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Oligoclonal T-cell populations in an inflammatory pseudotumor of the pancreas possibly related to autoimmune pancreatitis: an immunohistochemical and molecular analysis

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Abstract Inflammatory pseudotumors (IPT), also known as inflammatory myofibroblastic tumors (IMT), are benign inflammatory processes that may have an infectious etiology and are very rare in the pancreatico-biliary region. Recent studies suggest a biological distinction between IPT and IMT, the latter being a true neoplastic process. We describe a case of pancreatic IPT, originally diagnosed as malignancy, which presumably recurred 4 months after the operation. Histologically, the tumor consisted of a smooth muscle actin and CD68-positive spindle cell population and a more abundant mononuclear inflammatory cell population, primarily composed of macrophages and T-lymphocytes. Inflammatory cells were the source of connective tissue growth factor and transforming growth factor-β1 and tended to accumulate around nerves and blood vessels, as well as around residual pancreatic parenchymal elements, where an intense angiogenetic response was detected. Comparative genomic hybridization analysis of the tumor showed no chromosomal imbalances. Polymerase chain reaction-based analysis of T-cell receptor γ gene rearrangement revealed an oligoclonal pattern. These findings suggest that the pathogenesis of aggressive cases of IPT could be related to the development of an intense and self-maintaining immune response, with the emergence of clonal populations of T-lymphocytes. The relation of the pancreatic IPT to autoimmune pancreatitis is emphasized.

Keywords Inflammatory pseudotumor · Pancreas · TCRγ-rearrangement · Autoimmune pancreatitis

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Introduction

Inflammatory pseudotumors (IPT), also termed inflammatory myofibroblastic tumors (IMT), are uncommon mass lesions whose origin and pathophysiology are still controversial. They consist of collagen fibers, smooth muscle actin (SMA)-expressing spindle cells (so-called "myofibroblasts") and an intense, mostly lymphoplasmacellular, inflammatory infiltrate [13]. IPT were originally described in the lung and the gastrointestinal tract [7, 29, 33], but they can occur in virtually every anatomical site [12]. The spindle cell component may display atypical features, and it is mandatory to differentiate these lesions from mesenchymal tumors that show histological similarities (e.g., inflammatory fibrosarcoma) [11]. Moreover, recent studies have demonstrated the presence of monoclonality [30], aneuploidy [4] and cytogenetic anomalies [27] in some cases of IMT of various origins. Balanced chromosomal translocations involving the anaplastic lymphoma kinase (ALK) gene have been found in some (but not all) cases of IMT of the lymph node and spleen [27]. Accordingly, the existence of two groups of biologically distinct lesions—namely IMT, which are ALK-positive, and IPT, which are ALK-negative—has been proposed. Nevertheless, the two terms are often used synonymously.

Several investigators have proposed an infectious etiology for IPT/IMT. Members of the herpesvirus family, including Epstein-Barr virus (EBV) [3] and human herpesvirus-8 [18], have been detected by in situ hybridization in the nuclei of the spindle and/or lymphocytic components. DNA fragments with sequence homology to *Pseudomonas veronii* have been isolated from a mesenteric lymph

node of a patient affected by ileo-cecal IPT [9]. Cytokines produced by the microorganisms have been con- sidered responsible for the systemic symptoms of fever, night sweats, fatigue and weight loss frequently reported in IPT.

The two entities of IPT/IMT have been described in the pancreatico-biliary region as single case reports or small series [2, 26, 34, 36, 38], without a clear-cut distinction between them. Here, we report a case of IPT/IMT of the pancreas. We further provide a characterization of its cell population, with particular attention paid to the inflammatory cell component, in view of the fact that the inflammatory cells seem to play a fundamental role in the pathogenesis of the lesion through the production of cytokines and growth factors that, in turn, influence the phenotypic characteristics of the spindle cell and connective tissue elements [23, 28]. We also discuss the potential relationship between IPT and autoimmune pancreatitis.

Clinical history

A 69-year-old male patient presented with a short history of upper abdominal pain and discomfort. Computed tomography scan revealed the presence of a large pancreatic body–tail tumor mass, in close proximity to the superior mesenteric vessels, but without encasement of the vessels themselves (Fig. 1). Fine-needle aspiration cytology and open surgical biopsy of an enlarged left supraclavicular lymph node were performed. The diagnosis was hyperplastic changes and a small lymphangioma, in the absence of malignant cells. At the time of surgery, neither ascitis nor liver or peritoneal metastases were found. A left pancreatectomy with splenectomy and colon splenic flexure resection was performed. An intraoperative frozen section of the tumor mass was interpreted as adenocarcinoma.

