here a case of a duodenal neuroendocrine tumor (NET) in a NF1 patient accompanied by life-threatening vascular lesions.

Case Report

A 45-year-old woman was referred to our hospital for the investigation of fecal occult blood. She was referred to our department for a thorough examination and, if necessary, surgical treatment based on the examination results. She had a history of NF1 diagnosed at the age of 18 years. None of her second-degree relatives had a history of NF1. Mobility in her left leg was limited due to dislocation of her hip joint at the age of 21 years. Exploratory laparotomy (drainage only) was performed for massive intra-abdominal hemorrhage of unknown origin 8 years ago. Physical examination showed some café-au-lait maculae and multiple cutaneous NFs all over her body. There were no abdominal symptoms. Laboratory investigations showed no significant abnormalities except mild elevation of alkaline phosphatase. Colonoscopy showed no abnormalities in the lower GI tract. A contrast-enhanced abdominal computed tomography (CT) scan showed a duodenal tumor that was a 4-cm mass-like wall thickening centered on the submucosa (**Figure 1A**). The surface close to the mucosa was strongly stained and the mass was unevenly stained, and a submucosal tumor was suspected. The mass showed a slightly higher intensity on T2-weighted magnetic resonance imaging (MRI) and low intensity on T1-weighted (fat suppression) MRI. Gastroduodenoscopy revealed a partially stenosed irregular mass in the postbulbous area of the duodenum (**Figure 1B**). Several submucosal tumors were seen from the second to the third part of the duodenum. Endoscopic ultrasound fine-needle aspiration biopsy revealed a NET-G1 with a Ki-67 index of less than 1%, and GI stromal tumors (GISTs).

Thus, the final diagnosis was duodenal NET (G1) with some GISTs. A subtotal stomach-preserving pancreaticoduodenectomy (SSPPD) was performed. The intraoperative findings were as follows: abdominal structures – including the vascular systems – were fragile, and it was very difficult to achieve satisfactory hemostasis even with the use of energy devices. The total amount of blood loss was 7580 mL. Postoperatively, sudden massive intra-abdominal bleeding occurred on postoperative day (POD) 3. She developed progressive hypotension and hemorrhagic shock. After stabilization of the cardiovascular dynamics by blood transfusion, emergent angiography revealed the bleeding point at the stump of the gastroduodenal artery (GDA) (**Figure 2A**). TAE was performed immediately. Angiography also revealed another aneurysm of the posterior gastric artery (**Figure 2B**). Hemostasis was successfully achieved with TAE, and the vital signs stabilized. However, an

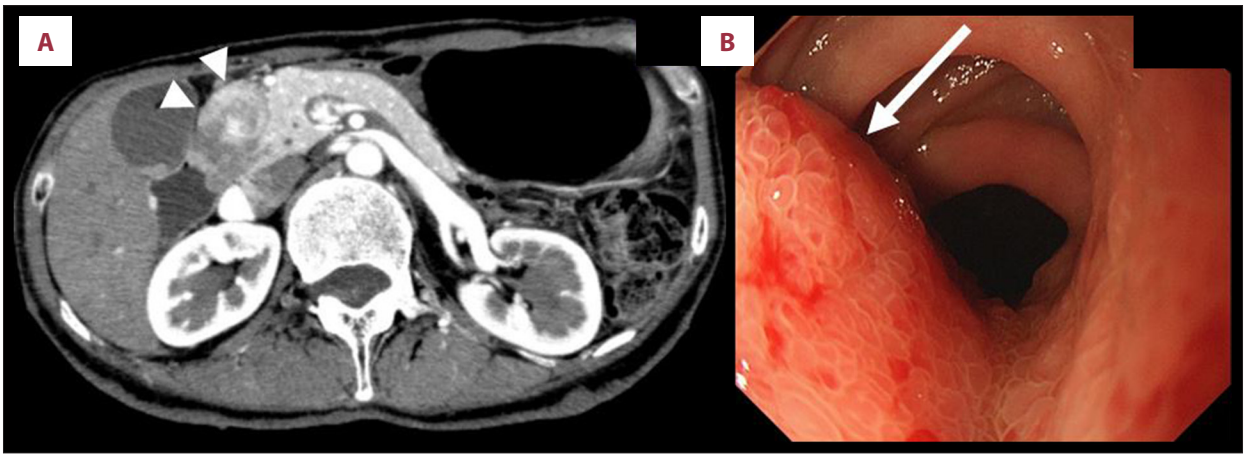

Figure 1. A contrast-enhanced abdominal computed tomography showing that the duodenal tumor was a 4-cm mass-like wall thickening centered on the submucosa (arrowhead) (**A**). Gastroduodenoscopy revealed a partially stenosed irregular mass in the postbulbous area of the duodenum (arrow) (**B**).

