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By Mariam Hachimi Idrissi

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23 2. Abstract

24 **Introduction** : Pancreatic tuberculosis is an extremely rare form of extrapulmonary
25 tuberculosis. This condition can be challenging to diagnose due to its rarity, nonspecific
26 symptoms, and radiological features that may mimic a neoplastic origin.

27 **Case report:** A 46-year-old immunocompetent patient with no past history of tuberculosis
28 exposure, presented with spontaneously resolving jaundice over the past month, accompanied
29 by non specific fever episodes and general fatigue with no other associated digestive
30 symptoms. Abdominal CT and MRI scans revealed a poorly defined, partially necrotic mass in
31 the pancreatic head with heterogeneous hypodensity and enhancement after contrast injection.
32 Additionally, there were nodal and hilar macro-nodal lesions with necrotic appearances, as well
33 as peripancreatic lymphadenopathy. The patient was scheduled for an Endoscopic ultrasound
34 (EUS) examination which revealed the presence of a heterogeneous lesion with areas of
35 necrosis in the posterosuperior aspect of the head and isthmus of the pancreas, accompanied
36 by perilesional and celiac lymphadenopathies with necrotic centers. EUS-guided tissue
37 sampling allowed the diagnosis of pancreatic tuberculosis, with both histological examination
38 and GeneXpert MTB/RIF testing rapidly positive for *Mycobacterium tuberculosis*, followed
39 by culture on solid Loewenstein-Jensen medium. The patient responded well to antitubercular
40 chemotherapy .

41 **Conclusion:** Pancreatic tuberculosis, though rare, should be considered in cases of pancreatic
42 masses, especially in endemic regions. Tissue samples with necrosis should be tested for
43 *Mycobacterium tuberculosis* using GeneXpert and Loewenstein-Jensen culture. This work
44 highlights the GeneXpert MTB/RIF test as highly sensitive, specific, and fast, making it ideal
45 for diagnosing extra-pulmonary tuberculosis, particularly when smear results are negative.

46

47 3. Data Summary

48 No data was generated during this research or is required for the work to be reproduced.

49

50 4. Introduction

51 Pancreatic tuberculosis is an exceedingly rare form of extrapulmonary tuberculosis
52 even in endemic countries where cases account for less than 5% as demonstrated by autopsy
53 studies (1). This particular form of pseudotumoral mass presentation mimicking a pancreatic
54 neoplasm but also other pancreatic disorders like chronic pancreatitis, pancreatic cystic
55 neoplasms, and autoimmune pancreatitis can be challenging to diagnose due to its rarity,
56 nonspecific symptoms, and radiological features that may mimic a neoplastic origin.
57 (2)Diagnosis often relies on imaging tests such as computed tomography or magnetic
58 resonance imaging, as well as pancreatic tissue sampling (3). The presence of granulomas is
59 the most common finding on histological examinations, but due to its non-specific nature,
60 the bacteriology laboratory plays a crucial role in diagnosing pancreatic tuberculosis by
61 conducting various microbiological tests to detect the presence of *Mycobacterium tuberculosis*
62 in the collected samples. Real-time PCR is an invaluable tool for diagnosing extrapulmonary
63 tuberculosis. Its use increases the sensitivity of detecting the *M. tuberculosis* complex. It does
64 not replace traditional diagnostic methods but complements them to achieve better sensitivity
65 and faster results with a sensitivity of 87.5% for biopsies. (4). We report a case of pancreatic
66 tuberculosis in a 45-year-old patient presenting as a pancreatic mass.

67

68 5. Case Presentation

69 A 45-year-old immunocompetent patient with no significant medical history and no history of
70 tuberculosis exposure, presented with a three-month history of non specific fever with chills
71 without other associated signs. During the following month, he presented with spontaneously
72 resolving jaundice with no abdominal pains, digestive bleeding, or transit disorders. This
73 occurred in the context of asthenia, anorexia, and unspecified weight loss. Abdominal
74 examination revealed a non-distended abdomen, with palpation showing no tenderness or
75 hepatosplenomegaly. There was no palpable mass, nor peripheral lymphadenopathy. The rest
76 of the clinical examination was normal.

