Peritoneal Carcinomatosis from Solid Pseudopapillary Neoplasm (Frantz's Tumour) of the Pancreas Treated with HIPEC

C. HONORE[1], D. GOERE[1], P. DARTIGUES[2], P. BURTIN[3], F. DUMONT[1] and D. ELIAS[1]

Departments of [1]Surgical Oncology, [2]Pathology and [3]Medical Oncology
Gustave Roussy Institute, Cancer Center, Villejuif, France

Abstract. *Solid pseudopapillary neoplasm (SPN) is a rare malignant tumour accounting for 0.1% to 2.7% of all pancreatic neoplasms and affecting young women. Peritoneal carcinomatosis (PC) is even rarer, with only 11 reported cases. We describe a twelfth case occurring 13 years after the resection of an SPN which ruptured peroperatively. This 35-year-old woman had first undergone complete cytoreductive surgery (CCRS) alone and disease had relapsed within 8 months. Ultimately, further CCRS was combined with hyperthermic intraperitoneal chemotherapy (HIPEC) with oxaliplatin and irinotecan. The patient is now alive and disease free 31 months after her last operation. In the literature, the surgical treatment of PC from an SPN has yielded disappointing results, with a 58% recurrence rate at intervals ranging from 1 to 19 years. As none of these patients developed distant metastases, indicating a strictly peritoneal disease, HIPEC might be a solution for preventing such recurrences.*

Solid pseudopapillary neoplasm (SPN) of the pancreas is a rare malignant tumour of the pancreas, accounting for 0.13% to 2.7% of all pancreatic tumours (1-4) and by the year 2005, only 718 cases had been reported (5). In 1959, Frantz was the first to histologically describe this entity (6). It affects women in 83 to 96% of cases (sex ratio of 8.25 to 9.78/1), and is predominantly diagnosed between the age of 30 and 40 (5, 7-9). Eighty-five to 90% of lesions are diagnosed at an early stage and metastases occur in 10 to 15% of patients. Only 11 cases of peritoneal carcinomatosis (PC) from SPN have been so far reported in the literature (7, 10-19). We, here, report a twelfth case and discuss its management.

Correspondence to: Dr. C. Honoré, Department of Surgical Oncology, Institut Gustave Roussy, 114, rue Edouard Vaillant, 94805, Villejuif, Cedex, France. E-mail: chhonore@hotmail.com

Key Words: Cancer, solid pseudopapillary neoplasm, Frantz's tumour, peritoneal carcinomatosis, hyperthermic intraperitoneal chemotherapy, cytoreductive surgery.

Case Report

A 35-year-old woman was admitted to a general hospital for lower abdominal pain. Her medical history included a distal splenopancreatectomy for a benign somatostinoma at the age of 22 years, multiple sclerosis and a smoking habit. A multiloculated pelvic mass was depicted on the CT scan (Figure 1). The chest CT scan and tumour markers were negative. The patient was scheduled for surgery. The peroperative exploration showed diffuse PC associated with a massively invaded right ovary. The surgeon performed peritoneal biopsies and resected the right ovary which was suspected to be responsible for the pain. The pathological diagnosis was a low-grade ovarian sarcoma and the patient was referred to our tertiary care centre. She had no signs of extraperitoneal disease and was scheduled for complete cytoreductive surgery (CCRS). This surgery required multiple peritoneal resections, a rectal resection, a hysterectomy and an omentectomy. Surprisingly, the pathological diagnosis was a massive peritoneal carcinomatosis arising from a solid pseudopapillary neoplasm of the pancreas (SPN). Histological samples of the distal splenopancreatectomy performed 13 years earlier in a third hospital were reviewed and confirmed the diagnosis of SPN with signs of malignancy (*i.e.* venous invasion, diffuse growth pattern, significant nuclear atypia), while the diagnosis of somatostinoma was ruled out. A retrospective analysis showed a tumour rupture had occurred during the initial pancreatic surgery. No adjuvant chemotherapy was administered and a radiological follow-up was planned. On the first abdominal CT scan 8 months after this third operation, 4 nodules were observed under the left diaphragm (Figure 2). A biopsy under endoscopic ultrasound confirmed the second peritoneal recurrence from an SPN. The patient was scheduled for a fourth surgical procedure. The peroperative work-up showed diffuse peritoneal disease with