The postoperative course was complicated by formation of an intraabdominal abscess and colonic distension. The final histopathological diagnosis was "inflammatory myofibroblastic tumor of the pancreas." The patient was discharged after 1 month of hospitalization. He developed jaundice due to multiple strictures along the extrahepatic bile duct, from the hepatic hilus to the distal choledocus (Fig. 2), 4 months after surgery. He died after 7 months of hospitalization due to sepsis. Serological tests for the detection of EBV, cytomegalovirus (CMV) and human T-cell lymphotropic virus were negative. Laboratory tests revealed serum bilirubin 7 mg/dl, alkaline phosphatase 355 U/l (normal, 40–170 U/l), γ-glutamyl transpeptidase 106 U/l (normal, 3–28 U/l), glutamic pyruvic transaminase 42 U/l (normal, <24 U/l), glutamic oxalacetic transaminase 32 U/l (normal, <18 U/l). Serum total IgG were increased (25.3 g/l, normal 7–16 g/l), but the levels of IgG4 were in the normal range (0.49 g/l, normal 0.052–1.2 g/l).

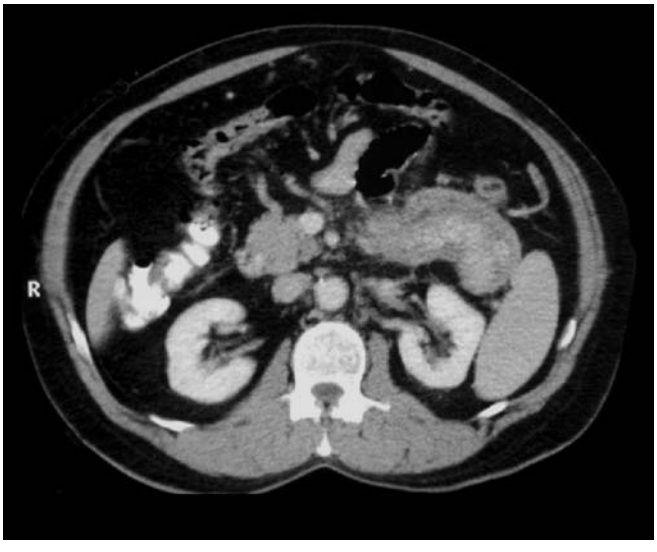

Fig. 1 Contrast-enhanced computed tomography reveals a diffuse mass in the pancreatic body–tail

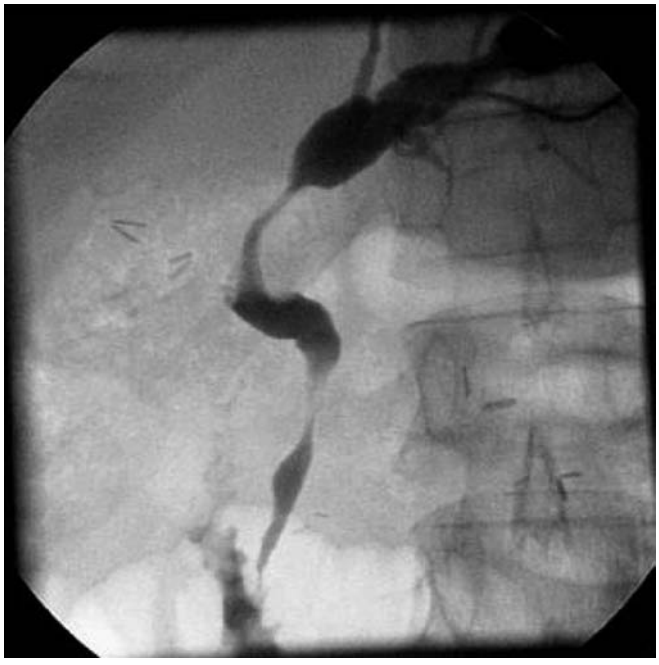

Fig. 2 Endoscopic retrograde colangiography showing the presence of multiple strictures along the common bile duct

