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EUS-guided Transgastric Drainage to Manage a Postoperative Pancreatic Fistula After Distal Pancreatectomy and Splenectomy in Recurrent Ovarian Cancer: A Case Report

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Abstract. *Background/Aim: Postoperative pancreatic fistula after distal pancreatectomy represents the most frequent procedure-related complication; however, a standard treatment is currently not available. Case Report: We herein report a case of postoperative pancreatic fistula after distal pancreatectomy and splenectomy in a patient affected by a platinum-sensitive ovarian cancer recurrence. The 59-year-old patient developed a pancreatic fistula on postoperative day 4. An endoscopic transgastric double-pigtail drainage was placed on postoperative day 13. The patient was discharged after 5 days and referred to adjuvant medical treatment. A month later, computed tomography revealed complete resolution of the fistula, the drainage was removed, and the patient continued chemotherapy. She recovered uneventfully at a 3-month follow-up. Conclusion: EUS-guided drainage is a viable option in the management of postoperative pancreatic fistula, which can lead to a rapid resolution of peripancreatic fluid collections and to initiation of adjuvant chemotherapy with the slightest delay in ovarian cancer patients.*

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Due to a late-stage presentation at the time of primary diagnosis, ovarian cancer still remains one of the most challenging diseases in gynecologic oncology. The postoperative macroscopic residual tumor mass is the most relevant clinical factor for both progression free and overall survival in the primary disease. The surgical management of recurrent disease is still subject to an international discussion. However, the available data show improvements in the prognosis also in the setting of recurrence when a complete cytoreduction is performed. Therefore, the surgical management of ovarian cancer may involve complex upper abdominal procedures for both primary and recurrent disease in order to obtain a macroscopically complete resection (1-5). Upper tumor localizations of the ovarian cancer theoretically may occur anywhere and the complexity of this kind of radical surgery means that the gynecologic oncologists must be prepared also to manage its potential complications. Distal pancreatectomy (DP) has been reported as a part of extensive upper abdominal surgical procedures in 0.5-41% of cytoreductions for advanced-stage and recurrent ovarian cancer (6-12). Postoperative pancreatic fistula (POPF) remains the main reason of major morbidity and mortality after pancreatic resection and despite all the

efforts made during this past decade to prevent it, the incidence of this dreaded complication still ranges between 3-45% of pancreatic operations at high-volume centers (13). Despite the technical simplicity of DP compared with pancreaticoduodenectomy, as a pancreatoenteric anastomosis is rarely needed, effective closure of the pancreatic remnant to prevent POPF remains a challenge (14).

The first widely accepted definition of POPF comes from the work of 37 pancreatic surgeons that formed in 2005 an International Working Group (15). A POPF was defined as "an abnormal communication between the ductal pancreatic epithelium and other epithelial surfaces that contain pancreatic-derived, enzyme-rich fluid" and more precisely as "drain output of any measurable volume of fluid on or after postoperative day 3 with an amylase content greater than 3 times the serum amylase activity." A grading system was also established which stratified patients from a relatively benign clinical course (grade A fistula), moderately unwell patients requiring medical or minimally invasive intervention (grade B), and critically ill patients, often with sepsis, requiring invasive intervention (grade C) (16). This first definition was revised by the same Group in 2016 and restricted to only those conditions that were "associated with a clinically relevant development/condition related directly to the postoperative pancreatic fistula" (*i.e.*, grade B and C) (13).

Treatment algorithms for POPF are currently not standardized (17). We herein describe a case of grade B POPF after DP and splenectomy in a patient affected from a platinum-sensitive ovarian cancer recurrence that was successfully conservatively treated with an endoscopic transgastric drainage. To our knowledge this is the first report in a patient with ovarian cancer.

Case Report

A 59-year-old patient with prior history of FIGO stage IIIA2 high-grade serous hereditary ovarian carcinoma was admitted to our service with the diagnosis of first platinum-sensitive recurrence with a simultaneous triple-negative breast cancer. A germline mutation in the breast cancer susceptibility gene, the Breast Related Cancer Antigens-1 (*BRCA1*), was discovered.