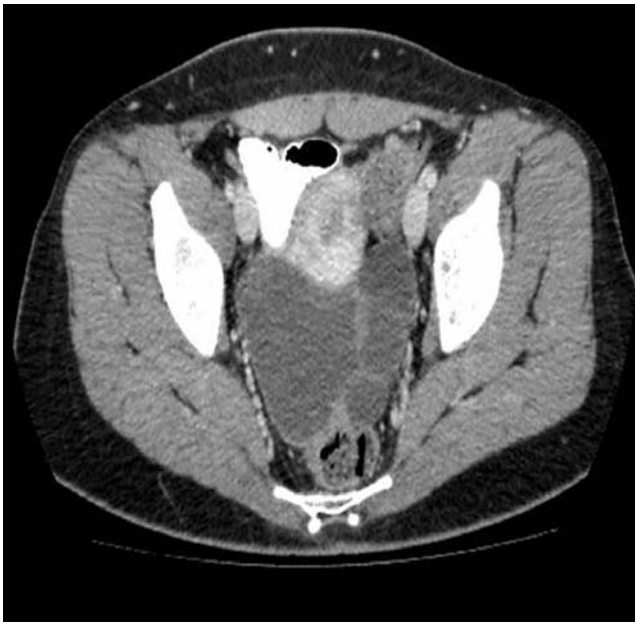

Figure 1. *Multiloculated pelvic mass on the comptuted tomographic scan.*

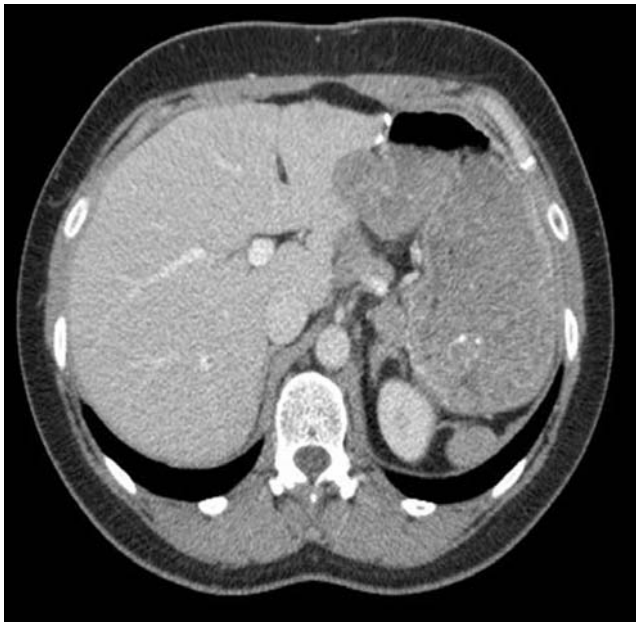

Figure 2. *Nodules under the left diaphragm on the comptuted tomographic scan.*

tumour nodules on the bladder, on the promontory, on the anterior aspect of the rectum, on both sides of the diaphragm and on the liver (Figure 3). CCRS required multiple peritoneal resections, a partial resection of the rectum and was combined with hyperthermic intraperitoneal chemotherapy (HIPEC) with oxaliplatin and irinotecan at a temperature of 43˚C for 30 min. No adjuvant chemotherapy was administered. The patient is now alive and disease free 31 months after CCRS plus HIPEC.

Discussion

This case report shows that SPN can give rise to extensive peritoneal seeding with a high recurrence rate, requiring four operations over a 15-year period for our patient. This disease was probably ultimately controlled with CCRS plus HIPEC. Peritoneal carcinomatosis in SPN is very rare, with only 11 cases reported in the literature (7, 10-19). All cases in the literature described a history of tumour spillage, when such information was mentioned, during the first surgical procedure, as observed in our patient (Table I). This strongly highlights the importance of operative care to obviate this type of recurrence. Once tumour spillage occurs, recurrences arise after a longer interval than in other cancer types (13 years in our patient; 1 to 19 years in the literature) (7, 11, 13-5, 17, 19). This interval should be acknowledged so that follow-up is prolonged in comparison with that applied for other types of cancer.

