ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2023 April 6; 11(10): 2123-2362

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

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NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

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PUBLICATION DATE
April 6, 2023

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World Journal of Clinical Cases

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World J Clin Cases 2023 April 6; 11(10): 2181-2188

DOI: 10.12998/wjcc.v11.i10.2181

ISSN 2307-8960 (online)

MINIREVIEWS

Cheesy material on macroscopic on-site evaluation after endoscopic ultrasound-guided fine-needle biopsy: Don't miss the tuberculosis

Hanane Delsa, Khadija Bellahammou, Hussein Hassan Okasha, Fahd Ghalim

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Chai NL, China; Thandassery RB, United States

Received: December 27, 2022
Peer-review started: December 27, 2022
First decision: January 22, 2023
Revised: January 28, 2023
Accepted: March 14, 2023
Article in press: March 14, 2023
Published online: April 6, 2023

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Abstract

Endoscopic ultrasound-guided fine-needle biopsy (EUS-FNB) is an excellent investigation to diagnose pancreatic lesions and has shown high accuracy for its use in pathologic diagnosis. Recently, macroscopic on-site evaluation (MOSE) performed by an endoscopist was introduced as an alternative to rapid on-site cytologic evaluation to increase the diagnostic yield of EUS-FNB. The MOSE of the biopsy can estimate the adequacy of the sample directly by the macroscopic evaluation of the core tissue obtained from EUS-FNB. Isolated pancreatic tuberculosis is extremely rare and difficult to diagnose because of its non-specific signs and symptoms. Therefore, this challenging diagnosis is based on endoscopy, imaging, and the bacteriological and histological examination of tissue biopsies. This uncommon presentation of tuberculosis can be revealed as pancreatic mass mimicking cancer. EUS-FNB can be very useful in providing a valuable histopathological diagnosis. A calcified lesion with a cheesy core in MOSE must be suggestive of tuberculosis, leading to the request of the GeneXpert, which can detect *Mycobacterium tuberculosis* deoxyribonucleic acid and resistance to rifampicin. A decent diagnostic strategy is crucial to prevent unnecessary surgical resection and to supply conservative management with antitubercular therapy.

Key Words: Pancreatic tuberculosis; Endoscopic ultrasound; Fine-needle biopsy; Macroscopic on-site evaluation; Cheesy material; GeneXpert

Core Tip: In this article, we discussed the role of endoscopic ultrasound with fine-needle biopsy as a diagnostic tool in patients with suspicious pancreatic tuberculosis. This review aims to provide knowledge on the utility of fine-needle biopsy and macroscopic on-site evaluation of the core to suspect pancreatic tuberculosis, in addition to diverting the attention of the endoscopists to consider tuberculosis when the core is cheesy.

Citation: Delsa H, Bellahammou K, Okasha HH, Ghalim F. Cheesy material on macroscopic on-site evaluation after endoscopic ultrasound-guided fine-needle biopsy: Don't miss the tuberculosis. *World J Clin Cases* 2023; 11(10): 2181-2188
URL: https://www.wjgnet.com/2307-8960/full/v11/i10/2181.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i10.2181

INTRODUCTION

Tuberculosis (TB) is a transmissible disease caused by *Mycobacterium tuberculosis* (MT). TB was the first cause of death worldwide from infectious diseases until the coronavirus disease 2019 (COVID-19) pandemic[1]. In 2020, approximately 10 million people developed TB, and almost 25% of the world's population has been infected with MT[1].

The most common site of TB is the lungs; however, in approximately 12.5% of cases, it can affect other sites (extrapulmonary TB), with abdominal localization in 11%-16%[2]. The diagnosis of extrapulmonary TB can be very challenging because the usual method based on the detection of MT is insufficiently sensitive, and other tools based on immune responses cannot always differentiate a latent infection from an active disease[3].

Pancreatic TB remains a rare site of abdominal TB, often misdiagnosed as pancreatic carcinoma. Nevertheless, endoscopic ultrasound (EUS) with pancreatic fine needle aspiration or biopsy (FNA/FNB) and a polymerase chain reaction (PCR) are important tools to make the definitive diagnosis and to initiate adequate treatment[4,5].

