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Cystic gastrointestinal stromal tumors of the pancreas simulating cystoadenocarcinoma. Report of three cases and short review of the literature

M.R. Ambrosio[1], B.J. Rocca[1], M.G. Mastrogiulio[1], A. Pesci[2], A. De Martino[3], M.A. Mazzei[3], L. Volterrani[3], F. Arcuri[4], M. Cintorino[3] and S.A. Tripodi[5]

[1]Department of Medical Biotechnologies, University of Siena, [2]Ospedale Sacro Cuore, Verona, [3]Department of Medical Sciences, Surgery and Neurosciences, University of Siena, [4]Department of Molecular and Developmental Medicine, University of Siena and [5]Azienda Ospedaliera Universitaria Senese, Siena, Italy

Summary. Gastrointestinal stromal tumors (GISTs) represent a distinct subset of mesenchymal tumours of the gastrointestinal tract. They are more common in the stomach and small intestine, and are characterized by the proliferation of spindle or epithelioid cells and by the expression of CD117. Extra-gastrointestinal stromal tumors are rare and only 13 cases of pancreatic GISTs have been reported in the literature, only 1 of which presented as a cystic lesion. Mutational analysis of *KIT* and Platelet derived growth factor receptor-α genes was performed only in two out of the 13 cases.

We report 3 cases of cystic GISTs of the pancreas, radiologically mimicking a cystoadenocarcinoma. Routine histopathology and molecular characterization of the tumours have been performed. In two of them, molecular analysis showed unusual genetic alterations (the internal repeat of codon 502 and 503 in exon 9 of the *KIT* gene and the *KIT* exon 9 single nucleotide substitution c.1427G>T).

Pancreatic GIST should be included in the differential diagnosis of both cystic and solid masses of the pancreas. The diagnosis should be accomplished by a combination of radiology, histology, immunohistochemistry and molecular biology. The evaluation of CD117 expression and the sequence analysis of *KIT* and Platelet derived growth factor receptor-α gene is mandatory for therapy.

Offprint requests to: Dr.ssa Maria Raffaella Ambrosio, Department of Medical Biotechnologies, Section of Pathology, University of Siena, Via delle Scotte 6, 53100 Siena, Italy. e-mail: maradot@libero.it

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Introduction

Gastrointestinal stromal tumors (GISTs) represent a distinct subset of mesenchymal tumours of the gastrointestinal tract (Fletcher et al., 2002). They are characterized by the proliferation of spindle or epithelioid, occasionally pleomorphic, cells and by the immunohistochemical expression of *KIT* (CD117) (Hou et al., 2004). Mutation of *KIT* leads to the constitutional activation of tyrosine kinase activity, which is responsible for cellular proliferation and resistance to apoptosis (Moskaluk et al., 1999; Morey et al., 2002). GISTs, which include most tumours previously classified as gastric or intestinal smooth muscle tumours, typically present in adults over 40 years (median age 55-60 years) and only exceptionally in children. The great majority of GISTs occur in the stomach (60-70%) and small intestine (25-35%) whereas oesophagus, colon, appendix and anus are rarely affected (Gharibo et al., 2008). Sometimes GISTs may affect omentum, mesentery, retroperitoneum, prostate and gallbladder; these tumors have been defined as "extra-gastrointestinal stromal tumors" (EGISTs) (Graadt van Roggen et al., 2001). Only 13 cases of pancreatic GISTs have been reported in the literature (Neto et al., 2004; Yamaura et al., 2004; Daum et al., 2005; Krska et al., 2005; Showalter et al., 2008; Yan et al., 2008; Harindhanavudhi et al., 2009; Trabelsi et al., 2009; Padhi et al., 2010; Saif et al., 2010; Rao et al., 2011;

Cecka et al., 2011; Vij et al., 2011). Only one of them presented as a cystic lesion (Harindhanavudhi et al., 2009) and only in two cases mutational analysis of KIT and Platelet derived growth factor-α (PDGFR-α) genes was performed, finding a deletion of six base pairs in exon 11 of *KIT* gene in one case and a polymorphism of L862L in exon-18 of *KIT* gene in the other one (Daum et al., 2005; Saif et al., 2010).

