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Pancreatic mucinous cystic tumor in Turner syndrome: How a tumor bends to a genetic disease

Marco Pizzi[a], Gianmaria Pennelli[a], Isabella Merante-Boschin[b], Matteo Fassan[a], Maria Rosa Pelizzo[b], Massimo Rugge[a,*]

[a] Department of Medicine DIMED, Surgical Pathology & Cytopathology Unit, University of Padova, Italy
[b] Surgery Unit, Department of Surgical Oncology and Gastroenterology Sciences, University of Padova, Italy

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ABSTRACT

INTRODUCTION: Mucinous cystic neoplasms (MCN) are uncommon tumors of the pancreatic corpus/tail occurring mostly in middle-aged women, with a variable clinico-biological behavior. On histology, MCNs concurrently show an epithelial mucosecreting component with ovarian-type stromal cells.
PRESENTATION OF CASE: This report describes the first case of a pancreatic MCN with no ovarian-type stroma in a patient with Turner syndrome (TS).
DISCUSSION: The mesenchymal component of MCN presumably results from the intra-pancreatic entrapment of ovarian stroma during embryogenesis. In our case, the absence of such stromal component may relate to the "dysgenetic" changes in the ovary involved in TS.
CONCLUSION: The present case of primary pancreatic MCN arising in a TS-patient triggers some original speculation on the morphogenesis of pancreatic MCN, also expanding the current clinico-pathological knowledge of this extremely rare entity.

1. Introduction

Pancreatic cystic neoplasms include both benign and malignant diseases. Within otherwise solid pancreatic tumors, cystic changes may result from necrosis/hemorrhage due to the neoplasm's growth (*i.e.* degenerative cysts).[1] Among "natively" cystic tumors, the neoplastic cells' phenotype distinguishes serous from mucinous subtypes. Based on its epidemiological, clinical and pathological profile, the mucinous subgroup is further divided into mucinous cystic neoplasms (MCN) and intraductal papillary mucinous neoplasms (IPMN). A distinctive histological feature of MCN is the coexistence of an epithelial mucosecreting component with ovarian-type stroma (which is lacking in IPMN).[1,2]

Turner syndrome (TS) belongs to the spectrum of the "premature ovarian failures", and is characterized by early ovarian demise with insufficient circulating levels of female sex steroids.

This report describes the first case of a primary pancreatic MCN with no ovarian stroma, occurring in a TS patient.

2. Case report

In September 2011, a 42-year-old Caucasian woman with TS was referred to the Surgery Department of Padua Teaching Hospital (Padua, Italy) with a cystic lesion (11 cm in size) of the tail of the pancreas. The lesion had initially been identified when the patient was 18 years old (an incidental ultrasound [US] finding), when it had been diagnosed as an "adrenal cyst". At the time of this initial assessment, the lesion had been 4.5 cm in size and featured a well-defined, thin wall and a homogeneous fluid content. Laboratory tests (including serum tumor markers) had revealed nothing of significance. Subsequent annual US follow-up showed a gradual enlargement of the cyst, with newly appearing mural nodules, and changes in the cyst's contents (from fluid to hemorrhagic/corpusculated). In 2007, a check-up revealed above-normal CA19-9 levels (901.6 U/mL [normal range: 0–37 U/mL]), and subsequent abdominal computed tomography definitively located the lesion within the pancreatic tail (Fig. 1). Neither endoscopic US, nor cytology of the cystic fluid were performed. The patient refused surgery until 2011, when a pancreatic tail resection with splenectomy was performed.

The gross surgical specimen featured a single, rounded cyst with a fibrous (focally calcified) pseudo-capsule. The cut surface disclosed a multi-locular cyst filled with hemorrhagic mucus; solid mural nodules coexisted with intra-luminal protrusions (Fig. 2A).

Abbreviations: IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; US, ultrasound echography; SPNP, solid-pseudopapillary neoplasm of the pancreas; TS, Turner syndrome.

* Corresponding author at: Surgical Pathology & Cytopathology Unit, Department of Medicine-DIMED, University of Padova, Via Aristide Gabelli, 61-35121 Padova (PD), Italy. Tel.: +39 049 821 8990; fax: +39 049 827 2277.
E-mail address: massimo.rugge@unipd.it (M. Rugge).

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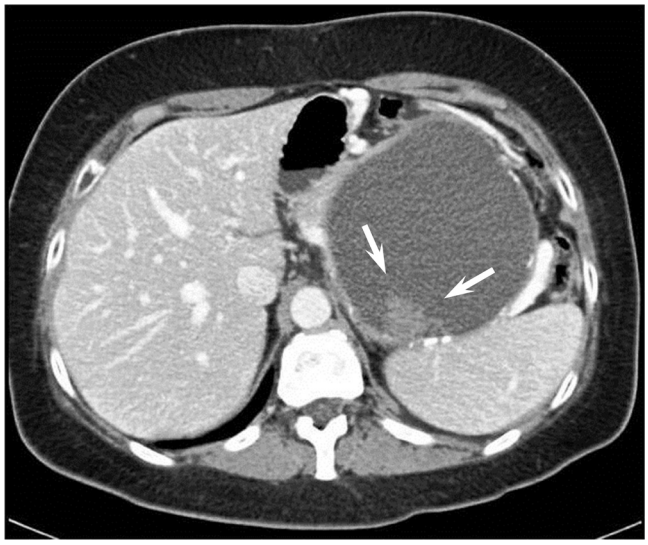

Fig. 1. Abdominal computed tomography (CT) of the pancreatic lesion. Contrast-enhanced abdominal CT discloses a large, well-demarcated cyst of the pancreatic tail displacing the stomach and spleen. The fluid content is barely corpusculated. Note the partially calcified pseudocapsule and the posterior intramural mass protruding into the cystic cavity (arrow).