Materials and methods

Immunohistochemistry

Formalin-fixed, paraffin-embedded or frozen tissue sections cut from the tumor mass were subjected to immunohistochemical analysis using the following primary monoclonal or polyclonal antibodies: pan-cytokeratin (Kl1, Serotec GmbH, Düsseldorf, Germany); cytokeratin 7 (OV-TL12/30, Dako, Carpenteria, CA, USA); vimentin (V9, Dako); SMA (1A4, Dako); CD68 (KP-1, Dako); CD45 (LCA, Dako); CD20 (L26, Dako); CD45RO (UCHL1, Dako); CD3 (Dako); CD4 (OKT-4, Sanquin, Amsterdam, The Netherlands); CD8 (OKT-8, Sanquin); CD43 (DF-T1, Dako); CD56 (Cell Marque, Hot Springs, AR, USA); ALK (Alk1, Dako); CD30 (BER-H2, Dako); CD34 (QBEND-10, Immunotech, Marseille, France); κ and λ chain (A8B5 and N10/2, Dako); tryptase (G3, Chemicon International Inc., Temecula, CA, USA); transforming growth factor beta 1 (TGF-β1) (Santa Cruz Biotechnology, Santa Cruz, CA, USA); connective tissue growth factor (CTGF) (Santa Cruz); Ki-67 (MIB1, Dako); Epstein-Barr virus latent membrane protein (LMP) (CS 1–4, Dako); and CMV early antigen (CCH2, Dako). The streptavidin-biotin-phosphatase method or the peroxidase, biotin-free EnVision+ System (Dako) was used to detect the binding of the primary antibodies.

TCRγ rearrangement

A semi-nested polymerase chain reaction (PCR) analysis of T-cell receptor gamma (TCRγ) gene rearrangement was used to assess

clonality of the lymphocytic population [5]. Briefly, 200 ng of genomic DNA from the tumor and from a peripancreatic hyperplastic lymph node (control) were amplified in two separate reactions, each using the following primers: $V1_{1-8}$ (5′-TGC AGC CAG TCA GAA ATC TTC C-3′) + $JGT_{1/2}$ (5′-AAG TGT TGT TCC ACT GCC AAA-3′) and $V1_{1-8}$ + JGT_3 (5′-AGT TAC TAT GAG C (TC) AGT CCC-3′). The second amplification round was performed with 1 µl of the first PCR product with primer sets $V2_{1-8}$ (5′-ACG GCG TCT TC (AT) GTA CTA TGA C-3′) + $JGT_{1/2}$ and $V2_{1-8}$ + JGT_3. PCR products of the second amplification were separated on a 6% polyacrylamide gel.

Comparative genomic hybridization

To detect possible chromosomal imbalances of the tumor, a comparative genomic hybridization (CGH) analysis was performed as previously described [22]. Briefly, tumor DNA was extracted from paraffin-embedded material. In a nick translation, tumor DNA was biotinylated, and normal human DNA was labeled with digoxigenin. The probes were then hybridized onto metaphase spreads. Avidin-conjugated fluorescein and anti-digoxigenin-rhodamin conjugate were used for signal detection of biotinylated tumor DNA and digoxigenin-labeled reference DNA, respectively. Hybridized metaphases (n=20) were then captured and analyzed using an inverted microscope (Zeiss Axiovert S 100), a charge-coupled device camera and CGH software (MetaSystems, Germany). Chromosomal gains were presumed if the ratio of tumor to normal signals reached or exceeded 1.25. The respective ratio for chromosomal losses was 0.80.

Results

Pathological findings

Macroscopically, a tumor mass without clear-cut demarcation from the surrounding parenchyma was identified in the pancreatic body–tail. The tumor was hard and yellowish gray, and the normal lobular architecture of pancreatic parenchyma was only partially preserved.

Histologically, the tumor consisted of bands of dense collagen tissue that surrounded lobules formed by residual pancreatic parenchyma, mostly represented by islets, degenerating acini and small ducts (Fig. 3A). Some larger ducts were still recognizable. These residual parenchymal elements were embedded in a dense, mostly mononuclear, inflammatory infiltrate, which showed a particular clustering around blood vessels (Fig. 3B, C) and nerves (Fig. 3E). Inflammation of the vessel walls (arteritis and phlebitis) was present (Fig. 3B, C). At the border between the pancreatic mass and the surrounding soft tissue, the connective tissue was more abundant, displaying large hyaline areas and forming a sort of "capsule" around the entire organ. Here, the inflammatory infiltrate was less dense, mostly consisting of lymphoid follicles with germinal centers. The bands of connective tissue contained spindle cells that were sometimes plump, but always cytologically typical. They exhibited vimentin immunoreactivity, indicating their mesenchymal origin, with a large subpopulation of SMA-positive elements (the so-called myofibroblasts) (Fig. 4A, B); some of them were also CD68 positive (Fig. 4C). Moreover, they expressed CTGF and TGFβ-1; CTGF was also extensively expressed in inflamed residual pancreatic ducts and degenerating acini and in the inflammatory infiltrate (Fig. 5A). TGFβ-1 had the same localization of CTGF, with the exception of a diffuse staining in the connective tissue bands, consistent with its secretion into the extracellular space by the fibroblasts (Fig. 5B), and a less frequent expression in inflammatory cells.

The inflammatory infiltrate mostly consisted of CD68-positive mononuclear cells, therefore, identified as macrophages (Fig. 4C). They were particularly abundant in the lobules of residual pancreatic parenchyma, but some of them could also be found in the connective tissue bands.