The first pitfall in this case was the initial pathological misdiagnosis after surgery of the pancreatic tail. Although rare, SPN should always be considered among the pancreatic tumours affecting young women (5, 7-9). Imaging can be confounding but a cystic component is present in 73% of cases (9). Pancreatic tumour markers [carbohydrate antigen 19-9, carcinoembryonic antigen (ACE), chromogranin A, endocrine pancreatic enzymes] are not overexpressed in this type of tumour (7-9). The final diagnosis of SPN requires specific immunohistochemical analyses. SPNs are mostly positive for CD10 and progesterone, they overexpress nuclear and cytoplasmic B-catenin, with a variable expression of synaptophysin and Neuron Specific Enolase (NSE) and are associated with loss or cytoplasmic migration of cadherin expression (20-23). The absence of chromogranin expression and, more recently, the identification of variation in the expression pattern of claudins, helps differentiate SPN from the main potential differential diagnoses which are endocrine tumours, pancreatoblastoma and acinar tumours (24). In our patient, the diagnosis should have been made at the first surgery; the strategy would have probably been the same as surgery remains the treatment of choice for SPN.

The second pitfall in this case was the tumour rupture during the initial pancreatic surgery. As the tumour biology is favourable, surgery yields very good long-term results with 5-year overall survival ranging from 93.4% to 100%, even in cases of locally advanced and metastatic disease (5, 8 ,23).