Herein we report three cases of pancreatic GIST, macroscopically presenting as a large cystic mass and simulating a cystic pancreatic neoplasm. Following molecular characterization, two unusual mutations (the internal repeat of codon 502 and 503 in exon 9 of the *KIT* gene and the *KIT* exon 9 single nucleotide substitution c.1427G>T), previously described only in gastrointestinal GISTs, were found. A short review of the literature is included.

Material and methods

Cases report

Case 1. A 72 year-old man presented with upper abdominal discomfort, pain and dyspnoea. On physical examination, a palpable indolent abdominal mass was found. No jaundice was present. Laboratory data revealed only elevation of Ca-125. Abdominal ultrasonography (US) and contrast–enhanced computed tomography (CT) evidenced a 180x135 mm cystic lesion of the pancreas head with an irregular thick-wall and intense enhancement, suspicious for pancreatic cystic adenocarcinoma (Fig. 1A,B). There was neither retroperitoneal pathological lymphadenopathy nor ascitic fluid or hepatic metastases. On surgery, a cystic mass filling the epiploon retrocavity, and displacing the stomach and the omentum was found. The cyst originated from the pancreatic head; its anterior wall was easily separated from the omentum while it was partially adherent to the posterior wall of the stomach. Two months later, the patient presented with an important loss of weight (6 Kg), thus an abdominal CT scan was performed which revealed a metastatic lesion in the left lobe of the liver. Therefore, the resection of the lesion was carried out. On histology, the tumour showed the same morphological and immunohistochemical features as the primary neoplasm. The patient was treated with Imatinib mesylate (400 mg/day) but died 8 months after surgery.

Case 2. A 50 year–old woman presented with a palpable abdominal mass on physical examination. Laboratory data revealed low haemoglobin level [10.1 gr/dL (reference range: 12.0-15.5 gr/dL)] and mean corpuscular volume of 74 fL (reference range: 78-100 fL). Whole body CT-scan demonstrated a 7-cm cystic mass in the pancreatic head. The mass did not show solid components, calcifications or signs of acute pancreatitis. No vascular structures were infiltrated by the lesion. Lymphadenopathies were absent. Four years later, the patient showed no recurrence or metastases.

Case 3. A 40 year-old man presented with weakness, anorexia and post prandial pain in the upper abdomen. The patient also reported a loss of weight (5 kg) of three months duration. On physical examination, an epigastric mass was found; no jaundice was present and tumour markers were negative. Abdominal US demonstrated a large (7 cm) cystic mass originating in the pancreatic body characterized by intracystic hyperechoic debris. CT-scan showed a cystic lesion with low-density values in the central part and strong enhancement in the arterial phase. The surrounding parenchyma showed signs of involution. No dilatation of the biliary and pancreatic ducts was observed. Duodenum was displaced by expansion of the tumour. Eighteen months later, a complete remission has been obtained.

Methods

The specimens were fixed in 10% buffered formalin and embedded in paraffin. From each block, tissue sections (4-μm thick) were obtained and stained with hematoxylin-eosin. Immunohistochemical stainings were employed by the Leica BOND-III fully automated system (Leica Biosystem, Milan - Italy) and using the Ultravision Detection System Anti-Polyvalent HRP (LabVision, Fremont, CA, USA) and diaminobenzidine (DAB, Dako-Milan, Italy) as chromogen. The following antibodies were checked: CD117 (clone T595, dilution 1:50), smooth muscle actin (SMA) (clone asm-1, dilution 1:100), cytocheratins AE1/AE3 (clone AE1/AE3, dilution 1:100), Ki-67 (clone K2, dilution 1:100), and CD34 (clone Qbend/10), desmin (clone DE-R-11), vimentin (clone SRL33), DOG-1 (clone K-9), S-100 (polyclonal), chromogranin (clone 5H7), synaptophysin (clone 27G12), Neurone specific enolase (NSE) (clone 22C9), all ready to use. The antibodies were all purchased by Novocastra (Leica Biosystem, Milan - Italy). Sequence analysis of kit exons 9, 11, 13 and 17 as well as PDGFR-α exons 12 and 18 was also carried out. The analysis was performed by PCR amplification followed by direct sequencing of both the forward and the reverse strands with an ABI 310 Genetic Analyzer (Applied Biosystems, Foster city, CA, USA).

Results

In all the three cases a classic Whipple pancreaticoduodenectomy was performed and the surgical specimen consisted of pancreatic head and body, duodenum, gallbladder and antrum.