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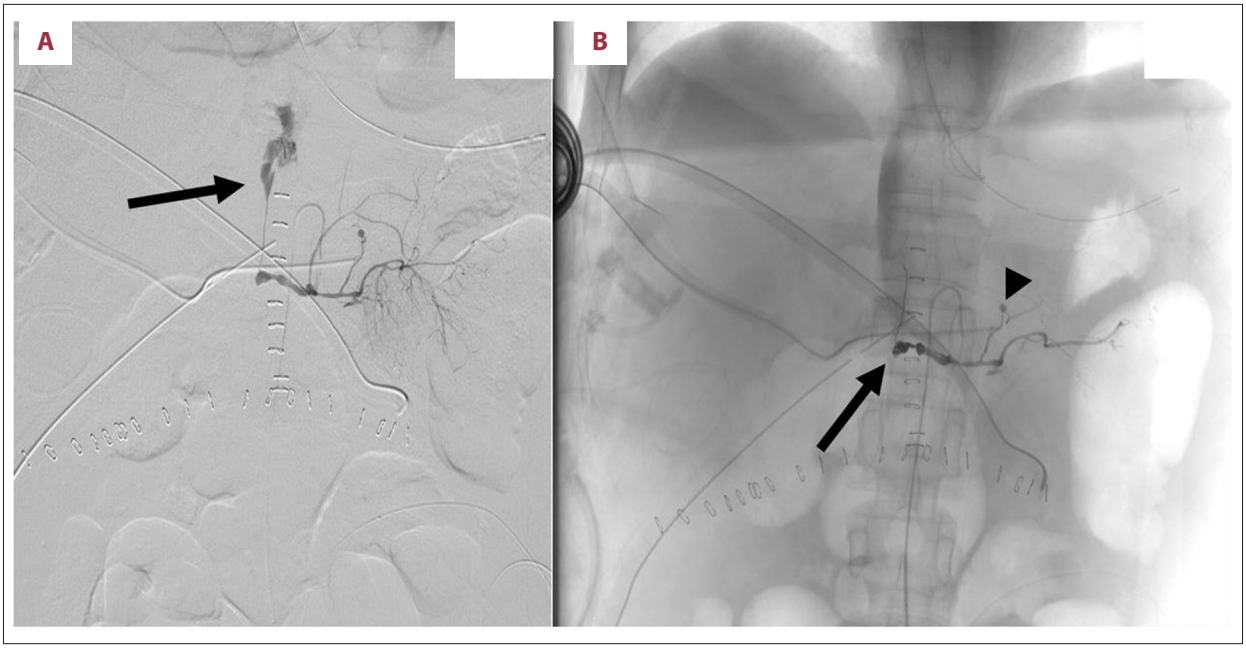

Figure 2. Angiography showing the bleeding point at the stump of the gastroduodenal artery (arrow) (**A**). Postembolization angiography showing successful embolization (arrow). Additionally, another aneurysm is seen in the posterior gastric artery (arrowhead) (**B**).

increase in the volume of hemorrhage from the drain was seen again on TAE the next day, with lowering of blood pressure and progression of anemia. Although drug administration and massive blood transfusions were initiated to perform TAE or surgical hemostasis, blood pressure could not be maintained, and it was difficult to provide treatment. She developed fatal arrhythmias due to acute renal and hepatic failure. Despite the TAE, she died of multiple organ failure (MOF) on POD 5.

Immunohistochemically, the main tumor cells were positive for the CD56 antibody and expressed markers such as chromogranin A and synaptophysin. Furthermore, the positive ratio of the MIB-1 antibody for the main tumor cells was less than 1% (**Figure 3**). Neurofibroma cells proliferated into the pancreatic parenchyma and the surrounding blood vessels. Some arteries were also ruptured by the tumor cells (**Figure 4**). Immunohistochemistry staining with S-100 antibody was positive for NF cells surrounding the vascular wall (**Figure 5**). The final histopathological diagnosis of the main tumor was duodenal NET-G1 associated with NF1. Multiple small GISTs were also observed in the duodenal wall. In this case, the immunohistological findings of the GISTs were positive for the *c-kit* gene mutation. The tumor stage was classified as pT3N1M0, G1, stage IIIB (UICC 7th edition).