77 Morphological exploration by abdominal-ultrasound revealed highly hyperechoic hilar hepatic
78 lymph nodes, nearly liquefied, with the largest measuring 23.1 mm in the minor axis,

79 accompanied by a discreet peri vesicular fat infiltration. Abdominal ¹⁰ CT scan showed a lesion
80 in the head of the pancreas, poorly delineated, with heterogeneous density, partially necrotic,
81 and enhanced after injection. This lesion encompassed the hepatic hilum, including the hepatic
82 artery and portal trunk, both of which remained patent. Additionally, there were nodal and hilar
83 macro-nodal lesions with necrotic appearances, as well as peripancreatic lymphadenopathy,
84 leading to dilation of the main biliary duct, especially at the hilum, not recognizable within the
85 pancreas (**Figure 1**).

86 Further abdominal MRI ³⁰ revealed a lesion involving the head and isthmus of the pancreas,
87 measuring 57 x 20 x 26 mm in size, with a few fluid-filled compartments and retro pancreatic
88 lymph nodes with necrotic centers. This lesion remained distant from vascular structures and
89 was consistent with a cystic tumor of the pancreatic head with necrotic lymphadenopathy.
90 (**Figure 2**)

91 ¹⁷ Laboratory tests revealed an elevated C-reactive protein (CRP) level at 19.9 mg/l. Serum
92 alanine aminotransferase activity was 16 UI/L, aspartate aminotransferase was 18 UI/L, total
93 bilirubin was 28 mg/l gamma-glutamyl transferase was 64 UI/L, and alkaline phosphatase
94 was 75 mg/l. White blood cell count was 9100/mm³. Lipase levels were 55 UI/l. Tumor
95 markers were within normal limits.

96 Given the pseudo tumoral appearance of the lesion and the presence of peripancreatic
97 lymphadenopathy with areas of necrosis, an abdominal endoscopic ultrasound (EUS) was
98 performed, revealing a heterogeneous lesion with areas of necrosis and lobulated contours in
99 the posterosuperior aspect of the head and isthmus of the pancreas, measuring 64 x 40 mm,
100 accompanied by perilesional and celiac lymphadenopathies with necrotic centers. (**Figure 3**)

101 EUS-guided tissue sampling using ²¹ Fine Needle Aspiration (EUS-FNA) was performed, and
102 was sent both to pathology and for bacteriological examination.

103 In the bacteriology laboratory, fluorescent staining with Auramine as well as Ziehl-Neelsen
104 staining were performed, both yielding negative results after careful examination of the slides.

5
105 The Xpert MTB/RIF test, performed on a fragment of pancreatic biopsy confirmed the
106 diagnosis: MTB detected at a low level with no detected resistance to Rifampicin, as well as
107 no detection of mutations.

108 Culture was performed on Lowenstein Jensen solid medium, which tested positive after 26
109 days with the appearance of 3 colonies with a cream-beige hue, dry, rough-surfaced, verrucous,
110 and cauliflower-like in appearance. (Figure 4)

111 The histopathological examination of the pancreatic biopsy favored a chronic epithelioid and
112 giant-cell inflammatory reaction with eosinophilic caseous necrosis, consistent with a
113 tuberculous origin. (Figure 5)

114 The chest X-ray and search for *Mycobacterium tuberculosis* in sputum, was negative.

115 Medical treatment consisting of antibacterial chemotherapy was initiated, following the
116 therapeutic regimen 2RHZE/4RH, which includes a combination of isoniazid, rifampicin,
117 ethambutol, and pyrazinamide for two months, followed by a two-drug regimen of isoniazid
118 and rifampicin for six months. After 4 months of treatment, there was a resolution of jaundice,
119 with CT imaging showing regression of the pancreatic lesion and normalization of the
120 biological profile.