Case 1. On macroscopic examination a 19x14x12 cm tumour was found in the head of the pancreas. The distance from the pancreatic resection margin was less than 1 mm. The tumour was cystic exhibiting a firm whitish 3-cm thick wall and showing yellowish papillary projections into the cystic cavity. The lumen contained a dark liquid. The lesion was well demarcated by pancreatic parenchyma but seemed to infiltrate focally the gastric wall. Histologically the tumour showed both

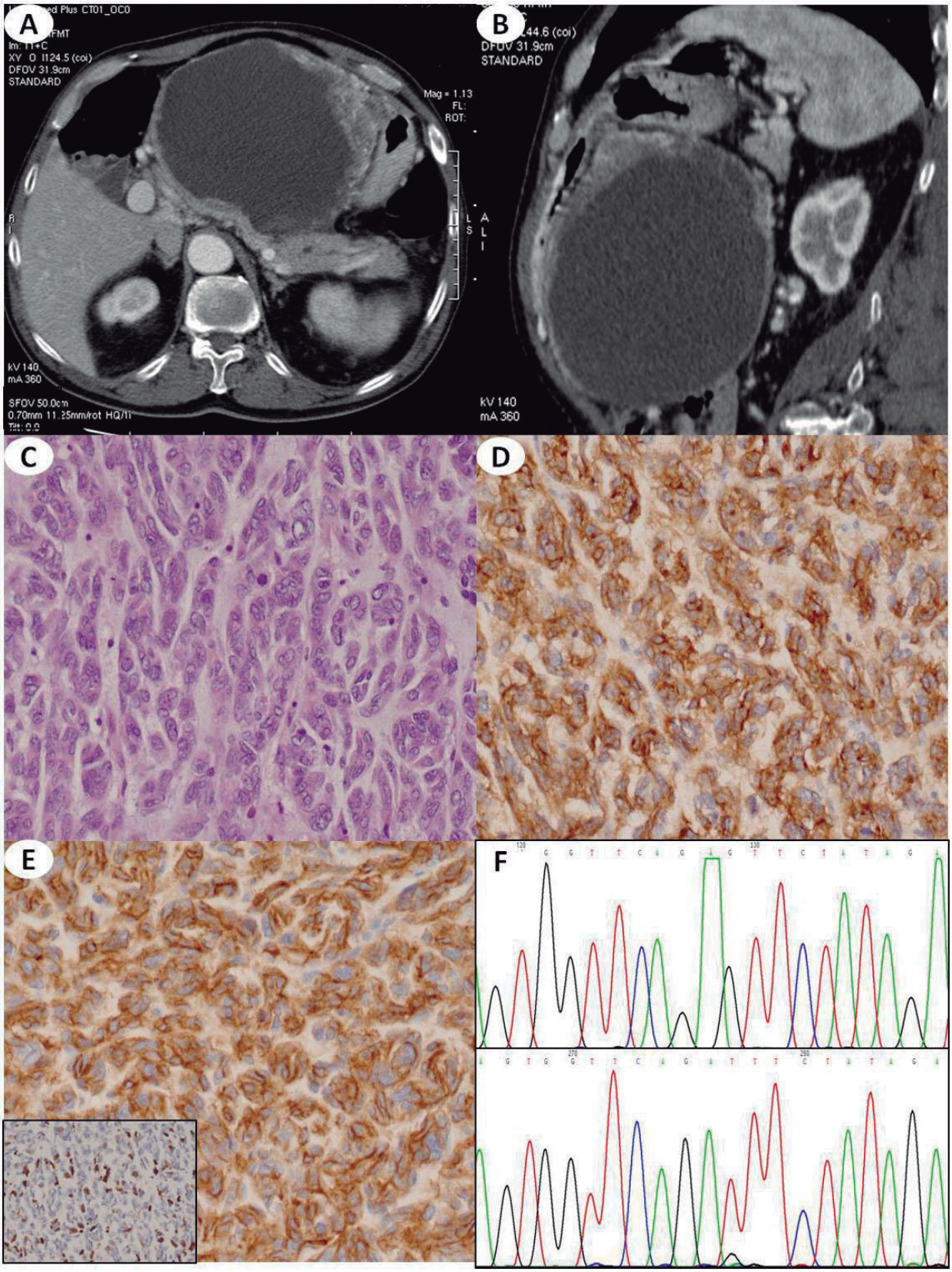

Fig. 1. CT scan showing a 180x135 mm cystic lesion **(A-B)**, histologically composed by epithelioid and spindle cells (**C**) positive to CD117 **(D)** and DOG-1 **(E)** with a proliferative index of 30% (**E**, bottom left). DNA sequencing identified the single nucleotide substitution (c.1427G>T) **(F)**. C, haematoxylin and eosin (H&E). C-E, x 20