T-lymphocytes, identified by CD3 and CD45RO immunostaining, were a predominant component of the inflammatory infiltrate. They accumulated around blood vessels, especially small veins (Fig. 3D), and around nerves (Fig. 3F). T-lymphocyte subtyping revealed a slight preponderance of the CD4-positive over the CD8-positive cells. B-lymphocytes (CD20+) and a polyclonal population of plasma cells (κ and λ-chain immunostaining) were also present, although to a lesser extent. CD30 and ALK-expressing lymphocytes were absent, as well as CD56-positive natural killer lymphocytes. At the periphery of the pancreas, lymphocytes were mostly organized in lymphoid follicles with well-developed germinal centers; whereas, in the context of the pancreatic parenchyma, they were part of the diffuse inflammatory infiltrate. Mast cells, identified by specific tryptase immunostaining [17], were mostly found in the lobules of the destroyed pancreatic parenchyma, around degenerating acini and inflamed ducts. Scattered eosinophils were also present.

Angiogenesis, evaluated by means of CD34 immunostaining of endothelial cells, was extremely developed in the degenerating pancreatic parenchyma (Fig. 5C). Immunohistochemical analysis of cell proliferation by identification of the proliferation-associated antigen Ki-67 revealed scattered positivity (proliferating index <5%) in inflammatory cells and regenerating pancreatic ductal cells. The myofibroblast compartment displayed a lower proliferating index (Fig. 5D). Neither EBV-LMP nor CMV-early antigen immunoreactivity was detected.

TCRγ rearrangement

PCR analysis of TCRγ-gene rearrangement revealed three prominent bands in the tumor DNA and a smear in the DNA from the peripancreatic lymph node when the set of primers $V1_{1-8}$ + $JGT_{1/2}$ was used (Fig. 6). This result suggests the existence of an oligoclonal population of T-lymphocytes within the tumor mass and a polyclonal population in the surrounding lymph nodes.

CGH analysis

No chromosomal imbalances were detected by comparative genomic hybridization analysis.