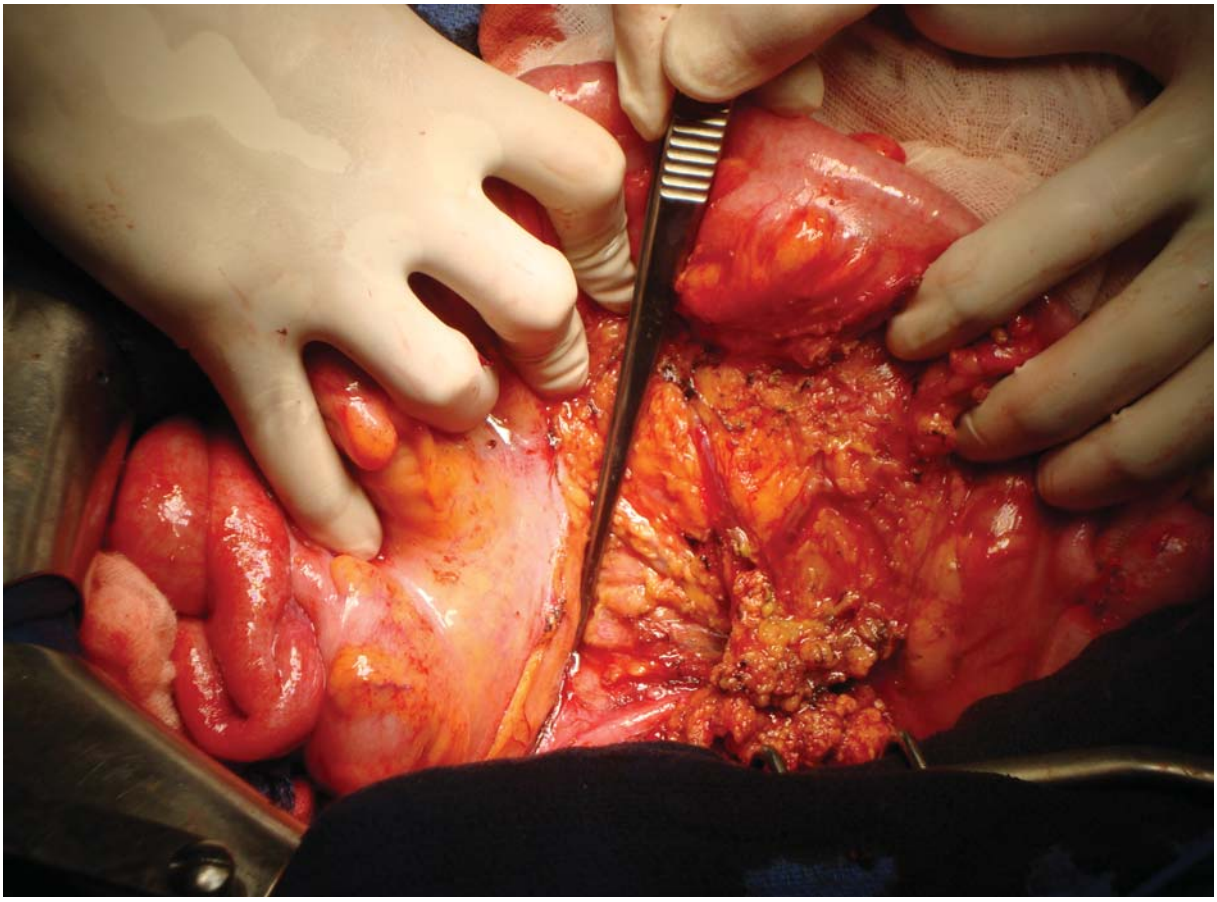

Figure 3. *Peroperative view of the diffuse peritoneal carcinomatosis.*

Table I. *Reported cases of peritoneal carcinomatosis arising from solid pseudopapillay neoplasm of the pancreas in the literature.*

First author (ref)	Year	Follow-up (years)	PR	Time to PR (years)	Spillage history	Note
Benjamin and wright (10)	1980	2	No		NA	
Todani *et al*. (11)	1988	17	Yes	19	Tumour biopsy	*
Cappellari *et al*. (13)	1990	5	Yes	13	External tumour drainage	
Hernandez-Maldonado *et al*. (12)	1989	1	No		NA	
Horisawa *et al*. (16)	1990	6	No		NA	
Matsunou and Konishi (14)	1990	14	Yes	3	Tumour biopsy	**
Nishihara *et al*. (15)	1993	11	Yes	3	Incomplete surgery	**
Lévy *et al*. (17)	1997	1	Yes	6	External trauma	
Zhou *et al*. (18)	2001	4	No		NA	
Andronikou *et al*. (19)	2003	6	Yes	2	External trauma	
Tipton *et al*. (7)	2006	9	No	1	Incomplete surgery	

PR, Peritoneal recurrence; NA, not available; CCRS, complete cytoreductive surgery. *Patient reoperated on for progressive disease, **Patient died of progressive disease.

Nevertheless, locoregional recurrence, estimated at between 2 and 7% in major series, occurred in 100% of the cases after an incomplete resection or tumour rupture (7-8, 25-26). In a recent study of 41 patients with SPN, all patients who underwent an R2 resection ultimately died of their disease after 37 months of follow-up (9). Preoperative treatments have been used successfully to shrink the tumour and avoid this spillage. One team reported a reduction in the tumour size

from 15 cm to 3.5 cm after 6 months of 5fluorouracil/cisplatin in an SPN, initially invading the mesenteric vein, which was ultimately resected (27). Another team reported response of an initially locally advanced SPN after four cycles of cisplatin, ifosfamide, etoposide, and vincristine, which enabled a complete resection (28). In our opinion, this properative chemotherapy is the best option for locally advanced tumours in which complete resection may be jeopardised.

Concerning the treatment of the peritoneal carcinomatosis from SPN, surgery alone has yielded disappointing results, with a 58% (7/12) peritoneal recurrence rate (7, 10-19). This is probably an underestimation of the real rate because follow-up in some of these patients was relatively short compared to the natural history of SPN. According to the literature, recurrences occur after a mean interval of 6.7 years and fewer than half of the reported cases had already reached this endpoint (7, 11, 14-15). Although this rate is very high, none of these patients developed distant metastases, indicating that the disease was confined to the peritoneum (7, 10-19). Considering our good results in rare tumours of the peritoneum (pseudomyxoma peritonei, malignant mesothelioma) and because this patient had an early recurrence after CCRS, performed in an experienced centre, we decided to add HIPEC to the fourth surgical intervention, although there are no data in the literature to support this approach (29-30). After a 31-month follow-up, this option seemed to be beneficial as no recurrence has to date been detected on imaging (third imaging follow-up examination). Based on the literature results, we plan to extend the length of surveillance to at least 10 years.