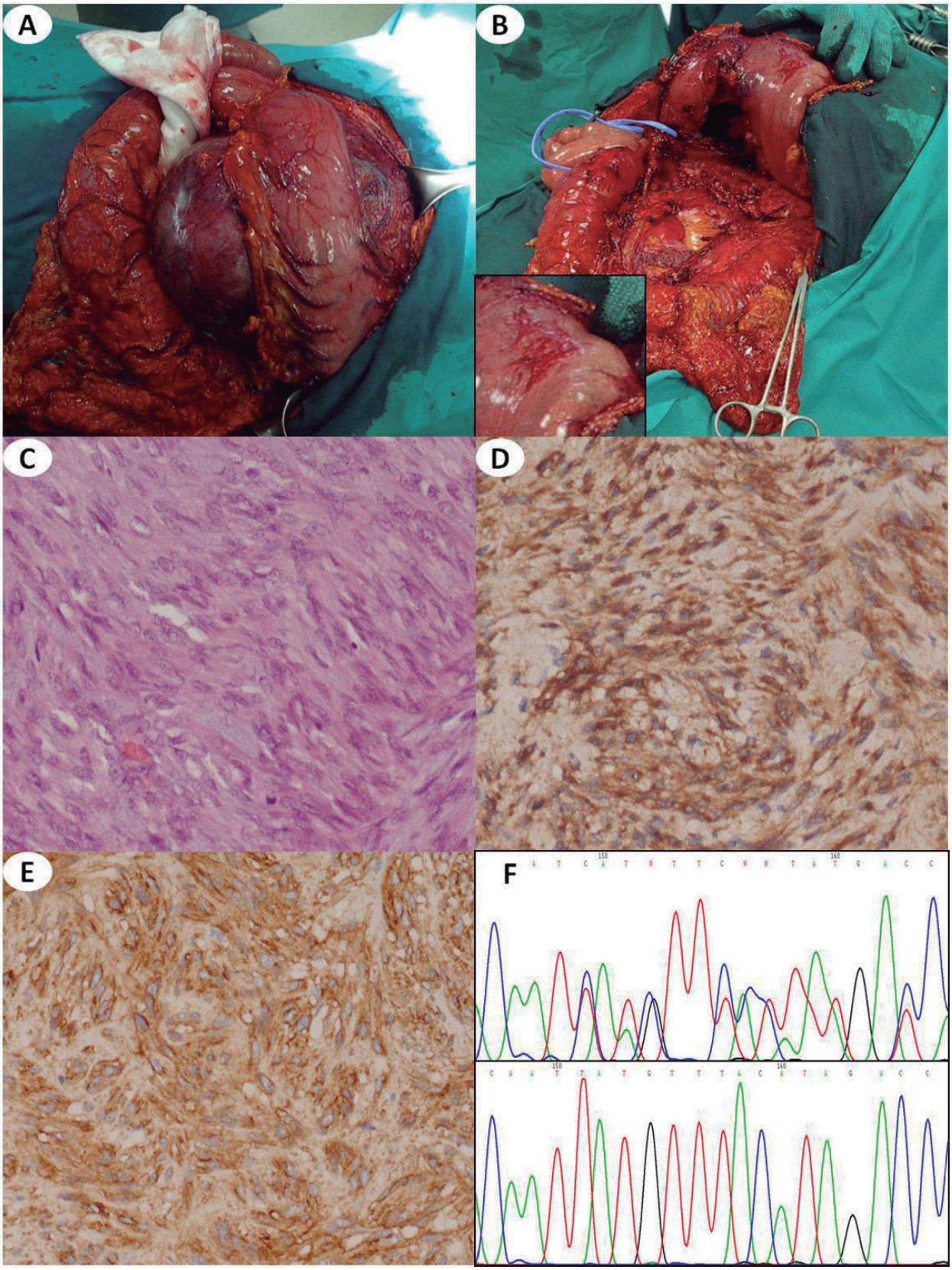

Fig. 2. On surgery, a 7x4 cm cystic lesion replacing the head of the pancreas was observed **(A-B)**. Histologically the tumour consisted of spindle cells with plump nuclei **(C)** positive to CD117 **(D)** and DOG-1 **(E)**. DNA sequencing showed a deletion of 4 pairs in exon 11 of KIT **(F)**. C, H&E. C-E, x 20

