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Pancreatic Tuberculosis – An Unsuspected Diagnosis: Case Report and Literature Review

Baldi F[1,2*], Gonella R[3,4], Mastracci L[4,5], Seitun S[6], Nicolini L[2], Ballestrero A[3,4], Bassetti M[1,2], Maria AD[1,2]

[1]Department of Health Sciences (DISSAL), University of Genoa, 16132 Genoa, Italy

[2]Infectious Diseases Unit, Ospedale Policlinico San Martino-IRCCS, 16132 Genoa, Italy

[3]Department of Internal Medicine, Università degli Studi di Genova, Genova, Italy

[4]IRCSS Ospedale Policlinico San Martino, Genova, Italy

[5]Department of Integrated Surgical and Diagnostic Sciences, University of Genoa, 16132 Genoa, Italy

[6]Department of Radiology and Interventional Radiology, IRCCS San Martino University Hospital, IST– National Institute for Cancer Research, Genova, Italy

***Corresponding author:**

Federico Baldi,
Department of Health Sciences (DISSAL), University of Genoa, Infectious Diseases Unit, Ospedale Policlinico San Martino-IRCCS, 16132 Genoa, Italy,
E-mail: fede.bld@gmail.com

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Abbreviations:

TB: tuberculosis; EPTB: extrapulmonary tuberculosis; PTB: pancreatic tuberculosis; EUS: endoscopic ultrasounds; FNA: fine-needle aspirations; ATT: antitubercular therapy; PCR: polymerase chain reaction; CT: computed tomography; CBC: complete blood count; AST: aspartate aminotransferase, ALT: alanine amino transferase; GGT: gamma glutamiltransferase; ALP: alkaline phosphatases; HIV: human immunodeficiency virus; ANA: antinuclear antibodies; FDG-PET: fluorodeoxyglucose positron emission tomography; SUVmax: standardized uptake value; BALF: bronchoalveolar lavage fluid; ZN: Ziehl Neelsen; BK: Koch's bacillus.

1. Abstract

1.1. Background: Tuberculosis remains a public health concern, with almost 10 million new cases and 1.4 million deaths every year. Although the vast majority of TB cases involve the lungs, approximately 15%– 20% are extrapulmonary, with abdominal TB accounting for 11%–16%, including infections of different combinations of the gastrointestinal tract, lymph nodes, peritoneum, and intra-abdominal organs. Pancreatic TB (PTB) is an entity often disregarded by clinicians because of its exceeding rarity. Indeed, fewer than 100 cases of isolated pancreatic mass and fewer than 200 cases with concomitant different abdominal foci have been reported so far. PTB is a challenging diagnosis sometimes littered with initial workup mistakes since it may mimic pancreatic cancer or other clinical entities, such as chronic pancreatitis with pseudocystis, autoimmune pathology, and sarcoidosis. For this reason, PTB must be considered when dealing with a pancreatic mass lacking fit with specific patterns or without a clear histopathology. Awareness of PTB has been increasing in recent years, mainly related to the progressive improvement of diagnostic techniques. However, surgical procedures are usually necessary for diagnosis, and data on optimal treatment duration are still scarce. The present work aims to better define PTB by reporting a clinical case and reviewing the current literature, focusing on the differences in the diagnostic process and clarifying choice and duration of antitubercular therapy.

1.2. Case Presentation: A 31-year-old immunocompetent man from Morocco with a history of abdominal pain and a pancreatic mass underwent endoscopic ultrasound (EUS) fine-needle aspiration (FNA) for a suspected neoplastic mass. FNA was diagnostic for PTB, avoiding unnecessary surgery. A nine-month standard ATT was started with resolution of symptoms and signs of infection.

1.3. Conclusions: PTB presenting as isolated pancreatic mass remains a diagnostic challenge that should be suspected in patients coming from endemic areas independently from the patients' immune status. Clinical suspicion and further awareness are needed to

avoid unnecessary surgical diagnostic/therapeutic procedures.