The ovarian cancer was initially treated in 2016 with cytoreductive surgery without macroscopic residual tumor followed by six 3-weekly cycles of intravenous platinum-based chemotherapy [carboplatin (AUC 5) in combination with paclitaxel (175 mg/m^2) every 3 weeks for 6 cycles]. During the upfront surgery, she underwent a total abdominal hysterectomy, bilateral salpingo-ophorectomy, omentectomy and multiple peritoneal biopsies.

She remained disease free for four years after that. Unfortunately, a asymptomatic neoplastic lesion at the splenic hilum was detected at standard follow-up by an abdominal computerized tomography (CT) and a magnetic resonance imaging (MRI) and then confirmed by a positron emission tomography–computed tomography (PET-CT) (Figures 1 and 2). With a tumor size of 4.5×4 cm the mass stretched from the caudal portion of the pancreas, behind the stomach to the left upper abdomen near the spleen. No further suspicious lesions were detected. During physical examination no significant abnormalities were revealed. At laboratory tests serum amylase was 106 U/l (normal range=28-100 U/l) while lipase, liver panel, coagulation tests and complete blood count were unremarkable. Regarding tumor-markers, CA125 was 57.5 U/ml (normal range <35) and HE4 was 143 pmol/l with a postmenopausal ROMA-Score of 50.9%.

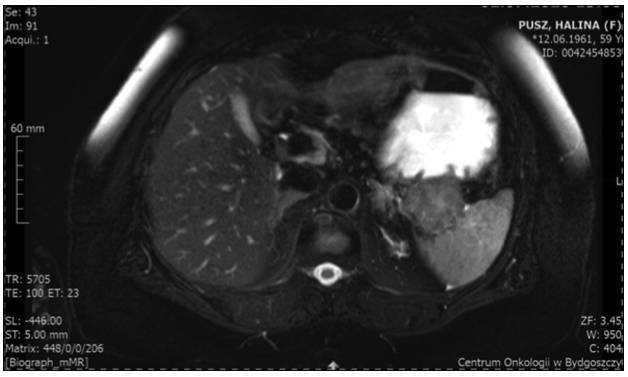

Figure 1. *Abdominal MRI reveals a neoplastic lesion measured 4.5×4 cm in the left upper quadrant.*

After discussing the case in our multidisciplinary tumor board, priority was given to the ovarian cancer recurrence and the patient underwent secondary cytoreduction followed by platinum-based chemotherapy and maintenance therapy with PARP inhibitors.

At laparotomy, there was neither ascites nor peritoneal carcinomatosis. The neoplastic mass in the left upper quadrant was identified once the omental bursa had been opened through the gastrocolic and gastrosplenic ligament. The tumor measured approximately 6×5 cm and there was apparent infiltration of the caudal portion of the pancreas and splenic hilum wrapping around the splenic vessels (Figure 3A). In order to remove completely the tumor without leaving macroscopic residual tumor, a DP with splenectomy as en bloc resection was performed. The splenic vessels were ligated and cut medially to the tumor mass (Figure 3B). The pancreatic parenchyma was cut and sealed with a 60 mm stapler and by the application of an additional reinforcement, the GORE® SEAMGUARD® Bioabsorbable Staple Line Reinforcement (Figure 3C and D). A three-way catheter was placed, near the cut surface of the pancreas, as a drain in order to facilitate, if necessary, a continuous intraperitoneal irrigation. Furthermore, Easy Flow Drain was placed to drain the pelvis.