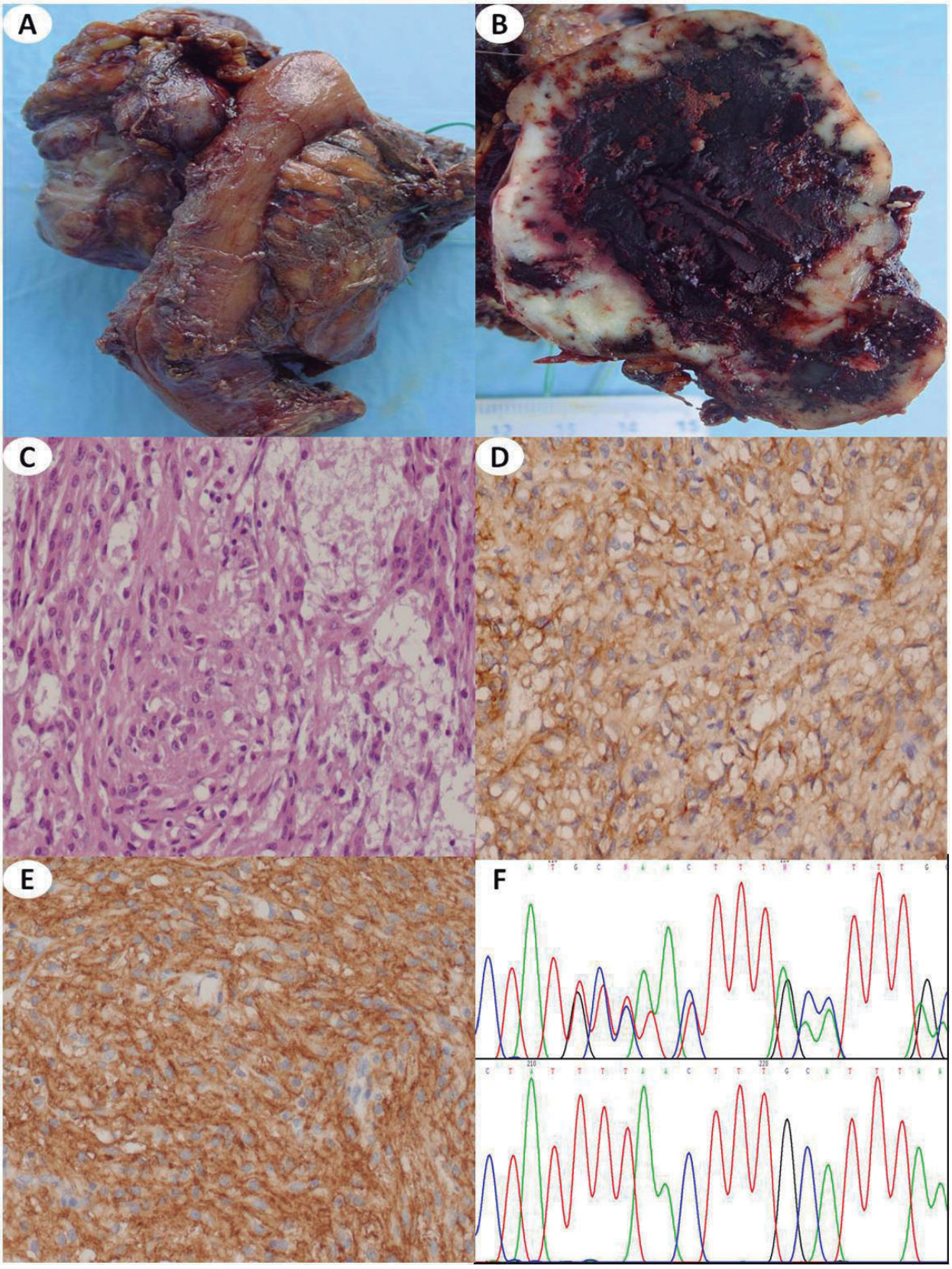

Fig. 3. Macroscopically a yellowish mass in the pancreatic body was observed **(A-B),** which was composed of spindle-shaped cells in a fascicular arrangement **(C)**, expressing CD117 **(D)** and DOG-1 **(E)**. DNA sequencing revealed an internal tandem repeat codon of 502 and 503 in exon 9 of KIT gene **(F)**. C, H&E. C-E, x 20

Table 1. Clinicopathological features of pancreatic gastrointestinal tumors.