Conclusion

Iatrogenic rupture of an SPN of the pancreas is a major risk factor for peritoneal carcinomatosis which can occur up to 19 years later. When treating peritoneal carcinomatosis, surgery alone yields disappointing results with a 58% recurrence rate. Complete cytoreductive surgery combined with HIPEC might be more efficient.

Acknowledgements

The Authors thank Lorna Saint Ange for editing.

References

1 Cubilla AL and Fitzgerald PJ: Surgical pathology aspects of cancer of the ampulla-head-of-pancreas region. Monogr Pathol *21*: 67-811, 1980.

2 Crawford BE: Solid and papillary epithelial neoplasm of the pancreas, diagnosis by cytology. South Med J *9*: 973-977, 1998.

3 Lam KY, Lo CY and Fan ST: Pancreatic solid-cystic-papillary tumor: clinicopathologic features in eight patients from Hong Kong and review of the literature. World J Surg *23*: 1045-1050, 1999.

4 Schwartz DC and Campos MA: A woman with recurrent abdominal pain. Am J Med Sci *321*: 352-354, 2001.

5 Papavramidis T and Papavramidis S: Solid pseudopapillary tumors of the pancreas: review of 718 patients reported in English literature. J Am Coll Surg *200*: 965-972, 2005.

6 Frantz VK: Tumors of the pancreas. Atlas of Tumor Pathology, section VII, Fascicules 27 and 28. Washington DC: Armed Forces Institute of Pathology, 1959.

7 Tipton SG, Smyrk TC, Sarr MG and Thompson GB: Malignant potential of solid pseudopapillary neoplasm of the pancreas. Br J Surg *93*: 733-737, 2006.

8 Reddy S, Cameron JL, Scudiere J, Hruban RH, Fishman EK, Ahuja N, Pawlik TM, Edil BH, Schulick RD and Wolfgang CL: Surgical management of solid-pseudopapillary neoplasms of the pancreas (Franz or Hamoudi tumors): a large single-institutional series. J Am Coll Surg *208*: 950-957, 2009.

9 Butte JM, Brennan MF, Gönen M, Tang LH, D'Angelica MI, Fong Y, Dematteo RP, Jarnagin WR and Allen PJ: Solid pseudopapillary tumors of the pancreas. Clinical features, surgical outcomes, and long-term survival in 45 consecutive patients from a single center. J Gastrointest Surg *15*: 350-357, 2011.

10 Benjamin E and Wright DH: Adenocarcinoma of the pancreas of childhood: a report of two cases. Histopathology *4*: 87-104, 1980.

11 Todani T, Shimada K, Watanabe Y, Toki A, Fujii T and Urushihara N: Frantz's tumor: a papillary and cystic tumor of the pancreas in girls. J Pediatr Surg *23*: 116-121, 1988.

12 Hernandez-Maldonado JJ, Rodriguez-Bigas MA, Gonzalez de Pesante A and Vazquez-Quintana E: Papillary cystic neoplasm of the pancreas. A report of a case presenting with carcinomatosis. Am Surg *55*: 552-559, 1989.

13 Cappellari JO, Geisinger KR, Albertson DA, Wolfman NT and Kute TE: Malignant papillary cystic tumor of the pancreas. Cancer *66*: 193-198, 1990.

14 Matsunou H and Konishi F: Papillary-cystic neoplasm of the pancreas. A clinicopathologic study concerning the tumor aging and malignancy of nine cases. Cancer *65*: 283-291, 1990.

15 Nishihara K, Nagoshi M, Tsuneyoshi M, Yamaguchi K and Hayashi I: Papillary cystic tumors of the pancreas. Assessment of their malignant potential. Cancer *71*: 82-92, 1993.

16 Horisawa M, Niinomi N, Sato T, Yokoi S, Oda K, Ichikawa M and Hayakawa S: Frantz's tumor (solid and cystic tumor of the pancreas) with liver metastasis: Successful treatment and long-term follow-up. J Pediatr Surg *30*: 724-726, 1995.