2. Case Presentation

A 31-year-old male patient from Morocco was admitted to the internal medicine department of our institute for abdominal pain in the upper regions of the abdomen and nausea that started one month earlier; no fever was reported. He has been living in Italy for one year, and his previous medical history was unremarkable. Blood tests revealed a mild increase in gamma-glutamyl transpeptidase (GGT) and alkaline phosphatase at 99 and 174 U/L, respectively (upper normal limit, ULN, 50 and 116 U/L, respectively), while bilirubin and liver enzymes were within normal limits. White cell count, amylases, and lipases were also normal. Infection with HIV and viral hepatitis was ruled out. The patient's data are all summarized in (Table 1). Abdomen ultrasound (US) showed multiple pancreatic nodules. Thus, a CT scan was performed and showed (1) multiple hypoattenuating well-defined lesions within the head and tail of the pancreas with rim enhancement and thickening: one nodule in the head of the pancreas of 36×20 mm and four smaller nodules in the tail of 27 mm, 24 mm, 25 mm and 15 mm; (2) mild ascites with irregular thickening of the peritoneum and micronodular omental thickening; and (3) abrupt occlusion of the distal splenic vein encased by a pancreatic tail lesion. Distal splenic thrombosis was compensated by collateral gastric vessels and a mesenteric venous channel via a large omental vein in the left abdomen in communication with the splenic vein at the splenic hilum. Associated findings included some peripancreatic/periportal lymphadenopathies and mild reactive right basal pleural effusion with an area of plate-like atelectasis (Figure 1). Pancreatic involvement was primarily attributed to pancreatic tumor. Differential diagnosis included chronic pancreatitis with pseudocysts, autoimmune pathology, sarcoidosis, and tuberculosis. Chronic pancreatitis was considered improbable given that the patient did not report alcohol use, and imaging techniques did not evidence pancreatic lithiasis. Autoimmune disease and sarcoidosis were both deemed possible, as antinuclear antibodies (titre 1:160) and angiotensin converting enzyme (ACE) test were positive. To assess the risk of TB, an IGRA test was performed and resulted positive. However, preliminary research of mycobacteria on urine and feces was negative (DNA-PCR and direct microscopy both negative). A total-body FDG-PET showed increased glucose uptake of the pancreatic nodules with a maximum standardized uptake value of 15 (SUVmax 15).

Finally, EUS-FNA was performed. Histology showed mixed inflammatory infiltrate with lymphocytes, plasma cells, histocytes, and necrotic debris but no malignant cells and no acid-fast bacilli on AFB stain (Figure 2A–B). Thus, the presence of M. tuberculosis was investigated in multiple samples, including urines, stools, bronchioalveolar lavage (negative NAAT, Ziehl-Neelsen microscopy and culture), and blood cultures. All of them tested negative. An infectious diseases consultant suggested a histologic review of pancreatic biopsy material. A nested PCR specific for M. tuberculosis complex DNA was performed on the pancreatic material, with a positive result. To address the involvement of abdominal lymph nodes and peritoneum, as suggested by the CT scan, an omental biopsy and samples of peritoneal fluid were collected during a laparoscopic procedure. Histology of the omentum showed multiple coalescent granulomatous nodules without necrosis (Figure 3A–D). The patient received a classical four-drug regimen ATT with isoniazide, rifampicin pyrazinamide, and ethambutol starting March 21, with the intent of treating PTB for at least six months, considering the possibility to extend the treatment up to nine months if a clinical and radiological response at the follow-up did not occur. Anticoagulation with LMWH was started as well for inferior cava thrombosis. During the stay, a single episode of fever with negative blood culture occurred, and the patient well tolerated the ATT with no side effects. He was then discharged from our department on March 29, 2021, still referring to our outpatient clinic for medications and blood tests. An abdominal CT scan on day 75 of treatment showed imaging resolution of all the known multiple pancreatic lesions except for one at the pancreatic tail, which was mildly reduced, and resolution of thrombosis of the inferior vena cava (Figure 4).