Case no.	Author	Sex	Age	Location	Clinical presentation	Pathology	Treatment	Sequence analysis	Follow-up
1	Neto et al., 2004	F	67	Body	Epigastric pain, weight loss	20 cm solid mass with necrotic foci; mitotic count: 120/50HPF	S and I	n.p.	One month later, peritoneal and retroperitoneal lymph nodes involvement
2	Yamaura et al., 2004	F	54	Tail	Incidental finding	14 cm solid mass with cystic degeneration; mitotic count: 3/50HPF	S	n.p.	CR 30 months after surgery
3	Krska et al., 2005	F	38	Body and head	Abdominal pain	17 cm solid mass; mitotic count: 1/50HPF	S	n.p.	CR 30 months after surgery
4	Daum et al., 2005	F	70	Head	Incidental finding	10 cm solid mass; mitotic count: 2/50HPF	S and I	Deletion of six base pairs in exon 11 of KIT gene	CR 6 months after surgery
5	Showalter et al., 2008	F	72	Tail	Incidental finding	7 cm solid mass with necrotic foci; mitotic count: 3/50HPF	S	n.p.	CR 27 months after surgery
6	Yan et al., 2008	M	47	Uncinate process	Nausea and vomiting	2.4 cm solid mass with necrotic foci; mitotic count: 3/50HPF	n.a.	n.p.	n.a.
7	Harindhanavudhi et al., 2009	F	63	Body	Fatigue and weakness	16 cm hemorrhagic cyst; mitotic count: <5/50HPF	S	n.p.	n.a.
8	Trabelsi et al., 2009	F	52	Head	Epigastric pain	10.5 cm solid mass; mitotic count: 6/50HPF	S	n.p.	CR 10 months after surgery
9	Padhi et al., 2010	F	42	Body and Tail	Abdominal pain, weight loss	35 cm solid mass	S	n.p.	CR 10 months after surgery
10	Saif et al., 2010	M	31	Head	Abdominal pain, weight loss and hematemesis	5 cm solid mass; mitotic count: 24/50 HPF	S and I	Polymorphism of L862L in exon 18 of KIT gene	Liver metastasis 9 months after surgery
11	Rao et al., 2011	M	40	Body and Head	Abdominal pain, weight loss	6.5 cm solid mass; mitotic count: 8/50 HPF	S and I	n.p.	Liver metastasis 24 months after surgery. No evidence of disease at 30 months
12	Vij et al., 2011	M	38	Head	Weakness, abdominal pain and fever	6.5 cm firm mass	S and I	n.p.	Liver metastasis 24 months after surgery
13	Cecka et al., 2011	F	70	Tail	Mesogastric abdominal mass	11 cm solid mass	S		CR 66 months after surgery

S: surgery; I: imatinib mesylate; CR complete remission; n.a.: not available; n.p.: not performed

diffuse epithelioid and spindle cells in a thin reticular framework (Fig. 1C). Epitheliod cells formed thick digitations in the lumen simulating a papillary pattern, whereas spindle cells showed a fascicular or storiform arrangement. No skeinoid fibres were seen. Mild nuclear atypia and focal cytoplasmic vacuolization were present as well as areas of coagulative necrosis. Mitotic index was >5 mitoses/50 high-power fields (HPF). The neoplastic cells were separated from the pancreatic parenchyma by a thick fibrous capsule. Immunohistochemical analysis revealed positivity of the neoplastic cells for CD117 (Fig. 1D) and DOG-1 (Fig. 1E). CD34 expression was also strong and diffuse. Vimentin and SMA were expressed only weakly and focally. Neuroendocrine markers, cytokeratins AE1/AE3, S-100, and desmin expression was absent. The proliferative index (Ki-67) was about 30% (Fig. 1E, bottom left). Sequencing of tumour tissue DNA identified the *KIT* exon 9 single nucleotide substitution (c.1427G>T), leading to a Ser476Ile aminoacidic change (Fig. 1F). The morphology and the immunohisto-chemical features indicated the diagnosis of GIST. The tumour was reported as high-risk pancreatic GIST, according to Fletcher (Fletcher et al., 2002).