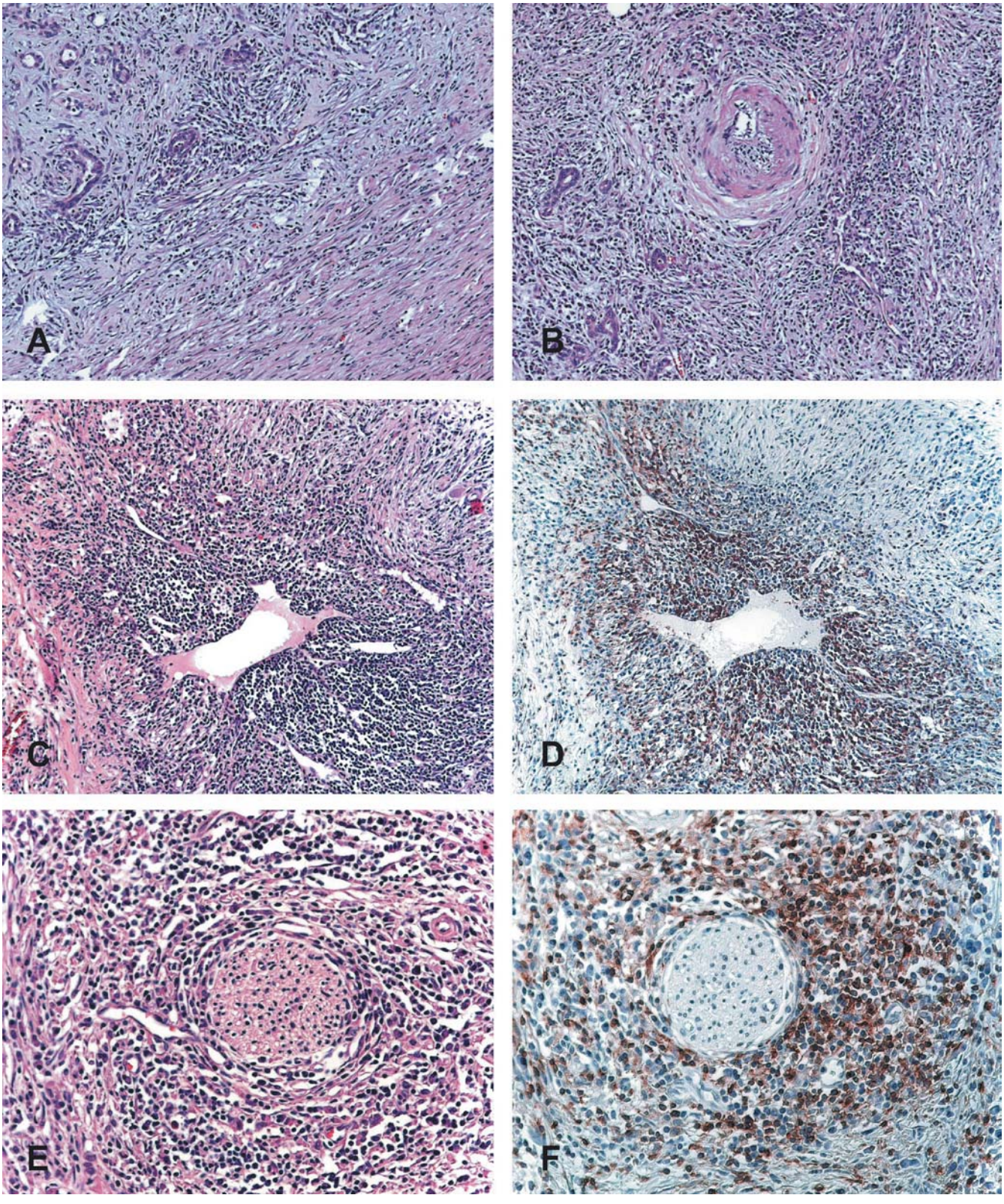

Fig. 3 Inflammatory pseudotumor of the pancreas. **A** The tumor mass consists of two main cell populations: spindle cells, arranged to form large bands of dense collagen (*right*) around and within the pancreatic parenchyma and mononuclear inflammatory cells that surround residual pancreatic ducts (*left*). **B**, **C**, **E** The inflammatory cells accumulate around and in the wall of arteries (**B**), veins (**C**) and around nerves (**E**). **D**, **F** Immunostaining for CD45 RO demonstrates a great preponderance of T-lymphocytes. Original magnifications ×100 (**A**–**D**), ×200 (**E**–**F**)