Discussion

NF1 is an autosomal dominant inherited disease characterized by NFs and café-au-lait spots on the skin. This disease has various concomitant lesions including characteristic bone lesions such as deformities of the spine and defects of the skull and face bones, eye lesions such as Lisch nodules, optic glioma, freckling in the groin and axilla, and others. NF1 is frequently accompanied by malignant tumors. Fuller et al. reported GISTs, GI ganglioneuroma, and carcinoid as major concomitant GI lesions in patients with NF1 [13].

NF1 has also been reported to be associated with various vascular lesions [12]. Although the exact incidence of vasculopathy due to NF1 is unclear, the vascular lesions are often clinically silent. Vascular lesions have been reported in 0.4–6.4% of patients with NF1 [12]. Despite the low incidence of NF1, destruction of the vascular wall rarely leads to fatal outcomes [14–16].

The treatment regimen for duodenal nonpapillary NET depends on the tumor diameter. Soga reported that the metastasis rate of duodenal carcinoid was 10.6% at size ≤5 mm, 13.9% at 6–10 mm, and 24.7% at 11–20 mm [17]. Regarding the treatment strategy for duodenal nonpapillary NETs, the European Neuroendocrine Tumor Society guidelines recommend surgical resection for tumors >20 mm in diameter or those with nodal involvement. In this case, we opted for SSPPD for a 4-cm-sized NET G1 considering age, duodenal stenosis, and risk of metastasis described above.

However, we did not realize that NF1 patients might have vascular involvement, including vascular fragility. Considering the history of hemoperitoneum, the cardiovascular surgeon was

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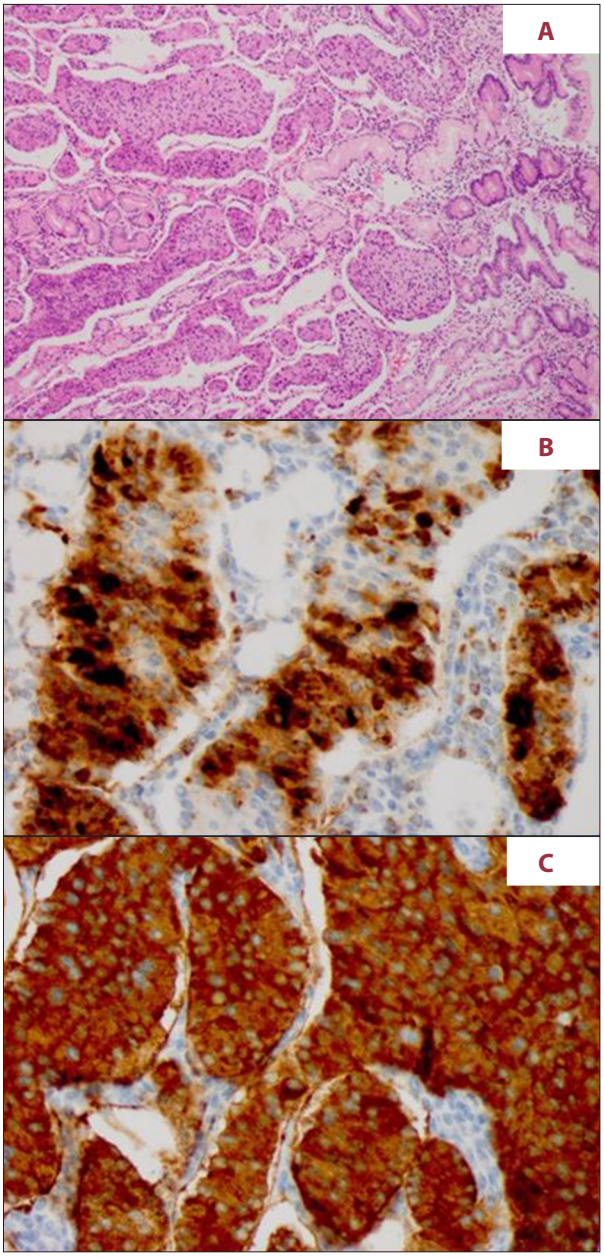

Figure 3. Hematoxylin and eosin staining of tumor invasion in the duodenum (original magnification ×100) (**A**). On immunohistochemistry, the main tumor cells stained positive with chromogranin A (**B**) and synaptophysin (original magnification ×200) (**C**).

consulted for preoperative evaluation of any vascular lesion. However, only contrast-enhanced CT was performed, and vascular lesions such as aneurysms and arteriovenous malformations could not be identified. Therefore, angiographic evaluation and the risk of vascular fragility and bleeding were not assessed.