Case 2. A 7x4x3 cm cystic mass, replacing almost entirely the head of the pancreas and compressing the duodenum wall, was observed (Fig. 2A,B). The lesion was well circumscribed with a brown greyish cut surface displaying haemorrhagic areas. The cystic cavity was full of necrotic debris. One peripancreatic lymph node was also identified, measuring 0.8 cm in its greatest dimension. Histologically, the tumour consisted of spindle cells with acidophilic cytoplasm and plump nuclei (Fig. 2C). The central part of the tumour was hypocellular showing necrosis, haemorrhage and mixoid changes of the stroma in which skenoid fibres were observed. Three mitoses on 50 HPF were found. The pancreatic parenchyma, the surgical resection margins and the peripancreatic lymph node were not infiltrated by neoplastic cells, whereas the tumour invaded the

muscolaris propria of the duodenal wall. Immunohistochemically, neoplastic cells showed diffuse positivity to vimentin, CD117 (Fig. 2D), DOG-1 (Fig. 2E) and SMA and were only focally positive to CD34. Desmin and S-100 were negative. Ki-67 was about 1%. On molecular genetic examination, a deletion of 4 base pairs in exon 11 of *KIT* was found (Fig. 2F). The tumour was reported as intermediate-risk pancreatic GIST (Fletcher et al., 2002).

Case 3. The resected specimen showed a yellowish mass measuring 7x5.5x3.5 cm, partially (5%) solid located in the pancreatic body (Fig. 3A-B). Light microscopy showed the solid component to be composed of spindle-shaped cells in a fascicular arrangement intermingled with epithelioid cells (Fig. 3C). The cystic component displayed massive necrosis and diffuse haemorrhage. The neoplasm extensively infiltrated pancreatic parenchyma and duodenal wall but not the surgical resection margins. Neoplastic cells showed centrally located pleomorphic nuclei with large nucleoli and a mild-to-moderate rim of eosinophilic cytoplasm. The mitotic count was 15 mitoses on 50 HPF. Immunohistochemical co-expression of vimentin, CD117 (Fig. 3D), DOG-1 (Fig. 3E), CD34 and SMA was detected (Fig. 3C-D). Ki-67 was about 40%. Sequence analysis revealed an internal tandem repeat of codon 502 and 503 in exon 9 of *KIT* gene (Fig. 3F). A diagnosis of high risk pancreatic GIST was made (Fletcher et al., 2002).

Discussion

Pancreatic gastrointestinal stromal tumor is rare; so far, only 13 cases have been described in the literature (Neto et al., 2004; Yamaura et al., 2004; Krska et al., 2005; Daum et al., 2005; Showalter et al., 2008; Yan et al., 2008; Harindhanavudhi et al., 2009; Trabelsi et al., 2009; Padhi et al., 2010; Saif et al., 2010; Rao et al., 2011; Vij et al., 2011; Cecka et al., 2011). The median age of the patients was 54.9 years (range: 31-72), with a female predominance (63%). The average diameter of the lesions was 15.8 cm. Only one of them was cystic (Harindhanavudhi et al., 2009). In 23% of cases, the diagnosis was incidental. Mutational analysis of *KIT* and *PDGFR-α* genes was performed only twice (Daum et al., 2005; Saif et al., 2010). The treatment was surgery in 53.8% of cases, and surgery plus imatinib mesylate in 38% of cases. Three patients developed liver metastasis during the follow-up. Clinico-pathological and therapy data of all the 13 cases are listed in table 1.

In this paper we describe 3 cases of pancreatic GIST clinically and radiologically mimicking a cystic neoplasm of the pancreas. For this reason, a Whipple pancreatoduodenectomy was performed (Steinberg et al., 2009).