Table 1: Patient's data

Sex	**Male**
Age	32
Symptoms	
Abdominal pain	Yes
Weight loss	No
Fever	No
Jaundice	No
Diarrhea	No
Pancreas involvement	
Head	1 nodule (36×20mm)
Body	No
Tail	4 nodules (27mm, 24mm, 25mm, 15mm)
Extrapancreatic involvement	Peritoneal and omental involvement; splanchnic vein thrombosis of splenic vein; peripancreatic/periportal lymphadenopathies; ascites

Diagnosis	
HIV	No
Histology	Inflammatory granulomas with giant cells, with no signs of necrosis
PCR BK	Positive
Ziehl-Nielsen	No
Culture for M. tuberculosis	Positive

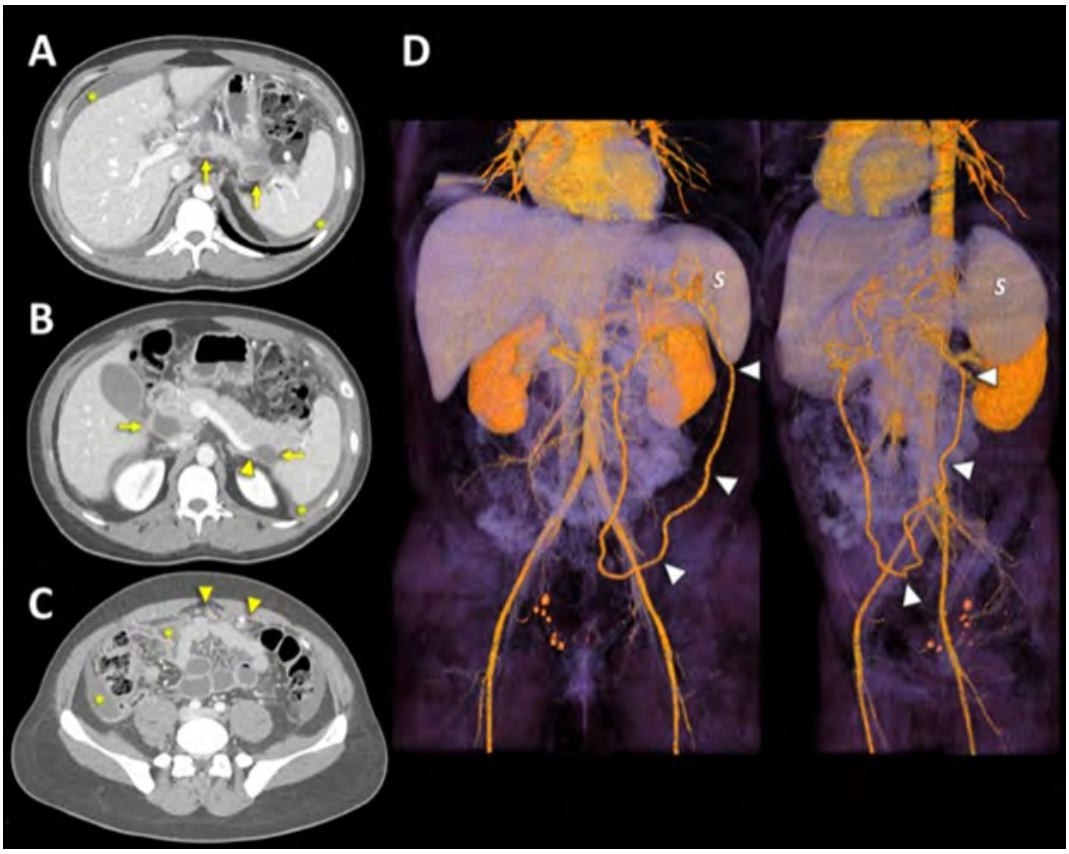

Figure 1: Axial CT images in the venous phase (A–C, from cranial to caudal) showing the enlargement of the pancreas presenting with multiple hypoattenuating lesions with peripheral rim enhancement and thickening (arrows in A and B). Note the abrupt cutoff and thrombosis of the distal splenic vein encased by the hypodense mass at the posterior margin of the pancreatic tail (arrowhead in B), the mild abdominal ascites with peritoneal thickening and enhancement (asterisks in A–C), and micronodular omental thickening (arrowheads in C). 3D image reconstructions (D) showing a compensatory mesenteric collateral vessel via a large omental vein in the left abdomen in communication with the splenic vein at the splenic hilum (arrowheads). *S*, spleen.

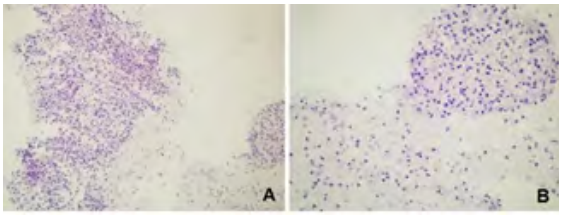

Figure 2: Fine-needle biopsy of pancreatic lesion showing a mixed inflammatory infiltrate with lymphocyte, plasma cells, histocytes, and necrotic debris (magnification 20x and 40x, panels A and B, respectively).