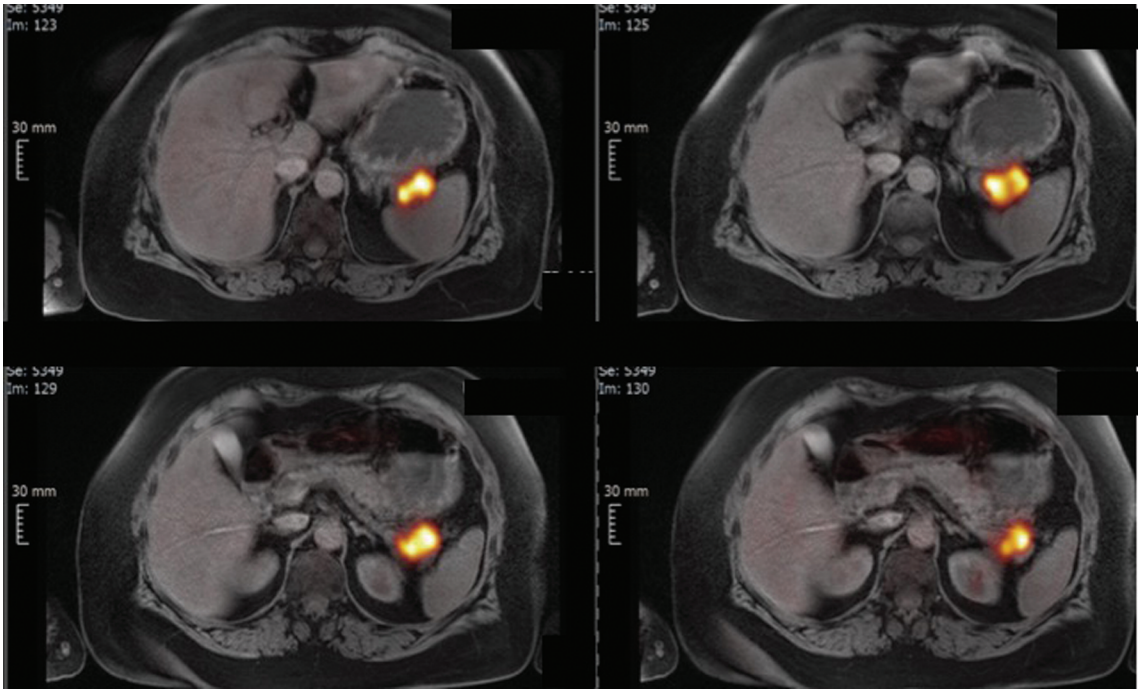

Figure 2. *Positron emission tomography–computed tomography (PET-CT) confirmed a neoplastic lesion in the left upper quadrant.*

The final pathology showed high-grade serous adenocarcinoma morphologically similar to the previously diagnosed ovarian cancer with cancer free surgical margins. According to the current evidence in the treatment of ovarian cancer relapses, a systemic platinum-based chemotherapy flanked and followed by PARP inhibitors was established by the tumor board. Before starting therapy, the breast cancer was marked with a clip.

Postoperative course. After the operation, the patient was admitted in the intensive care unit (ICU) according to an internal routine postoperative overnight ICU admission procedure. In the postoperative period, pancreatic fistulization occurred. On postoperative Day (POD) 2 a biochemical leak was detected by the elevated level of lipase in the fluid collected from the peripancreatic drainage (30,850 U/l). The patient, however, remained clinically well and asymptomatic. On POD 4 a slight upper abdominal pain was remarkable, but the patient still remained afebrile, commenced oral intake and her serum white blood cell count and serum levels of C-reactive protein were within the normal limits. However, the evolution in POPF grade B was suspected and a continuous intraperitoneal irrigation with 100 ml/h of saline solution flanked by a subcutaneous therapy with 100 μg somatostatin once daily and a low-fat diet were started. After initial relief of symptoms, the upper abdominal pain increased. On POD 7, after bilious vomiting, a CT revealed peripancreatic fluid collection of 5×2.2 cm, containing bubbles of gas and spreading from the resected pancreatic surface to behind the stomach (Figure 4). The posterior gastric wall appeared edematous and the wall continuity was not clearly determinable, suggesting the possibility of a gastric erosion or even perforation. The three-way catheter seemed to be temporarily obstructed. In addition, a peripheral pulmonary embolism was detected and treated with weight-based dosing of low-molecular-weight heparin. To exclude gastric perforation, a gastroscopy was performed. No mucosal lesions were identified from the esophagus to the duodenum.