On histology, both the cystic wall and the small papillary projections were lined by columnar epithelia with basally located nuclei and clear cytoplasm; foci of mild architectural/cytological atypia (*i.e.* low-grade dysplasia) were also faced (Fig. 2B). The large papillary fronds featured foci of high-grade dysplasia, where irregular papillae were lined by multiple layers of cubic/columnar epithelia with atypical/irregular nuclei, and prominent nucleoli (Fig. 2C). Micro-glandular nests (consistent with early stromal cancer invasion) were also visible at the implant of the papillary structures. The sub-epithelial fibrous stroma was consistently hypocellular, with no evidence of ovarian commitment (Fig. 2D). Moderate- to high-grade inflammatory infiltrate was associated with micro-invasive carcinoma.

Epithelial cells consistently expressed CK7, CK19, CK8/18, monoclonal CEA, and EMA. Nuclear staining for CDX2 and apical membrane staining for CD10 were also found, with a focal (but sharp) positivity for CK20 (Fig. 2E–G). Chromogranin, synaptophysin and nuclear β-catenin stains were negative. Both high-grade dysplasia and micro-invasive cancer cells showed consistent immunostaining for both p53, and Ki67. Fibrous (vimentin-positive) stroma featured no staining for either estrogen or progesterone receptors, and for smooth muscle actin antigen (Fig. 2D) (Table 1).

A diagnosis of mucinous cystic micro-invasive carcinoma of the pancreas (adjacent to low- and high-grade dysplasia) was finally established (pT2 N0 M0, stage IB; complete resection with negative histological margins [R0]). The patient recovered rapidly after surgery and is currently (January 2013) alive, with no evidence of disease on imaging.

3. Discussion

Turner syndrome (TS) is caused by the partial or complete lack of a sex chromosome, which occurs in about 40–50 per 100,000 live-born girls. The spectrum of the syndrome basically results from gene haplo-insufficiency on the X chromosome, which also leads to insufficient circulating levels of female sex steroids and premature ovarian failure, associated with ovarian stroma fibrosis and oocyte degeneration.[3,4]

Pancreatic MCN is a cyst-forming tumor in which mucin-producing neoplastic epithelia coexist with ovarian-type stroma.[1] The coexistence of these two neoplastic components (epithelial-mucinous and non-epithelial ovarian-type) is the histological hallmark of MCN and differentiates such tumors from IPMN,[1,2] although the ovarian-type stroma is variably represented[5] and may be hypocellular/fibrotic in some cases (mainly in large MCNs).[1]

In the present case, despite the lack of ovarian-type stroma, several clinico-pathological features firmly support a diagnosis of MCN rather than IPMN: (i) the tumor occurred in the pancreatic tail of a young (18-year-old) female; (ii) it consisted of a single multi-locular cyst (with a calcified pseudo-capsule); (iii) none of the serial histology sections obtained from the surgical specimens featured any communication between the cyst and the pancreatic duct tree; (iv) the neoplastic cells consistently expressed CDX2, CK20 and CD10 antigens. IPMNs, on the other hand, mainly affect elderly males, they are usually located in the pancreatic head and involve the main branches of the pancreatic ducts,[6,7] and they do not usually reveal staining for CDX2, CK20 and CD10.[8,9]

The occurrence of a cystic pancreatic tumor in a young female patient also suggests the differential diagnosis with a solid-pseudopapillary neoplasm of the pancreas (SPNP). The diagnosis of MCN, however, was supported by: (i) absence of solid areas consisting of poorly cohesive monomorphic cells, admixed with hyalinized/myxoid stromal bands; (ii) negative nuclear immunostain for β-catenin[10]; (iii) the absence of "regressive" features (*i.e.* cholesterol crystals) coexisting with foreign-body giant cells.

Table 1
Immunohistochemical profiling of the neoplasm.

		Clone	Working Dilution	Manufacturer	Immunostaining score[a]
Epithelial component	CK7	OV TL12/30	1:200	Cell-Marque, USA	3+
	CK8/18	503	1:50	Thermo Scientific, UK	3+
	CK19	RCIT 108	1:100	Bio Genex, NL	3+
	CK20	ITS20.8	1:50	Cell-Marque, USA	1+
	Monoclonal CEA	CEA31	1:400	Roche, France	2+
	EMA	E29	1:200	Thermo Scientific, UK	3+
	CD10	56C6	1:20	Dako, Denmark	3+
	CDX2	EPR2764y	1:100	Cell-Marque, USA	2+
	p53	D07	1:100	Cell-Marque, USA	3+
	Chromogranin A	DAK-A3	1:100	Dako, Denmark	0
	Synaptophysin	SY38	1:200	Dako, Denmark	0
Stromal component	ER	6F11	1:50	Leica, UK	0
	PR	LPGR312	1:100	Leica, UK	0
	Smooth muscle actin (SMA)	1A4	1:100	Cell-Marque, USA	0
	Vimentin	V9	1:200	Cell-Marque, USA	3+

[a] O: no expression; 1+: <30% of the cells; 2+: 30–60% of the cells; 3+: >60% of the cells.