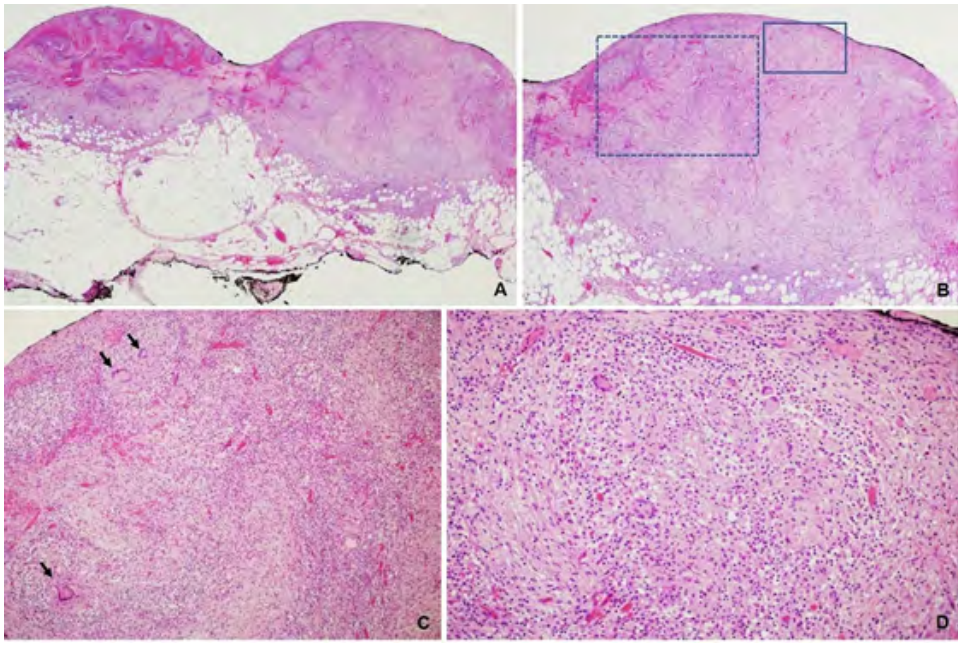

Figure 3: (A) Peritoneal biopsy showing multiple inflammatory nodules (magnification 2x); (B) higher magnification of A (4x), showing multiple coalescent granulomatous nodules without necrosis; (C) higher magnification of B (dot line square; 10x) showing multiple giant cells (arrows); (D) higher magnification of B (continuous line square; 20x) showing a granuloma with giant cells and mixed inflammatory infiltrate composed of lymphocytes, plasma cells, and histiocytic and epithelioid cells; necrosis is absent (magnification 20x).