The POPF was initially treated through interventional radiology. An additional peripancreatic double lumen drain was placed with real-time CT guidance. The fluid collection was drained and the area washed under continuous intraperitoneal irrigation. The symptoms quickly disappeared, and the patient was fed orally again. However, despite drain and irrigation, the levels of lipase in the fluid collected from peripancreatic drainage remained elevated (28,508 U/l, 36,053 and 50,146 on POD 10, 11 and 12, respectively). For improved and prolonged drainage of the peripancreatic fluid collection, endoscopic transgastric double-pigtail drainage was placed on POD 13 into the drainage channel of the radiologically placed external

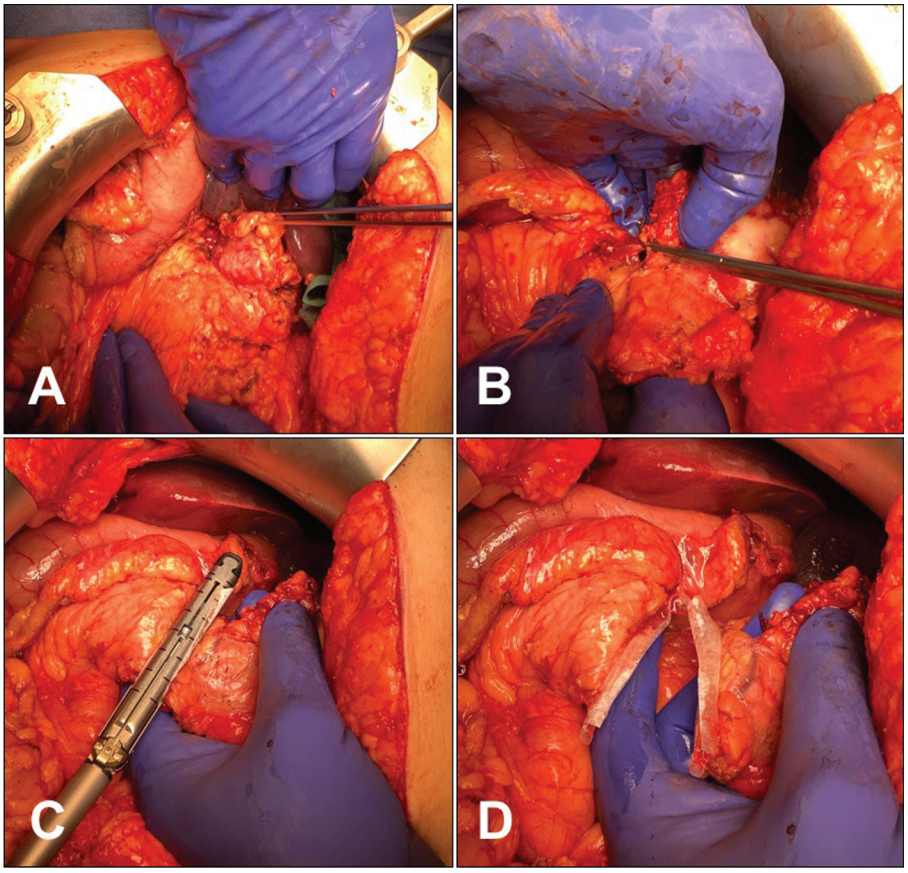

Figure 3. *Distal pancreatectomy with splenectomy: surgical steps. Tumor at splenic hilum involves the splenic vessels and the tail of the pancreas (A). The splenic vessels were ligated and cut medially to the tumor mass (B) while the pancreatic parenchyma was cut and sealed with a 60 mm stapler with an additional reinforcement, the GORE® SEAMGUARD® Bioabsorbable Staple Line Reinforcement (C and D).*

drainage. First, the two previous drains were visualized by EUS. The operatively placed drain was confirmed to be too lateral from the resected pancreatic surface while the drain placed with real-time CT guidance was correctly positioned and adjacent to the stomach. The canal of the latter was punctured under EUS-guidance. The access to the drainage canal was confirmed by contrast injection into the channel. Finally, a 10F double pigtail drainage was placed via a guidewire (Figure 5). The procedure was carried out without any complications by an expert endoscopist. A complete description of the procedure with video has been previously presented by Jürgensen *et al*. (17).