Recently, macroscopic on-site evaluation (MOSE) performed by an endoscopist was introduced as an alternative to rapid on-site cytologic evaluation (ROSE) to increase the diagnostic yield of EUS-FNB. The MOSE of the biopsy can estimate the adequacy of the sample directly by the macroscopic evaluation of the core tissue obtained from EUS-FNB[6]. In our practice, a cheesy core was found in all patients with isolated pancreatic TB, which led us to perform GeneXpert, which can detect MT DNA and resistance to rifampicin. This diagnostic strategy is critical for avoiding unnecessary surgical resection and for providing conservative management with antitubercular therapy.

In the present article, we reviewed pancreatic TB, discussed the role of EUS with FNA/FNB in diagnosis, and reported the correlation between cheesy core and tuberculosis. Based on this, we also discussed the usefulness of MOSE in avoiding misdiagnosing this rare disease.

PANCREATIC TB

Isolated pancreatic TB is an extremely rare disease, even in countries where tuberculosis is widespread. However, due to the development of new techniques like EUS, diagnosing pancreatic TB is becoming easier. EUS-FNB allows obtaining pancreatic specimens with cytopathology. Many cases have been published worldwide in the last few years with different and non-specific clinical manifestations (Table 1)[5,7-10].

The systematic review conducted by Panic, including 116 studies reporting data on 166 patients, revealed multiple symptoms dominated by abdominal pain in 74.8% of patients, followed by weight loss and fever in almost half of patients (51.6% and 46.5%, respectively). However, jaundice was found in 20.0% of cases. The most common presentations of pancreatic TB were pancreatic mass mimicking cancer (79.5%), pancreatic head (59.0%), body (18.2%), tail (13.4%), and neck (1.8%). Nonetheless, other pancreatic lesions were reported, like abscesses in 12.1% of patients and chronic or acute pancreatitis in 6.6% and 6.0%, respectively. As an extra-pancreatic localization of TB, peripancreatic lymph nodes were observed in 47.3% of cases. The other sites were rarely described: the spleen (8.3%), intestines (8.2%), liver (6.9%), and lungs (6.3%)[2].

In a study conducted by Ray, 16 pancreatic TB were identified, and the main symptoms were epigastric pain (81%), weight loss (75%), and anorexia (69%). Half of the patients had a fever, and 31% had jaundice[9].

As in pulmonary tuberculosis, immunocompromised individuals are the most affected, particularly in cases of advanced-stage malignant diseases and acquired immunodeficiency syndrome (AIDS), with a high rate of a pancreatic abscess (70%) and mortality (10.8%). In cases of delayed diagnosis and

Table 1 Clinical presentation and endoscopic ultrasound finding of pancreatic tuberculosis patients

Ref.	No. of patients	Age	Sex	Clinical presentation	EUS finding	Microbiological and histological findings
Diaconu *et al* [5], 2022	1	55	F	Fever, jaundice, and asthenia	Cephalic pancreatic lesion with changes suggestive of chronic pancreatitis	Positive culture
Miyamoto *et al*[7], 2022	1	19	F	Abdominal pain and weight loss		Positive PCR for MT, granulomas with caseous necrosis and acid-fast bacilli
Hoilat *et al* [8], 2020	1	26	M	Abdominal pain, increased nausea and vomiting	Hypoechoic lesion	FNA: Abundant fibrinopurulent exudate and necrotizing suppurative granulomatous inflammation
Ray *et al*[9], 2021	16	13-59	12 M, 4 F	Epigastric pain, weight loss, anorexia, fever, and jaundice		5 EUS-FNA; 5 CT-FNA; 6 Surgery
Chang-Xin *et al*[10], 2022	1	24	F	Jaundice		Granulomatous inflammation infiltrated by multinucleated giant cells in FNA; Positive tuberculin skin test and tuberculous infection of T cells spot test

CT: Computed tomography, MT: *Mycobacterium tuberculosis*, FNA: Fine needle aspiration; PCR: Polymerase chain reaction.

without proper treatment, pancreatic TB can be deadly, and the prognosis is grave due to the underlying disease[11,12].

EUS

EUS is considered the main tool for evaluating pancreatic masses and a valuable diagnostic modality for pancreatic TB. It can precisely determine the characteristics of pancreatic lesions (size, vascular invasion, and calcifications) and the aspect of peripancreatic lymph nodes. Combined with EUS-FNB, it has become an excellent investigation to diagnose pancreatic lesions and has established a high accuracy for its use in pathologic diagnosing[13,14].