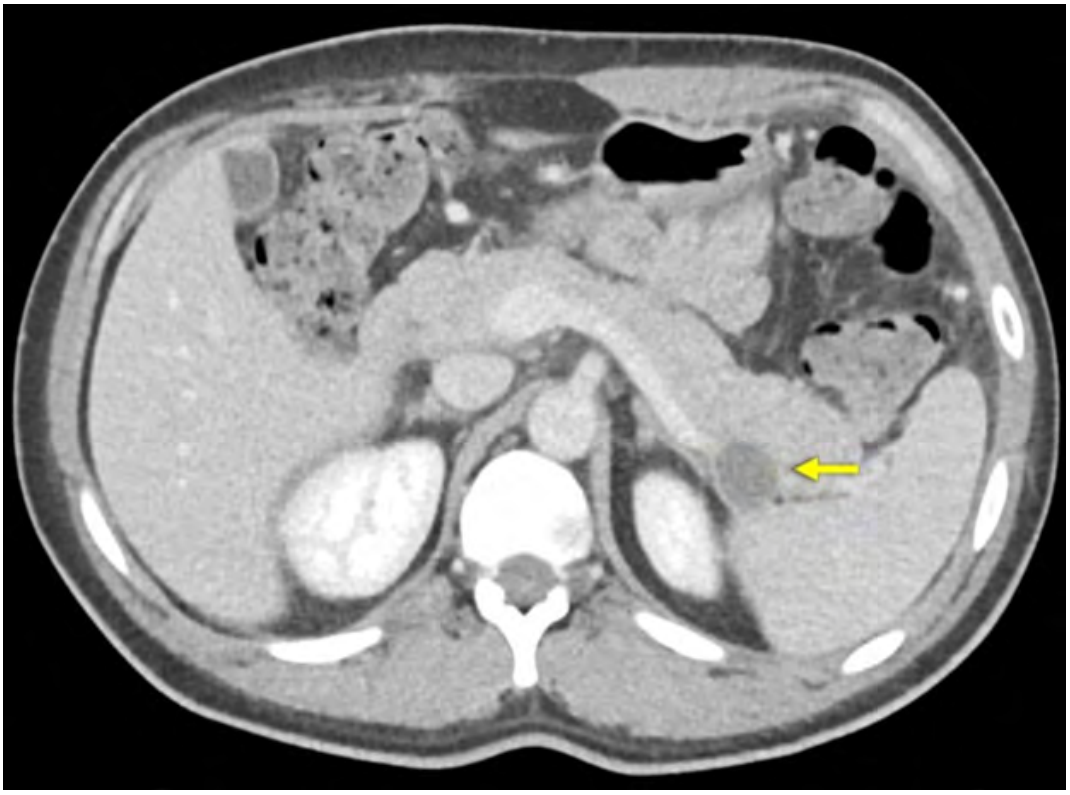

Figure 4: Axial CT image in the venous phase after 75 days of antitubercular treatment showing the resolution of all the pancreatic lesions except for one at the tail, which was mildly reduced (arrow). Note the resolution of the ascites.

3. Background

Tuberculosis (TB) remains a public health concern, with almost 10 million new cases and 1.4 million deaths every year [1]. Although the vast majority of TB cases are pulmonary, approximately 15%–20% are extrapulmonary (EPTB), with abdominal TB accounting for 11%–16% [2]. Abdominal TB includes infection of different combinations of gastrointestinal tract (especially the ileocecal region), lymph nodes, peritoneum, and intra-abdominal organs such as the spleen, liver, and pancreas [3]. Pancreatic TB (PTB) is a rare entity usually not considered by clinicians, with very few cases described in the literature both as isolated pancreatic mass, with less than 100 cases reported worldwide, and as localization of abdominal TB with other abdominal foci, with less than 200 cases [4]. Diagnosis can be challenging, and initial diagnostic workup mistakes are frequent, especially because PTB can mimic pancreatic cancer and other clinical entities, such as chronic pancreatitis with pseudocystis, autoimmune pathology, and sarcoidosis [5,6], and for this reason, PTB must be considered when dealing with a pancreatic mass lacking fit with specific patterns or without a clear histopathology. Recent works have initiated a literature review process presenting data on single case reports and their diagnostic challenges [4,7]. Additional clinical focus is however needed to further address aspects of PTB, and some questions still need to be answered: Is there a difference in the diagnostic techniques used over time? How did the diagnostic techniques influence the number of correct diagnoses of pancreatic TB with the passing of time? Is there a difference in diagnostic methods adopted in different centers and geographical areas?

Is PTB antitubercular therapy the same as for extrapulmonary TB, and what do we know about the optimal duration of therapy? To address these questions, raised by the previous case report, we performed a literature research on PubMed, looking for cases of PTB presenting as isolated pancreatic mass in the last 10 years (2010–2020).

4. Methods

To identify reports of PTC cases, a comprehensive literature search of PubMed database was conducted. The keywords "pancreatic tuberculosis case report" and the following MESH term "tuberculosis" OR "mycobacterium" AND "pancreas" OR "pancreatic" were used. As the aim of the review was to focus on challenges in diagnostic and therapeutic management of PTB, only cases of solitary PTB were included. Thus, cases of TB infection of any other organ were ruled out. A period of 10 years (2010–2020) was analyzed. The following data were extracted from every selected article: author name; year of publication; geographic area; age, sex, and immune status of the single patient at the time of the diagnosis; imaging techniques used for diagnosis (focusing on the pancreatic area involved: head, body, and tail); microbiological tests (direct microscopy, PCR, culture); histologic findings; peritoneal involvement; and antitubercular regimens and their durations. Data from the selected studies were then encoded into a Microsoft Excel spreadsheet for analysis [Suppl. Information 1].