The next course was uneventful. Therefore, the two previous operatively and radiologically placed external drainages were removed. On POD 18 the patient was discharged with a transgastric drainage in place, but without any external drainage and referred to adjuvant medical treatment. The removal of the transgastic drainage was scheduled 7 weeks after placement. Meanwhile the patient

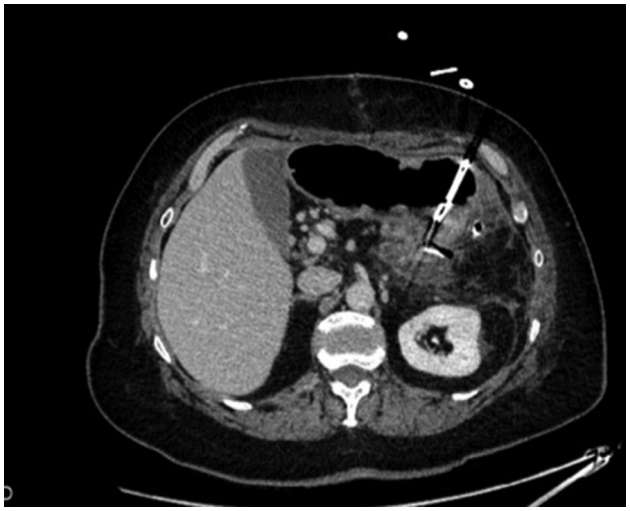

Figure 4. *On POD 7, enhanced computed tomography revealed peripancreatic fluid collections of 5×2.2 cm (arrowheads) spreading from the resected pancreatic surface to under the posterior gastric wall.*