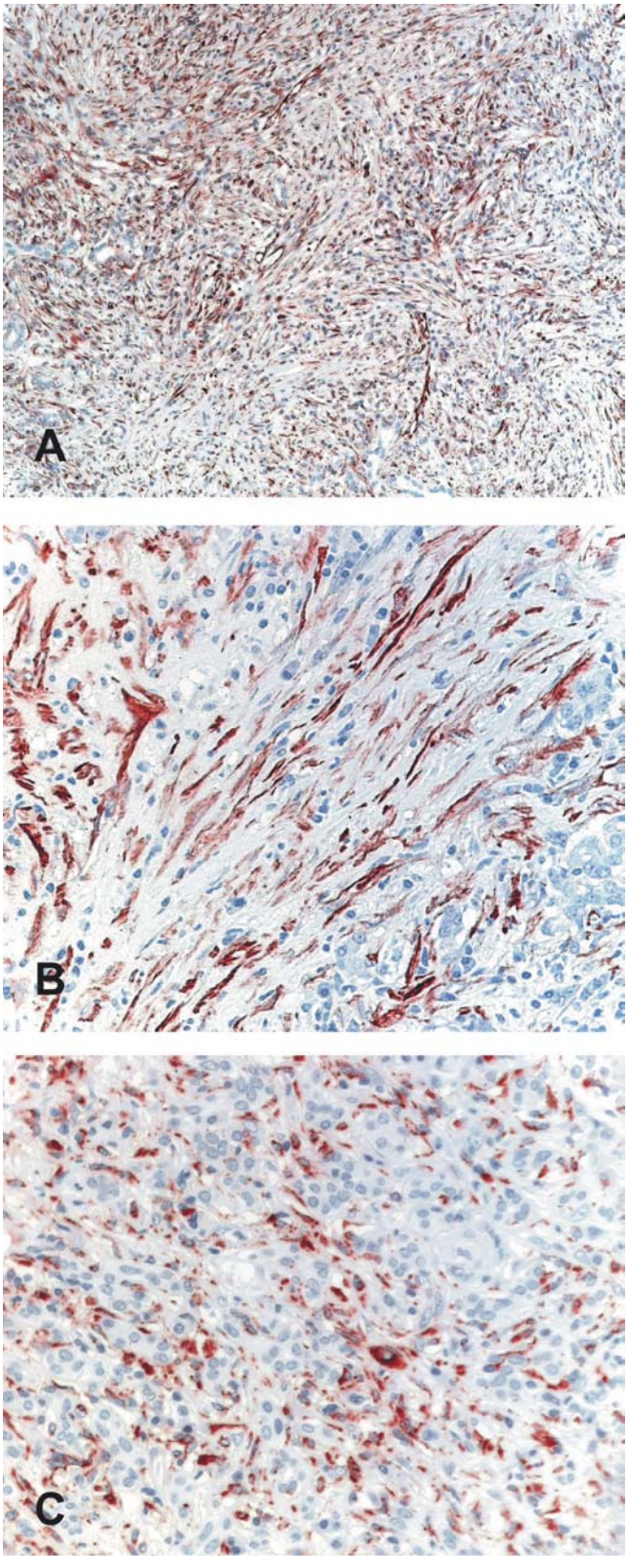

Fig. 4 Immunohistochemical characterization of the cell populations. **A** Immunostaining for vimentin shows a strong positivity in the spindle as well as in the inflammatory cell component. **B** The spindle cells exhibit immunoreactivity for smooth muscle actin. **C** Immunostaining for CD68 reveals that many of the inflammatory cells are macrophages. Original magnifications ×100 (**A**), ×200 (**B**–**C**)

Discussion

This paper describes a case of IPT/IMT arising in the pancreatic body–tail region, which presumably recurred in the pancreatic head–biliary region 4 months after resection. The importance of this pathological lesion, which has been described with increasing frequency in the literature, resides in the fact that it can be preoperatively mistaken for a malignant tumor. Besides this clinical relevance, the biology of IPT/IMT is challenging and not completely clarified. IPT of the pancreas have been described since 1984 [2], but only in recent years have they been better characterized from a biological point of view [26, 34, 36, 38]. This characterization mainly concerns the spindle cell component, consisting of vimentin and SMA-positive myofibroblasts. Table 1 summarizes the more relevant clinical data and immunohistochemical findings of the four studies cited above. Only two of them describe in more detail the inflammatory cell component of IPT/IMT, which mainly consists of macrophages, T-lymphocytes and, to a lesser extent, B-lymphocytes [26, 38]. The relevance of the inflammatory infiltrate in the pathogenesis of pancreatic IPT/IMT is suggested by the findings of the present study: inflammatory cells could play an active fibrogenetic role in IPT/IMT through the production of TGF-β1 and CTGF. These two factors are fundamental mediators of pathological processes characterized by extracellular matrix deposition and fibrosis, such as chronic pancreatitis [15], glomerulosclerosis and tubulo-interstitial fibrosis [8, 20], scleroderma [31] and liver cirrhosis [1]. In chronic pancreatitis, TGF-β1 and CTGF are produced by degenerating acinar cells and metaplastic ducts (tubular complexes), as well as by fibroblasts. In addition, TGF-β1, but not CTGF, is expressed by the inflammatory cell population [15]. In pancreatic IPT/IMT, it is likely that both the residual pancreatic parenchyma and the inflammatory cells induce myofibroblast accumulation through the expression of TGF-β1 and CTGF. A similar phenomenon has been described, for example, in animal models of lung fibrosis [37], where TGF-β1 and CTGF act as the main mediators of the fibrogenic response.

Another interesting and important finding of this study is the identification of clonal populations of T-lymphocytes in the tumor tissue but not in surrounding hyperplastic lymph nodes. Monoclonal T-lymphocytes have been described in inflammatory sclerosing disorders, such as idiopathic retroperitoneal fibrosis [14], which shares some morphological similarities with IPT/IMT. However, they have never been investigated in pancreatic IPT/IMT and have never been found in IPT arising in other anatomical sites [6, 28]. The significance and the origin of the clonal T-lymphocytes in this case of IPT/IMT are currently not known, but it can be speculated that they develop in the context of an intense and destructive, maybe also self-stimulating, inflammatory reaction. The largest number of inflammatory cells was found around residual pancreatic acini and in the walls of blood vessels; in the same areas, the highest proliferative activity of the inflammatory component was detected, as evidenced by Ki-67 immuno-