5. Results

According to the selection criteria, we included in the present analysis 56 case reports of single patients affected by PTB presenting as isolated pancreatic mass over the last 10 years (2010–2020) [8-63]. The majority of patients (41/56, 73%), were male with a male/female ratio of 2.5:1 and a median age of 40 years at clinical presentation (age range: 5–86). Cases were most frequently reported in Asia (31, 55%), 15 of which were from India. Almost a fifth of cases (12/56, 21%) were previously or simultaneously diagnosed with immunosuppression (mainly HIV infection and diabetes mellitus) or were under immunosuppressive regimens at the time of the diagnosis (Table 2). PTB was observed mainly in the head (66%), followed by the body (16%), and the tail (2%) of the pancreas. Multiple PTB localizations occurred in a minority of cases (16%), and four patients (7%) were also found to have ascites, peripancreatic enlarged lymph nodes, and/or deep venous thrombosis of portal/hepatic veins. With regard to invasive diagnostic procedures adopted to achieve a PTB diagnosis, most of the patients (n = 29, 52%) underwent EUS-FNA, 7 patients (12.5%) underwent CT-FNA, 7 (12.5%) were diagnosed through laparoscopy, 6 (11%) through laparotomy, and 7 (12.5%) underwent surgery with a Whipple procedure of duodeno-coephalo-pancreasectomy (Table 3). Different techniques were used to collect pancreatic material for diagnosis. Histology was performed in 48/56 cases (85%), with a pattern of necrotizing granulomas in 40/48 patients (83%), while 8/43 (17%) patients had a pattern of non-necrotizing epithelioid granulomas (17%). Microbiological detection of M. tuberculosis was available in 77% of cases (43/56), with Ziehl Neelsen (ZN) microscopy in 42% (18/43), PCR in 16% (7/43), and a positive culture for MTB in 19% (8/43). Overall, in 23% of cases (10/43), diagnosis was obtained combining two or more microbiological methods, and in almost a fourth of the cases (23%, 13/56), diagnosis was reached by histology alone, with microbiology testing negative or not performed (Table 4). Following diagnosis of PTB, a standard four-drug regimen (HRZE) was started in all but one case, while the last was treated with protionamide, ethambutol, pyrazinamide, amikacin, linezolid, and moxifloxacin because of rifampicin resistance. The length of therapy varied from 6 to 12 months; particularly, 16, 7, and 8 patients were treated for 6, 9, and 12 months, respectively. The remaining 25 case reports did not specify the length of treatment.

Table 2: Demographic and epidemiological data in a PTB case report literature review

Median age (years)	41
Age range (years)	5–86
Sex	
Male	41 (73%)
Female	16 (27%)
Immune status	
Immunocompetent	44 (79%)
Immunocompromised	12 (21%)
Origin	
Africa	4 (7%)
Asia	31 (55%)
Europa	13 (23%)
North America	6 (11%)
South America	2 (4%)
Oceania	0 (0%)

Table 3: Diagnostic procedures adopted to obtain a pancreatic sample

EUS-FNA	29 (52%)
CT-FNA	7 (12.5%)
Laparoscopy	7 (12.5%)
Laparotomy	6 (11%)
Whipple surgery of pancreas	7 (12.5%)

Table 4: Microbiological and histological diagnosis in a PTB case report literature review

TB Identification Method	
Positive histology	48/56 (86%)
Negative microbiologic testing, positive histology	13/56 (23%)
Histology only	13/56 (23%)
Microbiology only	8/56 (14%)
Positive microbiologic testing	43/56 (77%)
Microbiological Identification Method	
Ziehl Nielsen	18/43 (42%)
PCR	7/43 (16%)
Culture	8/43 (19%)

6. Discussion

Abdominal TB encompasses infection by Mycobacterium tuberculosis hominis of different combinations of the gastrointestinal tract, lymph nodes, peritoneum, and intra-abdominal organs such as the spleen, liver, and pancreas.