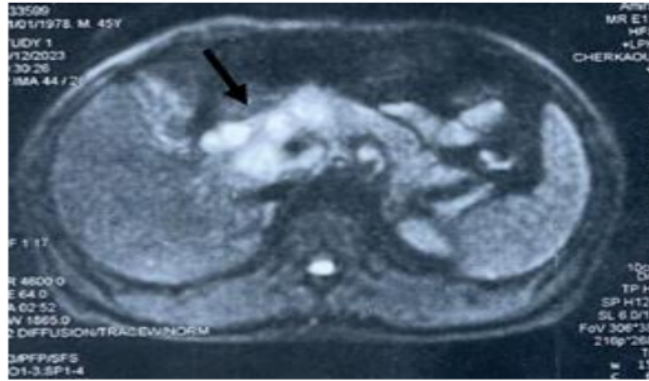
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122 6. Figures and tables



124

Figure 1: Abdominal CT scan: hypodense mass in the head of the pancreas (Cross)



125

Figure 2: Magnetic resonance imaging showing a lesion involving the head and isthmus of the pancreas (Arrow) with lymph nodes.



128

Figure 3: Endoscopic ultrasound showing heterogeneous lesion of the pancreatic head and isthmus, with irregular lobulated contours and containing some necrotic areas, measuring 64 x 40 mm.

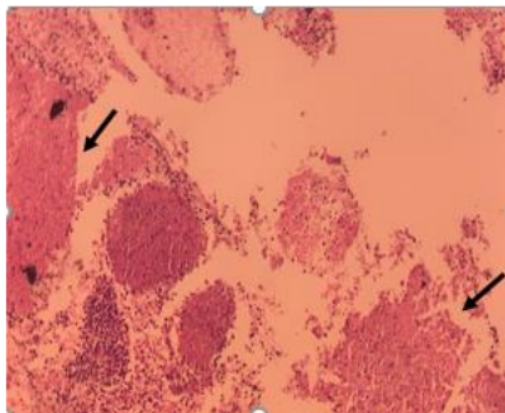
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133

134

135 **Figure 4:** Positive culture on solid Loewenstein-Jensen medium with the appearance of 3
136 colonies (Circle) with a cream-beige hue, dry, rough-surfaced, verrucous, and cauliflower-
137 like in appearance



138

139 **Figure 5:** The histopathological examination shows an epithelioid and giant-cell granuloma

140 (Arrow) with eosinophilic caseous necrosis compatible with a tuberculous origin.

141

142 7. Discussion

143 Pancreatic ³tuberculosis is a rare form of extrapulmonary tuberculosis, most often associated
144 with miliary tuberculosis. (5). Involvement of the pancreas alone is exceptionally uncommon,
145 and accounts for fewer than 5% of cases. (1) There are two possible explanations for the
146 pancreas's resistance to tuberculous infection. One possible explanation is anatomical; the
147 pancreas, being retroperitoneal, seems to be shielded from direct exposure to the environment.
148 Another explanation could be biochemical, related to the antibacterial properties of pancreatic
149 enzymes, especially lipase. Tuberculous infection of the pancreas consequently necessitates a
150 substantial inoculation of bacilli. This typically happens through contiguous spread from
151 involved peripancreatic lymph nodes, but can also occur, though rarely, through contiguous or
152 hematogenous spread from a hidden site (often originating in the lungs) or reactivation of a
153 latent infection. under the influence of immunosuppression, as in miliary tuberculosis with
154 multivisceral involvement. (1)

155 Auerbach documented the first case of pancreatic tuberculosis in 1944, based on his
156 examination of 1,656 autopsies of patients with tuberculosis . Pancreatic involvement was
157 found in only 14 cases, indicating an incidence of 4.7%. (1) Most studies of pancreatic
158 tuberculosis suggest a male preponderance among the reported cases, with the exception of two
159 reports from South Korea and China. (2). Published series typically report an average age of
160 onset for pancreatic tuberculosis ranging from 36 to 56 years, indicating that the condition most
161 commonly affects individuals during their forties and fifties. (2)