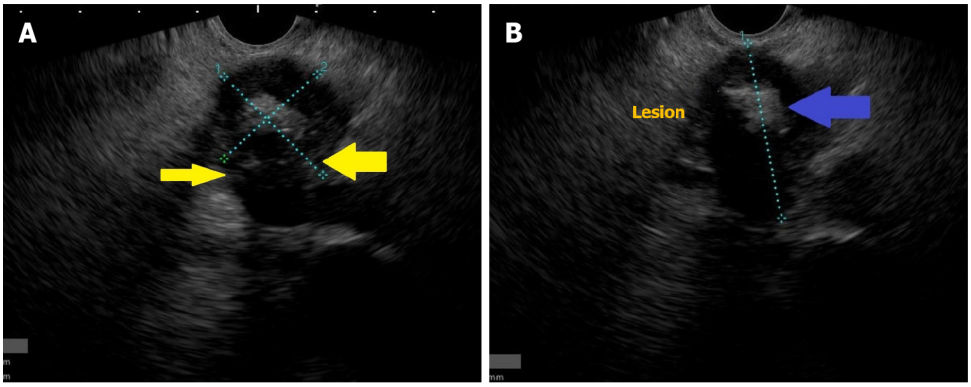
However, few studies have been published about EUS in pancreatic TB compared to other sites of TB [14]. In the EUS, it can appear as a solid mass or mixed solid cystic lesions, usually with hypoechoic or anechoic echotexture without vascular invasion[14]. Although vascular invasion has been reported in some cases of pancreatic TB, it cannot be used to confirm malignancy[9].

In addition, EUS can demonstrate pancreatic calcifications, reported in 56% of patients, and also detect extra-pancreatic localizations like abdominal or mediastinal lymphadenopathy[15,16]. In our cases, we observed pancreatic mass with central calcification, respecting all vessels (Figure 1).

In the brief communication of Rana *et al*[17] comparing 25 patients with pancreatic adenocarcinoma to 6 patients with pancreatic tuberculosis, the EUS appearances were similar between the two groups. However, in patients with pancreatic TB, EUS typically revealed hypoechoic lesions. However, the group with adenocarcinoma had some specific aspects compared to patients with TB: advanced age, high bilirubin levels, significant dilatation of the common bile duct, and sometimes a dilated pancreatic duct.

EUS elastography can help to characterize the pancreatic mass better and differentiate pancreatic TB from adenocarcinoma through the demarcated lesion characteristics. In TB, it showed stiffer tissue than the healthy pancreatic parenchyma. Nevertheless, pancreatic TB and autoimmune pancreatitis have a similar appearance in elastography. Therefore, EUS elastography has a limited contribution to diagnosing pancreatic TB[18].

In addition, EUS allows tissue acquisition by FNB or aspiration by FNA to exclude another diagnosis like adenocarcinoma or autoimmune pancreatitis. At the same time, the endoscopist can perform multiple biopsies of the abdominal or mediastinal lymphadenopathy and the suspicious pancreatic masses, even the smaller ones (less than 1 cm) located in the body and tail regions[19]. With these samples, histopathology can be performed; however, pancreatic fluid culture microbiology (Ziehl–Neelsen staining and acid-fast bacilli culture) and PCR assay (to detect mycobacterial DNA) are required to improve the diagnostic yield (up to 76% for TB *vs* 95% for cancer)[20]. The EUS-FNA has a good sensitivity (from 85% to 90%) and excellent specificity up to 100%[21].



DOI: 10.12998/wjcc.v11.i10.2181

Figure 1 Endoscopic ultrasound of pancreatic tuberculosis. A: Image showing a pancreatic lesion respecting vessels (yellow arrow), B: Pancreatic lesion with central calcification (blue arrow).

MOSE AND HISTOLOGY

In the past century, surgical procedures were the main tool to obtain tissue or liquid specimens from pancreatic masses. The development of the EUS with FNA/FNB as a less invasive method has become the procedure of choice for confirming the diagnosis of pancreatic TB[2].

First, after performing EUS-FNA/FNB, every endoscopist must observe the samples. This MOSE will assess the adequacy of histologic cores obtained during EUS-FNA/FNB. This evaluation of the quality and quantity of the core by the operator may help potentially decide the number of passes[22].