Bleeding from the tumor was observed during the surgery, and it was anticipated that the bleeding could be controlled

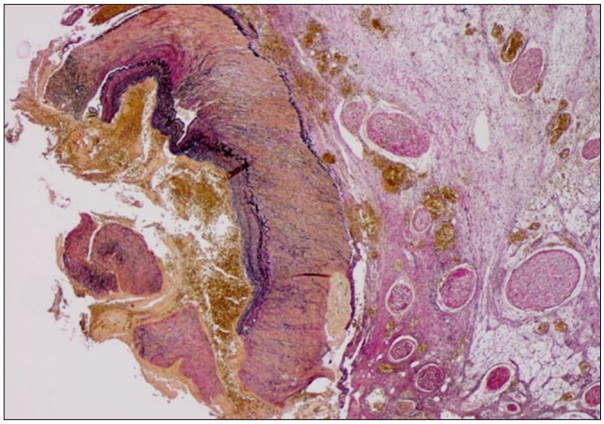

Figure 4. Elastica van Gieson staining of the vascular wall showed rupture and thinning of a part of the tunica intima and lamina elastic externa (original magnification ×100).

by ligation of the GDA, which was the feeding vessel. However, despite ligation of the GDA, the bleeding did not stop, and we noticed the vascular fragility when the hepatoduodenal mesentery was processed. At that time, it seemed that we should have switched to bypass surgery. Unfortunately, a massive hemorrhage occurred due to the fragility of the major arteries. If we had been aware of the possibility of fragility of the blood vessels in patients with NF1 before the surgery, we would have performed palliative bypass surgery.

Ishizu et al. reported the rupture of the thyrocervical trunk branch artery in a patient with NF1 [18]. They described that proliferation of the spindle cells positive for S-100 protein was found in the ruptured vessel's adventitia, which resulted in destruction of the arterial wall. Thus, they concluded that NF in the arterial wall caused dysplasia of the smooth muscle layer in the intima and tunica media, leading to the fragility of the vessel.

In our case, the resected specimen also revealed vasculopathy associated with NF1. The infiltration of NF cells led to the destruction of vascular smooth muscle. Consequently, the blood vessels could not function normally, leading to severe perioperative hemorrhage. Vascular fragility related to NF1 is very difficult to evaluate during pre- and perioperative examinations.

Not all blood vessels are vulnerable in patients with NF1. Contrast-enhanced CT and angiography are helpful in identifying the presence or absence of vascular lesions and the location of lesions such as aneurysms and arteriovenous fistulas in high-risk patients with NF1. Furthermore, confirmation of any abnormalities in the coagulation system or previous episodes of hemorrhage is also important. In our case, the previous episode of intra-abdominal hemorrhage might have been caused by vascular fragility associated with NF1.

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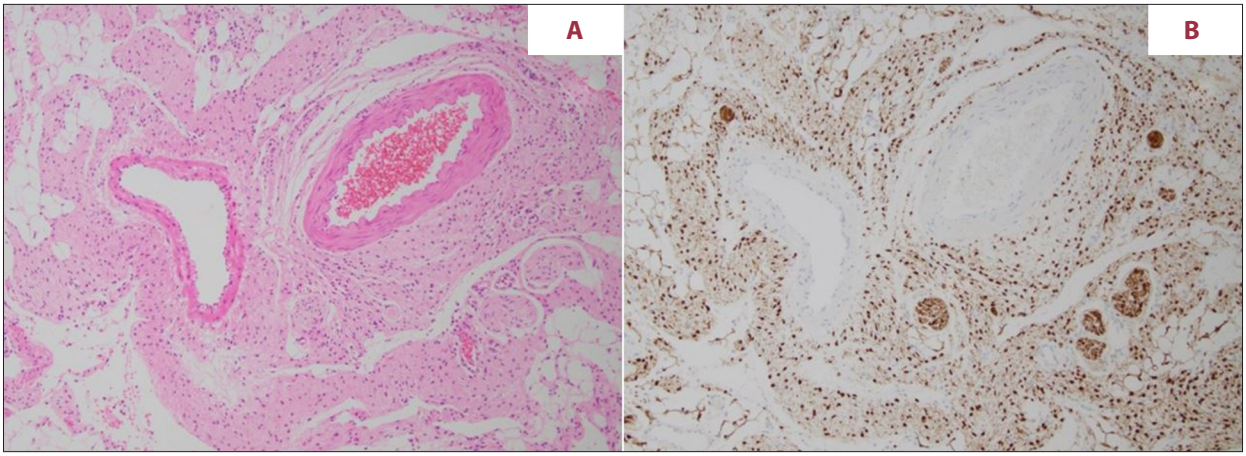