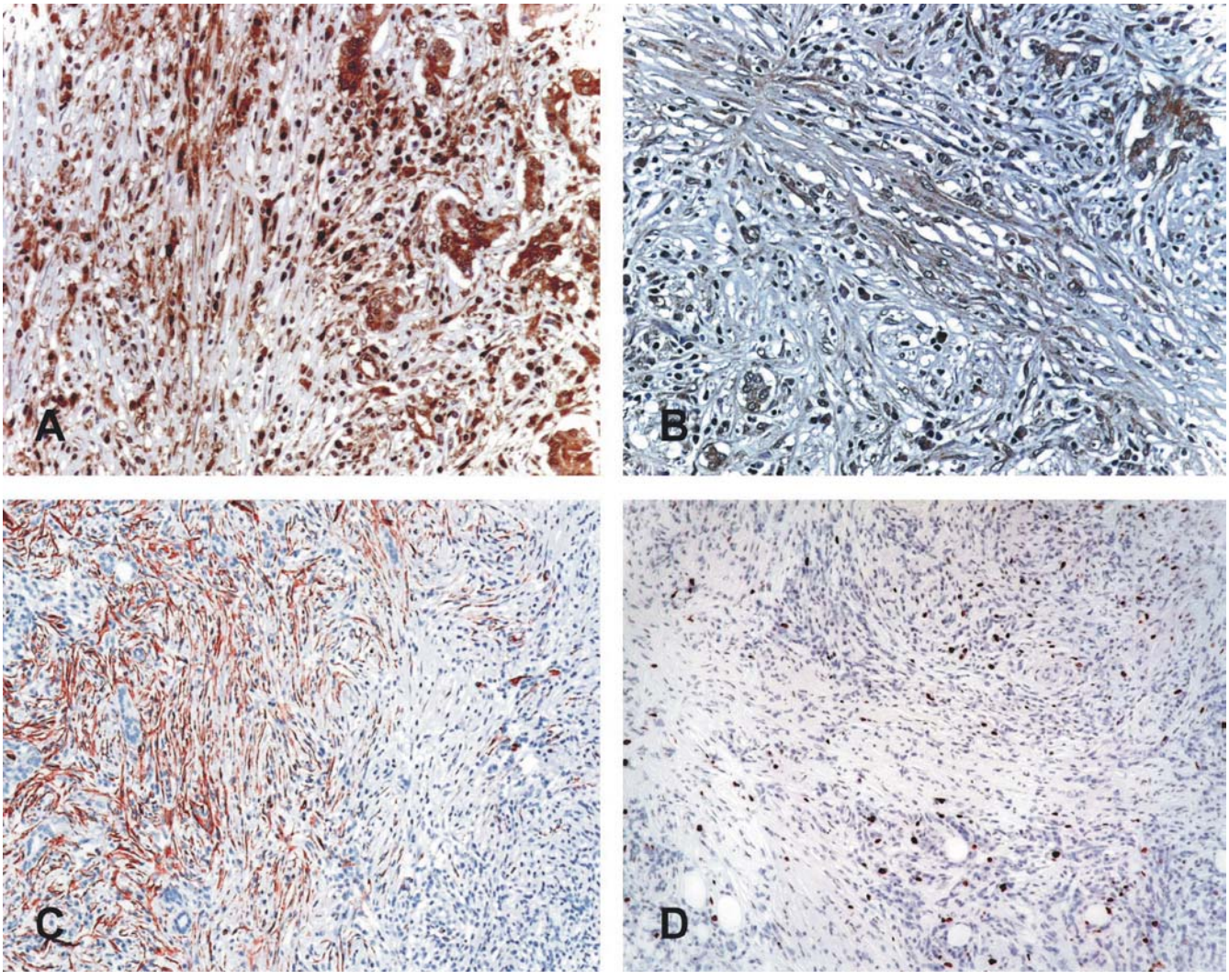

Fig. 5 Connective tissue growth factor (**A**) and transforming growth factor-β (**B**) expression in the proliferating pancreatic ducts, in the inflammatory cells and in the spindle cells. **C** Markedly high angiogenetic activity within the residual pancreatic parenchyma as shown by CD34 immunostaining. **D** The Ki-67 proliferative index is <5% and mostly confined to the inflammatory cells and the residual pancreatic parenchymal elements. Original magnifications ×200 (**A, B**), ×100 (**C**, **D**)

Table 1 Clinical and immunohistochemical characteristics of pancreatic inflammatory pseudotumors/inflammatory myofibroblastic tumors (IPT/IMT)

Author	Sex/age	Immunohistochemistry		Clinical behavior
		Spindle cells	Inflammatory cells	
Zanger P (2002) [38]	F/62	Vimentin+, SMA+	B-lymphocytes*, T-lymphocytes*, CD68 +	No recurrence after 6 months
Wreesman V (2001) [36]	M/62	Actin +, SMA +	Not assessed	No recurrence after 6 years
	M/56	Actin +, SMA +	Not assessed	No recurrence after 5 years
	M/50	Actin +, SMA +	Not assessed	No recurrence after 4 years
	M/45	Actin +, SMA +	Not assessed	No recurrence after 10 years
	F/57	Actin +, SMA +	Not assessed	No recurrence after 3 years
	F/32	Actin +, SMA +	Not assessed	No recurrence after 12 years
Walsh SV (1998) [34]	M/35	Vimentin +, SMA +	CD20 +, OPD4 +, CD8 +	Lung IMT after 6 years
Kroft SH (1995) [26]	F/42	Vimentin +, Actin −	Not assessed	No recurrence after 6 months

SMA: smooth muscle actin
*: no marker specified
OPD4: marker of T-helper/inducer lymphocytes