162 ²³Its clinical and radiological features may mimic those of pancreatic cystic neoplasms,
163 retroperitoneal lymph node metastases, or lymphoma, making it a challenging clinical
164 diagnosis. (6) This disease presents in imaging either as: a solid form, which should be
165 differentiated from pancreatic adenocarcinoma and focal chronic pancreatitis. ; a cystic form,
166 where the differential diagnosis mainly includes pancreatic cystic neoplasms (pseudocysts and
167 tumors) ; or a mixed form, where necrotic pancreatic adenocarcinoma should also be
168 considered. The presence of a pancreatic mass, peripancreatic lymphadenopathy, calcifications,

169 and even vascular invasion are common features of both tuberculosis and pancreatic
170 malignancy. Histopathological or microbiological evidence is the only reliable method to
171 definitively distinguish tuberculosis from other pancreatic diseases.

172 Symptomatology can be varied and nonspecific and may include abdominal pain, typically
173 localized to the epigastric region or the upper left quadrant of the abdomen, which is one of the
174 most common symptoms of pancreatic tuberculosis, anorexia, fever, and night sweats,
175 vomiting, diarrhea which may develop due to pancreatic dysfunction as well as jaundice, in
176 advanced stages due to obstruction of the bile duct by inflammatory lymph nodes or
177 compressive lesions. The presence of an abdominal mass has also been reported in a variable
178 number of patients in some reports. Bleeding in the gastrointestinal tract has also been
179 documented as well as the formation of arterial pseudoaneurysms. Other complications include
180 gastric outlet obstruction, portal hypertension, diabetes mellitus, abscess formation, and
181 recurrent acute pancreatitis. It is important to note that pancreatic tuberculosis may be
182 asymptomatic in some patients, particularly in the early stages of the disease. (2)

183 The presence of extra-pancreatic lesions, particularly pulmonary, on chest radiography can be
184 an indicator of pancreatic involvement by tuberculosis. Abnormal chest radiographs have been
185 reported in nearly 50% of patients with pancreatic tuberculosis. Other lesions such as the
186 thickening of the ileocecal region, pearly kidney, ascites, and lesions in the spleen have been
187 reported. Tuberculosis history has been noted in 44% of the cases. A positive tuberculin skin
188 test has been detected in 32 to 71% of patients with pancreatic tuberculosis, according to
189 various series. (2)

190 Abdominal computed tomography (CT) is often the initial imaging modality used for
191 evaluating patients with pancreatic tuberculosis. It provides valuable information about the size
192 and nature of tuberculous lesions, as well as the presence of ascites and lymphadenopathy. (2)
193 Pancreatic tuberculosis may manifest as hypo- or iso-dense pancreatic masses with variable
194 enhancement after contrast injection. These lesions can be focal or diffuse and may be
195 associated with thickening of the pancreatic duct walls. (2) In a study involving 32 patients
196 with pancreatic tuberculosis, 28 (87.5%) presented with a bulky, heterogeneous pancreas.
197 Additionally, 20 (62.5%) had multiple focal lesions, and 12 (37.5%) had a single focal lesion.
198 Lesions were observed in the body, head, and tail of the pancreas in 56%, 50%, and 9% of

199 patients, respectively. (7) In another study involving nine patients with pancreatic tuberculosis
200 (eight of whom underwent computed tomography), imaging revealed a mass in the pancreatic
201 head in five patients, a mass in the tail in one patient, cystic lesions in two patients, and
202 calcification and splenic vein thrombosis in one patient each. (8) The pancreatic head was the
203 most frequently involved region in most reports. (2) In our case, abdominal CT showed a lesion
204 involving the head of the pancreas, poorly delineated, with heterogeneous density, partially
205 necrotic, and enhanced after contrast injection. However, computed tomography cannot
206 distinguish tuberculosis from pancreatic carcinoma. The diagnostic hypothesis is further
207 strengthened when imaging reveals a hypodense mass surrounded by a thick, hyperdense
208 capsule, along with target-shaped enhanced lymphadenopathy with necrotic-centered
209 lymphadenopathy in the retro-pancreatic, celiac, mesenteric, or para-aortic regions.
210 Peripancreatic collections should also alert the radiologist to the possibility of pancreatic
211 tuberculosis, particularly in regions where tuberculosis is endemic. (9)