Figure 5. Hematoxylin and eosin staining (**A**) and S-100 immunoperoxidase (reddish-brown) staining (**B**) of the neurofibroma cells spreading around the vessel wall (original magnification ×100).

Even when the investigations do not show any abnormalities, the risk of vascular fragility and bleeding cannot be ruled out. However, if vascular lesions can be identified preoperatively through the investigations, in addition to indicating the possibility of vascular fragility, it provides a basis for determining whether a surgical approach or endovascular treatment should be considered for potential bleeding sources.

Emori et al. reported a ruptured artery aneurysm in a patient with NF1 disease [19]. Since surgical hemostasis was difficult to achieve because of the vascular fragility, they recommended interventional radiology (IVR). They mentioned that wiring or stent insertion during IVR might cause arterial injury [19].

Previous papers have reported bleeding from arteriovenous aneurysms in the head and neck region [20] and intratumoral hematomas due to vascular malformations [21] in patients with NF1. Luisa et al. reported that surgical hemostasis was performed for spontaneous hemothorax in patients with NF1; however, it was difficult to prevent mortality in these cases [22]. They reckoned that hemorrhagic shock caused unstable hemodynamics and that endovascular treatment was difficult. Surgical treatment was considered, but it was difficult to identify the source of bleeding because of the difficult approach. They concluded that timely endovascular treatment before shock is desirable.

In our case, hemostasis was performed using energy devices and ligation of blood vessels for intraoperative hemorrhage during the excision of the tumor. However, compared with conventional hemostasis, fragility of the vessel wall caused difficulty in hemostasis by ligation. When blood that oozed out was observed and the bleeding point was stopped, bleeding still occurred from another site. Hence, blood pressure could not be maintained during rebleeding after TAE, and surgical hemostasis was also difficult. TAE preparation for the preoperative bleeding was inadequate; the shock associated with rebleeding led to MOF. Hemostatic treatment for hemorrhage from the GDA increased the blood pressure and stabilized the hemodynamics. However, it was considered that this increase in blood pressure led to an increased load on the other vulnerable small blood vessels and caused the hemorrhagic shock again.

We were unaware that NF1 patients can have vascular lesions such as vascular fragility, which might lead to a risk of bleeding. With this knowledge, we need to further reflect on the lack of consideration of preoperative surgical procedures, assuming the occurrence of bleeding that would be difficult to control with TAE or surgical hemostasis. If preoperative examination reveals vascular lesions in patients with NF1, the ones that are treatable should be treated then. In cases where vascular lesions cannot be treated or the presence of vascular lesions cannot be confirmed, it is necessary to consider whether surgical procedures or alternative treatments are effective, keeping the risk of bleeding in mind. In patients with vascular lesions, if the surgical procedure of tumor resection is unavoidable, preoperative embolization of the feeding vessels and main arteries might be considered.

Patients with NF1 should be informed about the risk of vascular fragility before surgical treatment. It might be necessary to consider IVR treatment in cases of uncontrolled bleeding when a direct surgical approach is not recommended. Therefore, it might be important to prepare for an urgent IVR first.

Conclusions

Our patient with NF1 had a rare and unusual clinical course with fatal outcome due to vascular fragility. When planning a major surgery, it is necessary to consider the vascular lesions associated with NF1. Although it is important to confirm the

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presence and localization of vascular lesions before surgery, it is not always possible. Therefore, preparing for hemostatic treatment assuming the likelihood of bleeding and evaluating the adequacy of the surgical procedure might reduce the risk of fatal outcomes.

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Conflict of interest

None.

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