17 Lévy P, Bougaran J and Gayet B: Diffuse peritoneal carcinosis of pseudo-papillary and solid tumor of the pancreas. Role of abdominal injury. Gastroenterol Clin Biol *21*: 789-793, 1997 (in French).

18 Zhou H, Cheng W, Lam KY, Chan GC, Khong PL and Tam PK: Solid-cystic papillary tumor of the pancreas in children. Pediatr Surg Int *17*: 614-620, 2001.

19 Andronikou S, Moon A and Ussher R: Peritoneal metastatic disease in a child after excision of a solid pseudopapillary tumour of the pancreas: a unique case. Pediatr Radiol *33*: 269-271, 2003.

20 Abraham SC, Klimstra DS, Wilentz RE, Yeo CJ, Conlon K, Brennan M, Cameron JL, Wu TT and Hruban RH: Solid-pseudopapillary tumors of the pancreas are genetically distinct from pancreatic ductal adenocarcinomas and almost always harbor beta-catenin mutations. Am J Pathol *160*: 1361-1369, 2002.

21 Klimstra DS: Nonductal neoplasms of the pancreas. Mod Pathol *20*: S94-112, 2007.
22 Jani N, Dewitt J, Eloubeidi M, Varadarajulu S, Appalaneni V, Hoffman B, Brugge W, Lee K, Khalid A and McGrath K: Endoscopic ultrasound-guided fine-needle aspiration for diagnosis of solid pseudopapillary tumors of the pancreas: a multicenter experience. Endoscopy *40*: 200-203, 2008.
23 Goh BK, Ooi LL, Cheow PC, Tan YM, Ong HS, Chung YF, Chow PK, Wong WK and Soo KC: Accurate preoperative localization of insulinomas avoids the need for blind resection and reoperation: analysis of a single institution experience with 17 surgically treated tumors over 19 years. J Gastrointest Surg *13*: 1071-1077, 2009.
24 Comper F, Antonello D, Beghelli S, Gobbo S, Montagna L, Pederzoli P, Chilosi M and Scarpa A: Expression pattern of claudins 5 and 7 distinguishes solid-pseudopapillary from pancreato-blastoma, acinar cell and endocrine tumors of the pancreas. Am J Surg Pathol *33*: 768-774, 2009.
25 Martin RC, Klimstra DS, Brennan MF and Conlon KC: Solid-pseudopapillary tumor of the pancreas: a surgical enigma? Ann Surg Oncol *9*: 35-40, 2002.
26 Yu PF, Hu ZH, Wang XB, Guo JM, Cheng XD, Zhang YL and Xu Q: Solid pseudopapillary tumor of the pancreas: a review of 553 cases in Chinese literature. World J Gastroenterol *16*: 1209-1214, 2010.
27 Strauss JF, Hirsch VJ, Rubey CN and Pollock M: Resection of a solid and papillary epithelial neoplasm of the pancreas following treatment with cis-platinum and 5-fluorouracil: a case report. Med Pediatr Oncol *21*: 365-367, 1993.
28 Hah JO, Park WK, Lee NH and Choi JH: Preoperative chemotherapy and intraoperative radiofrequency ablation for unresectable solid pseudopapillary tumor of the pancreas. J Pediatr Hematol Oncol *29*: 851-853, 2007.
29 Elias D, Honoré C, Ciuchendéa R, Billard V, Raynard B, Lo Dico R, Dromain C, Duvillard P and Goéré D: Peritoneal pseudomyxoma: results of a systematic policy of complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Br J Surg *95*: 1164-1171, 2008.
30 Elias D, Bedard V, Bouzid T, Duvillard P, Kohneh-Sharhi N, Raynard B and Goere D: Malignant peritoneal mesothelioma: treatment with maximal cytoreductive surgery plus intraperitoneal chemotherapy. Gastroenterol Clin Biol *31*: 784-788, 2007.

Received December 23, 2011
Revised January 31, 2012
Accepted February 2, 2012