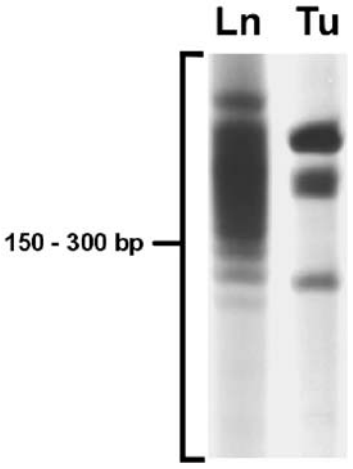

Fig. 6 Analysis of T-cell receptor gamma (TCR-γ) gene rearrangements by polymerase chain reaction and polyacrylamide gel electrophoresis. As detailed in the Materials and Methods section, two sets of primers for the V and J regions of the TCR γ gene were used. Three discrete bands were seen in the tumor DNA (*Tu*), suggesting the existence of oligoclonal populations of T-lymphocytes. Control DNA from a peripancreatic lymph node (*Ln*) gave a smear instead

staining. As a consequence of tissue destruction, new epitopes are exposed, and they trigger an "explosive" immune response that could culminate in the development of clonal populations of lymphocytes. The aggressive course of the disease, with a probable early relapse, could be explained by these considerations. The cause of such an intense immunological response is unknown; some of the main viral pathogens were investigated at the clinical or morphological levels, with negative results.

A recent editorial [12] points to the existence of different subtypes of IPT/IMT: one group arises in a younger population and its main cellular components have the phenotype of myofibroblasts [10], while the second group is represented by the infection-related IPT, and its main cellular components are CD68-positive spindle cells [9]. Accordingly, tumors that fall in the first category are better designated IMT. They can recur and display a sarcomatous progression; they are probably true neoplasms [16]. IMT, with evidence of clonality [30] or of chromosomal translocations involving the ALK receptor tyrosine-kinase locus [19], belong to this category. Therefore, although a histopathological diagnosis of IMT was made, the term IPT would be more appropriate in the case reported here, where the inflammatory component is predominant and the myofibroblastic component has a bland morphological and genetic appearance, as shown by immunostaining (low proliferative activity, no ALK expression) and CGH results. Recently, the relationship between IPT and autoimmune pancreatitis (also known as lymphoplasmacytic sclerosing pancreatitis or duct destructive chronic pancreatitis) has been discussed, and both diseases are considered part of the same disease spectrum. Autoimmune pancreatitis can be associated with the presence of an IPT-resembling tumor-like mass. Histologically, it is characterized by dense periductal lymphoplasmacytic infiltrates, mainly consisting of T-lymphocytes, periphlebitis and interstitial fibrosis [24, 35], features that were also prominent in the case reported here. Moreover, recurrent autoimmune pancreatitis can present with biliary strictures [24] and shows a dramatic response to steroid therapy [21, 32]. Although the diagnostic criteria for autoimmune pancreatitis were not completely fulfilled (e.g., absence of a "ductocentric inflammation," that is, the accumulation of the inflammatory cells around the ducts, with relative sparing of the acinar parenchyma; absence of abnormal IgG4-serum levels) it cannot be excluded that this case of IPT developed in the context of an autoimmune pancreatitis.

A striking aspect of this case of pancreatic IPT is the extraordinary generation of new vessels in the areas of tissue destruction, as revealed by CD34 immunostaining. Angiogenesis develops as a physiological response in the context of wound healing and tissue repair. At the same time, endothelial cells are directly involved in the inflammatory response through the expression of adhesion molecules that play a major role in the recruitment of circulating inflammatory cells [25]. Therefore, the intense angiogenetic response underscores once more the central role of inflammation in the destruction of the pancreatic parenchyma and, consequently, in the pathogenesis of IPT.

In summary, the case reported in this study has the characteristics of the category of IPT described above: the spindle cells are SMA and CD68 positive and do not show any kind of atypia; there are neither chromosomal aberrations nor ALK overexpression. Moreover, the spindle cell component is quantitatively very limited, compared with the number of inflammatory cells (macrophages and T-lymphocytes), and could be interpreted as merely "reactive." The clinical presentation and the morphological aspect strongly suggest an association between pancreatic IPT and autoimmune pancreatitis. These two entities could, therefore, be interpreted as different phases/manifestations of the same disease process. An immune response to an unknown trigger is the main mediator of tissue aggression and destruction and, due to the development of clonal populations of T-lymphocytes, is likely to be capable of self-maintenance. Inasmuch as clonal populations of T-lymphocytes have not previously been reported in IPT, it seems necessary to widen the spectrum of different processes included in the definition of IPT/IMT and to better investigate their relationship with lymphoproliferative disorders.

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