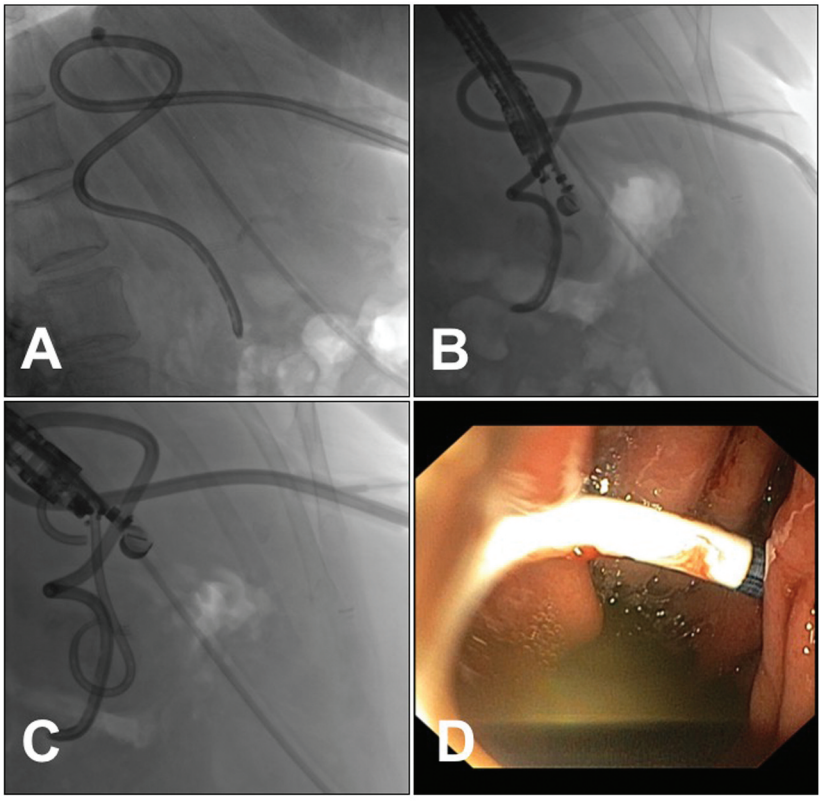

Figure 5. *EUS-guided application of a 10F double pigtail transgastric drainage under fluoroscopic control. The drain is visualized adjacent to the stomach (A). The drainage canal was punctured under EUS-guidance and a wire was advanced into the drainage canal. The access to the drainage canal was confirmed by contrast injection into the channel (B). The 10F double pigtail drainage was placed through the gastric wall (C and D).*

underwent a first cycle of platinum-based chemotherapy (carboplatin plus pegylated liposomal doxorubicin) 4 weeks after the secondary cytoreduction in outpatient environments. Four days after platinum treatment, undulant fever appeared, which was initially interpreted as a chemotherapy-related complication and treated with empiric antimicrobial therapy and antipyretic therapy. Unfortunately, fever was treatment-resistant and the patient was readmitted to our service a month after initial discharge. The patient complained of nausea, fatigue and left upper abdominal pain. A CT revealed complete resolution of POPF and the double-pigtail drainage was removed one week earlier than previously planned. A blood culture collected at the rehospitalization showed Staphylococcal (Staphylococcus epidermidis) Blood Stream Infections. A multi-drug resistant Escherichia coli was isolated from urinary tract culture. Both infections were successfully treated with 10-day intravenous antibiotics. After complete relief of symptoms, the patient continued chemotherapy with a 7-day delay in second chemotherapy cycle. The patient recovered uneventfully and is doing well at a 3-month follow-up.

Discussion

Despite the great progress accomplished in ovarian cancer treatment during the platinum era and the introduction of quality indicators for advanced ovarian cancer surgery used to audit and improve the clinical practice, ovarian cancer still remains an aggressive disease with a poor prognosis. Complete tumor resection has been identified as the most relevant prognostic factor for improved survival in these patients. As a result, radicality through a multivisceral approach has increased within the last decades (4) and in many centers, multidisciplinary teams comprising visceral, gynecological and oncological surgeons have been formed in order to increase the rate of complete cytoreduction even in cases presenting upper abdominal disseminated disease (11). Metastatic ovarian cancer to the pancreas parenchyma is very rare. In fact, although ovarian malignancies can metastasize through the lymphatic channels and the hematogenous route, the intraperitoneal route of dissemination is considered the most common. A pancreas involvement arises usually by direct extension from

retroperitoneal or mesenteric lymph nodes or from infiltrating peritoneal implants. Less common are isolated metastases to the pancreatic parenchyma, which involve more frequently the head of pancreas (18, 19). Splenic parenchymal metastases are also likely rare because of the splenic capsule's action as a shield, the lack of an afferent lymphatic route to the spleen, and the tortuosity of the parenchyma (20). Infiltrating peritoneal implants or metastatic splenic hilum lymph nodes are, on the contrary, less rare. Tumor cells in ascites may travel to the splenic hilum and implant in this region. Once the greater omentum is involved, upper abdominal space such as the transverse colon, left colic flexure, stomach, spleen or pancreas, will be affected by contiguous tumor spread using the route of the surrounding connective structures. Thus, metastasized tumors involving pancreatic tail and/or spleen are occasionally encountered during cytoreductive surgery for primary or recurrent ovarian cancer. In such cases, a pancreatic left resection with splenectomy is required to achieve optimal reduction with macroscopically complete resection (11, 12, 21).