Pancreatic localization of TB is rare, accounting for less than 1% of extrapulmonary forms of tuberculosis. This rarity might cause diagnostic delays. Possible pathways for abdominal TB infection include hematogenous spread from primary pulmonary TB, ingestion of infected milk products, ingestion of infected sputum from pulmonary TB, and direct invasion from an adjacent organ [64]. A literature search resulted in the finding of extremely few cases (< 100) reported worldwide presenting as isolated pancreatic mass [65]. Of these, only 56 were reported from 2010 to 2020 including the present, which represents the third case reported in Italy since 1995. In this review, we found that PTB is more frequently reported from low-income areas in Asia but has also been documented in well-developed settings such as Europe and North America. The typical patient is a young male adult without immunosuppression. Indeed, an immune disorder, such as HIV, or diabetes or administration of immunosuppressant drugs as predisposing factor are observed in only a minority (21%) of the reported cases. Our case report fits the overall picture of the search: a young non-immunosuppressed male from North Africa. Although Africa is a region highly endemic to tuberculosis according to WHO reports, isolated PTB is reported less frequently compared with other regions. This may be due to several factors including the prevalence of other diseases, limited access to healthcare and a setting with inadequate resources where endoscopic FNA may be limited to some areas, and limited interest/resources for academic literature. There is no well-defined clinical picture for PTB. Signs and symptoms are shared with other clinical entities. Ascites nausea and abdominal pain were the symptoms and signs leading to hospitalization in this case, in line with data from the present literature search.

Presentation of PTB on CT scan is variable and includes an isolated pancreatic mass, predominantly in the head, but may be also observed in the body and the tail of the pancreas according to the literature of isolated PTB cases. In general, imaging characteristics are nonspecific since pancreatic involvement can present with a variable spectrum of imaging findings. Pancreatic lesions can be solid or cystic-like and can mimic both solid or cystic pancreatic neoplasms and pseudocysts [25,28,30,31]. According to an imaging review of 32 cases from India, of which 16 were seropositive for HIV-1 infection, a bulky and heterogenous pancreas with peripancreatic enlarged lymph nodes was observed in most patients [66]. Most of the pancreatic lesions were solitary (63%), involving mainly the body (56%) followed by the head (50%) and tail (9%) of the pancreas, some of which showing peripheral enhancement. The main echocardiographic finding was the presence of hypoechoic well-defined collections in 91% of cases, followed by hypoisoechoic lesions in the remaining 9%. Ascites was frequently observed in more than half of cases, and other findings such as peritoneal and splenic vein involvement by the disease process were observed in 22% and 25% of cases, respectively [66]. Splenic vein thrombosis complicating PTB has been reported in the literature, potentially leading to extrahepatic portal hypertension. Peripancreatic and portal lymphadenopathy has been described in most of the reported cases, most of them showing central necrosis [66]. The present case had four mass lesions in the head, body, and tail of the pancreas, representing a minority of reports (16%) with multiple TB lesions at presentation, as well as a minority of patients with deep venous thrombosis (7%).

The diagnostic approaches in the literature of isolated PTB cases

consisted predominantly of an abdominal CT scan, followed by EUS-FNA (52%) or CT-FNA (12%). Abdominal surgery with laparoscopy and laparotomy, even adopting an invasive Whipple procedure, are still some of the diagnostic approaches available. Here, EUS-FNA followed by microbiology led to the correct diagnosis as in the majority of reports. Before the advent of improved diagnostic approaches such as EUS-FNA, the diagnosis was made by histological exam after surgery, in patients resected for a presumed pancreatic malignancy. This approach is superseded in current guidelines and protocols in favor of EUS-FNA and histology/microbiology/molecular biology, with an extremely low risk of peritoneal dissemination especially when the pancreatic mass seems malignant [6]. In the present literature review, a correct PTB diagnosis with FNA (EUS/CT) was obtained in 36 of 56 cases (64%), thus avoiding unnecessary surgery, and is in line with a study performed between 2003 and 2007 on 21 patients with pancreatic TB where EUS-FNA correctly diagnosed pancreatic TB in 16 patients (76.2%) [67, 68].

Among TB identification methods used in reported cases of PTB, histology was used more frequently than microbiologic testing (48 vs. 43). A possible explanation is that in the majority of cases, the primary clinical suspicion was pancreatic tumor, and pancreatic material has been sent only for histology and not for microbiological testing.