212 Magnetic resonance imaging has occasionally been utilized in the assessment of pancreatic
213 tuberculosis. Magnetic resonance cholangiopancreatography may reveal dilation of the bile and
214 pancreatic ducts due to obstruction caused by a tubercular mass in the pancreatic head. (10)

215 Endoscopic ultrasound has emerged as a valuable modality for evaluating the
216 pancreaticobiliary system. Not only does it allow assessment of pancreatic lesion and size, but
217 it also aids in determining the presence of ductal dilation, lymphadenopathy, vascular invasion
218 and calcifications. It also enables sampling of these lesions, providing material for
219 microbiological and cytological evaluation. (2)

220 The bacteriological diagnosis primarily relies on the detection of mycobacterial cultures on
221 Lowenstein-Jensen medium. However, the major drawback is the slow growth of these
222 cultures, which can take up to 6 weeks. (11)

223 Currently, diagnosing extra-pulmonary tuberculosis remains a challenge for clinicians and
224 microbiologists worldwide. The difficulty in accessing specific sampling sites leads to
225 paucibacillary samples, which reduces the sensitivity of conventional diagnostic tests.
226 Additionally, this form of tuberculosis is often difficult to suspect during clinical examinations
227 due to its variable clinical presentations. The introduction of molecular tests appears to offer

228 significant improvements in diagnosing extra-pulmonary tuberculosis, particularly in cases
229 involving paucibacillary samples , even when staining techniques and tissue sample cultures
230 show negative results. (12) (11)

231 ²⁸ The diagnosis of pancreatic tuberculosis is confirmed by histopathological examination of
232 specimens obtained via laparotomy, percutaneous radio ³³ guided fine needle aspiration, or
233 endoscopic ultrasound, as was the case for our patient, thus avoiding unnecessary laparotomy.
234 It allows for the identification of the pathognomonic lesion of tuberculosis: the epithelioid-
235 giant cell granuloma with caseous necrosis. (9)

236 The treatment relies on the prompt initiation of anti-tubercular chemotherapy, lasting from 6
237 to 9 months, comprising the following therapeutic regimen: ¹³ Rifampicin, Isoniazid,
238 Pyrazinamide, and Ethambutol (RHZE) for 2 months, followed by Rifampicin and Isoniazid
239 (RH) for 4 to 7 months. This treatment may be extended up to 12 months if the isolated strain
240 is resistant. In case of complications, surgical intervention may be considered. (13)

241

242 8. Conclusion

243 ²⁰ Pancreatic tuberculosis is rare but should be considered in the diagnosis of extrapulmonary
244 infections caused by *Mycobacterium tuberculosis*. It requires high suspicion, especially in
245 endemic countries, due to its potential to mimic pancreatic cystic neoplasms, retroperitoneal
246 lymph node metastases, or lymphoma. When a pancreatic mass with necrosis is detected, tissue
247 samples should be sent for both bacteriological and pathological analysis to look for
248 *Mycobacterium tuberculosis*

249 The role of the bacteriology laboratory is crucial in confirming the infection, utilizing a
250 combination of microbiological techniques. Real-time PCR is a very useful tool for diagnosing
251 extrapulmonary tuberculosis, which remains a serious infectious disease with sometimes
252 lengthy diagnostic procedures. These forms, which account for 27% of tuberculosis cases, are
253 particularly challenging to diagnose. (14)

254

255 9. Author statements

256 9.1 Author contributions

257 M.H.I contributed to the initial drafting of the manuscript, while J.B, A.Z, S.H, Y.E, EL. B and
258 Y.B revised it. M.C. provided final approval for the version to be published.

259

260 9.2 Conflicts of interest

261 The authors declare that there are no conflicts of interest.

262

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265 or not-for-profit sectors.

266

267 9.4 Consent for publication

268 Written informed consent was obtained from the patient to publish this report in accordance
269 with the journal's patient consent policy.

270

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