In the differential diagnosis, pancreatic cystic lesions were excluded on the basis of morphology and immunohistochemistry (i.e. absence of epithelial cells lining the cyst and CD117 negativity) (Rosai, 2003). Retroperitoneal mesenchymal lesions were also considered. The intra-abdominal fibromatosis presents CD117 positivity in 75% of cases but it is characterized by a spatially homogeneous proliferation of wavy spindle cells without atypia, associated with collagen deposition (Rosai, 2003). The peritoneal solitary fibrous tumour shares CD34 positivity but lacks CD117 expression; the smooth muscle tumors, the GI-schwannomas and the undifferentiated sarcomas show some of the histological features of EGISTs but lack CD117 expression. (Yantiss et al., 2000; Graadt van Roggen et al., 2001).

To date, the origin of pancreatic GISTs remains controversial considering that the presence of Cajal cells has not yet been documented in the pancreas (Wang et al., 2011). It has been hypothesized that EGISTs may result from the extensive extramural growth of mural GISTs, resulting in partial or complete loss of contact with the muscularis propria (Wang et al., 2011). Others suggested that the interstitial cells of Cajal may not be the actual cells of origin, but that EGISTs could arise from a common precursor of Cajal and smooth muscle cells, explaining their growth within and outside the gastrointestinal tract (Wang et al., 2011).

To date, few data on the prediction of malignant potential of EGIST are available. According to Fletcher et al. (Fletcher et al., 2002) the main prognostic factors are tumor size and mitotic rate, although a low mitotic index and a small size do not guarantee a benign clinical course. Reith et al. (2000) analyzed 48 cases of EGISTs in order to determine their similarity to tumors arising from the gastrointestinal tract and reported that their malignancy was higher and similar to that of GISTs arising in the more distal part of the GI tract. Miettinen (Miettinen et al., 1999; Lasota et al., 2000) agreed with Reith et al. and proposed distinct guidelines for gastric GIST and for intestinal and extra-intestinal stromal tumours.

Approximately 75-80% of GISTs have mutations of the *KIT* gene (67% in exon 11, 10% in exon 9, 1% in exon 13 and 1% in exon 17). Mutations of *KIT* lead to the constitutional activation of tyrosine kinase activity, which is responsible for cellular proliferation and resistance to apoptosis. Eight per cent of GISTs showed *PDGFR-α* gene mutations (exon 12, 14, 18) and 12-14% were wild-type, i.e. they do not have mutations either in *KIT* or in *PDGFR-α* gene (Moskaluk et al., 1999; Morey et al., 2002; Bateman et al., 2008). Several studies reported a correlation between molecular alterations and biological behavior, prognosis and response to treatment. Wild-type GISTs have the worst prognosis, being resistant to imatinib treatment (Gharibo et al., 2008). *KIT* mutations in exon 11 are associated to better prognosis, usually found in GISTs with low risk features. As far as exon 9 mutations are concerned, exon 9 mutant GISTs are more aggressive than exon 11 mutants (Grabellus et al., 2010). Thus, among patients with advanced-stage GIST, those with exon 9 mutations show imatinib response, progression-free and overall survival

intermediate between GIST with exon 11 mutation and wild-type GIST (Shimomura et al., 2010). Moreover, exon 9 mutations have been described only in gastrointestinal GISTs. In our cases, two unusual mutations of *KIT* gene were observed, both affecting exon 9. One of them [exon 9 single nucleotide substitution c.1427G>T (p.Ser476Ile)] has been previously described only in a 44-year-old male with a GIST of the stomach (Grabellus et al., 2010). Patient 1 reported in the present work and showing the same mutation, had a progression-free interval of 8 months which is shorter than that (14 months) of patients with the usual *KIT* exon 9 mutation under imatinib standard therapy. Owing to the absence in the literature of other pancreatic GISTs showing this particular mutation, the biological significance of exon 9 single nucleotide substitution remains unclear. The internal tandem repeat of codon 502 and 503 in exon 9 of the *KIT* gene, shown in patient 3, had been previously described only in a child with small intestine GIST (Shimomura et al., 2010). Shimomura hypothesized that this type of mutation may be associated to a better prognosis and response to imatinib mesylate. Unfortunately, limited follow-up (18 months) in our patient and the absence of other patients with pancreatic GISTs exhibiting the same mutation, does not allow us to confirm such a correlation.

Even though uncommon, pancreatic GISTs should be included in the differential diagnosis of both cystic and solid masses of the pancreas. Diagnosis should be achieved by the combination of radiology, histology, immunohistochemistry and molecular biology.

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