A DP may be part of a primary cytoreduction for ovarian cancer in up to 41% of cases (6-12). In these patients the closure of the pancreatic remnant still remains a surgical challenge with regard to the risk of POPF development, which represents the most frequent procedure-related complication (22). In a recent systematic review and meta-analysis of 122 studies including 22376 patients the total POPF rate (pooled grades B and C) after DP was 15.5% (n=3767) (23). Regarding extensive cytoreductive surgery for ovarian cancer, pancreatic surgery remains the surgical procedure associated with the most severe complications (10). Starting from the 2000s large studies have been conducted on efficacy and safety of extensive upper abdominal surgical procedures in ovarian cancer. Kehoe *et al*. reported a 23% pancreatic leak/fistula rate in a series of 17 patients who underwent DP with splenectomy during primary cytoreductive surgery between January 2001 and December 2006. Seven (41%) out of 17 patients had an optimal cytoreduction status at the completion of surgery (8). In a more recent series of 156 patients with FIGO stage IIIC-IVB ovarian, fallopian tube, or primary peritoneal cancer who underwent splenectomy with or without DP, during primary, interval, or secondary cytoreductive surgery, treated between January 2007 and December 2017, POPF following DP still was a relatively frequent complication (27.3%) (24). Despite the high incidence rate, a standard treatment for POPF is currently not available and a significant heterogeneity is observed in literature regarding prevention and management of POPF. All this has led to the publication of several studies presenting new proposals or technical innovations to manage POPF, such as through the use of interventional radiology or endoscopy (17, 25). The evolution of interventional radiology has dramatically reduced the need for unplanned re-laparotomy after pancreatic resection in patients with POPF (16) while Ultrasound-guided drainage is considered by some authors the first-line modality for drainage of symptomatic of pancreatic fluid collections (26, 27).

We describe here our experience of successful resolution of a grade B POPF by means of an EUS-guided transgastric drainage. According to the 2016 International Study Group on Pancreatic Surgery Definition and Grading of POPF (13) our patient presented initially a biochemical leak, which on POD 4 evolved in grade B POPF. The increased amylase activity was associated with a clinically relevant condition and required a change in the management of the expected postoperative pathway. In fact, an additional peripancreatic drainage through interventional radiology was inserted to "decompress" the undrained intra-abdominal fluid collection from the operatively placed drains. However, a complete clinical resolution of POPF in our patient was only achieved through an EUS-guided transgastric double-pigtail drainage. In a retrospective analysis comparing percutaneous versus EUS-guided drainage to manage peripancreatic fluid collections, Kwon *et al*. showed a comparable safety and effectiveness in both procedures. However, as the authors themselves explained, the endoscopic approach has the big advantage of not requiring an external drainage setting. External catheters, left in place after interventional radiology procedures, compromise the patient's quality of life, require daily care and maintenance, may cause localized skin irritation and infections, and are a constant reminder of the patient's underlying disease state (28). Jürgensen *et al*. recently reported that EUS-guided drainage led to a rapid resolution of peripancreatic fluid collections in a median of 8 days as compared with 25 days for percutaneous drainage and 248 days for surgery. Furthermore, when applied as a rescue intervention, EUS led to clinical resolution in 96% of cases (17). In our patient, affected by first platinum-sensitive ovarian cancer recurrence with a simultaneous triple-negative breast cancer, delay in chemotherapy could lead to serious complications. Despite EUS-guided transmural drainage of pancreatic fluid collections have seen considerable advances in the last decade, it's not a complications-free procedure and requires a special skill level. Studies have reported various types of complications, including bleeding and perforation (29, 30).

In conclusion, pancreatic surgery may be necessary during cytoreductive procedures and gynecologic oncologists must be prepared also to manage its potential complications. A multidisciplinary approach with general surgeons, interventional radiologists and endoscopists can lead to a more rapid resolution of possible complications, such as POPF, and the initiation of the adjuvant chemotherapy with the slightest delay.

Conflicts of Interest

The Authors have no commercial, proprietary, or financial interest in the products or companies described in this article. The Authors received no financial support for the research, authorship, and/or publication of this article.

Authors' Contributions

All Authors have participated in the drafting of the manuscript and read and approved the final version of the manuscript. Conception & Design of Study: Am, CJ, RC, JS; Data collection: AM, RC, SC. Data Analysis & Interpretation: AM, CJ, RC, SC, BG, JS. Responsible Surgeon or Imager: RC, SC.

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