However, when microbiological testing was successful, we observed a predominance of positive acid-fast bacilli (18) in 42% of cases, positive cultures for MTB (8) in 19% of cases, and a positive PCR for MTB (7) in around 16% of cases; 10 cases (23%) were diagnosed with a combination of the techniques mentioned above. This scattered diagnostic approach in reported cases over the last 10 years may be related to a more recent introduction of RT-PCR as a diagnostic test and with unexpected TB in a cancer diagnostic workup. This observation confirms that histological examination was the most frequently used standard method for the diagnosis of pancreatic TB before the advent of molecular techniques and redirecting diagnostic workup in isolated cases including the present one. Indeed, analysis of isolated PTB reported cases indicates that when standard microbiology could not ascertain the presence of M. tuberculosis, histology succeeded, thus suggesting that always combining the two methods in the absence of neoplastic disease improves diagnostic yield. In the present case, diagnosis was reached by RT-PCR on FNA of the pancreatic lesion, when initial histology revealed an absence of neoplastic disease and instead the presence of epithelioid granulomas by pathological analysis. Epithelioid granulomas are an unusual pattern compared with the more often observed granulomatous necrosis reported in the present literature review. Overall, the approach in the present case confirms that histology drives further microbiologic workup and is in line with evidence from the literature indicating that combining EUS-FNA histological and microbiological/molecular analysis is an optimal standard for the diagnosis of pancreatic TB. Accordingly, EUS-FNA should be always considered to avoid unnecessary surgery, reducing costs, shortening time to diagnosis and avoiding the unnecessary morbidity/mortality associated with surgical procedures. In this regard, we did not detect geographical differences in the use of diagnostic methods for PTB, confirming that FNA-EUS is equally a highly effective and safe diagnostic method in reports from Europe, America, and Asia. Regarding PTB treatment, some variability in the duration of antitubercular regimen emerged from the present analysis. Excellent cure rates, when reported (some patients were lost at follow-up), were obtained with standard antitubercular therapy given for at least six months, as with the presently reported patient. However, some gray areas may persist, since in some patients treatment was extended up to 9–12 months. Further data are needed to determine the best duration of the therapy of PTB or conditions which could advise more prolonged treatment.

7. Conclusions

PTB presenting as an isolated pancreatic involvement remains a diagnostic challenge that needs to be suspected particularly in patients from endemic areas independently from immunosuppression or immune disorders. Clinical suspicion is important to avoid further unnecessary and potentially risky diagnostic and/or therapeutic procedures, including surgery. In this literature review, we noted a temporal evolution of diagnostic techniques in favor of less invasive methods (FNA-EUS) compared to surgery and postsurgical histological examination. Meanwhile, we did not notice geographical differences in the diagnostic methods adopted, observing how the use of FNA-EUS was equally described as a highly effective and safe diagnostic method in reports from Europe, America, and Asia. From these real-life reported PTB cases, it is clear that diagnostic methods have evolved over the decades, and even when a more limited 10-year horizon is considered, they are rapidly moving from only histological diagnosis on the surgical piece to a more recent and global use of EUS-FNA with histology and molecular biology. In this respect, adopting rtPCR for mycobacteria on histological preparations is effective and helps in case of inconclusive histological examination. There are no randomized clinical trials on the optimal duration of antitubercular therapy in pancreatic TB, but excellent healing responses have been observed with a minimum duration of 6 months, extendable up to 9–12 months. There is no conclusive evidence so far suggesting whether the minority of PTB with deep vein thrombosis, multiple pancreatic nodules, or more extensive involvement could benefit from more prolonged treatment courses.

Solitary PTB is a challenging clinical entity that should be kept in mind to avoid misdiagnosis. Once diagnosed, a standard HRZE regimen for at least six months is usually effective. Further studies are needed to address the optimal treatment management.

8. Acknowledgments

None

9. Author Contributions

All authors cared for the patient and supervised diagnostic and therapeutic strategies.

LM supervised and performed histological examination.

SS provided CT scan and interpretations.

RG, AB, MB, LM, SS, and LN reviewed the manuscript.

FB and ADM wrote the manuscript.

FB performed literature review and analysis and provided concepts.

ADM supervised the analysis and provided concepts.

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