Iwashita introduced this concept of MOSE in 2015 when he published his cohort of patients that underwent EUS-FNA with a 19G needle. In this pilot study, the authors observed better diagnostic yield when the macroscopically visible core on MOSE was superior to 4 mm[23].

Nowadays, some authors have proposed performing MOSE of the core as an alternative to ROSE, which requires a cytopathologist's presence[22]. Gaia proposed a classification in his study published in 2022, which included 76 patients performing EUS-FNB for pancreatic and extra-pancreatic solid masses (Table 2)[24].

However, no studies described the sample's aspect based on the final diagnosis. Diaconu reported a case of pancreatic TB with a cephalic pancreatic lesion and changes suggesting chronic pancreatitis; the EUS-FNB revealed purulent material with a positive culture for TB[5]. Therefore, when the EUS-FNA/FNB shows purulent material, a cytological and bacteriological examination must be performed to exclude pancreatic TB.

Caseous material was described in tuberculosis as a unique type of tissue aspirate. The gross appearance can be soft, white, or cheesy-looking (caseating) material[25]. In many studies, cheesy material was noted as an aspect of tuberculosis at different sites (Table 3)[26-30].

This cheesy-looking appearance was initially reported intraoperatively. However, in the study of Lakhey, which included 122 patients with tubercular lymphadenitis, the acid-fast bacilli (AFB) positivity rate of fine needle aspiration cytology was higher when cheesy material was aspirated (82.3%)[29].

In our series, a young patient was presented with a pancreatic mass with central calcification. Respecting all vessels, EUS-FNB was performed with 3 passes. The core of the first two passes was cheesy, and the third one was also cheesy but a little bloody (Figure 2). This cheesy appearance leads us to perform GeneXpert, which can detect MT DNA and resistance to rifampicin. Positive GeneXpert results and benign-looking histopathology confirmed the diagnosis of pancreatic TB.

A definitive diagnosis of pancreatic TB is commonly based on the microbiological and histopathological examination of a core obtained directly from the pancreas or the peripancreatic lymphadenopathy.

The most common histopathological finding of pancreatic TB on specimens is necrotizing granuloma, reported in more than 50% of cases[15,31]. It is not specific to pancreatic TB as it occurs in other diseases such as Crohn's, sarcoidosis, and autoimmune pancreatitis. Contrary to caseous necrosis, multinucleated giant cells and the identification of AFB are more specific[12].

GENXPERT MT OR XPERT MTB/RIF ASSAY

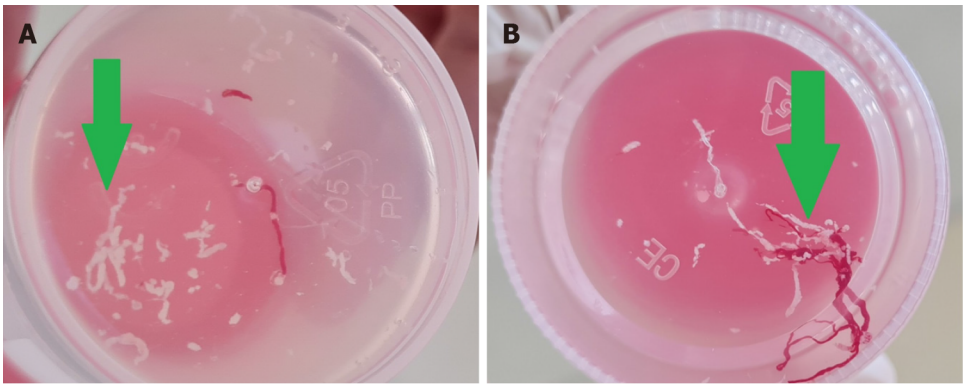
The diagnosis of pancreatic TB is challenging, and histopathology is not always specific. To have a definitive diagnosis, scientists promoted the development of more sensitive and quick tests such as interferon-gamma release assays, Xpert Ultra, and Xpert MTB/RIF[32].

Table 2 Macroscopic on-site evaluation score and sample classification[24]

Score	Aspects of the core	Classification of the biopsy
0	No material	Negative
1	Haematic or necrotic material	Acceptable
2	≥ 1 core tissue with ≤ 2 mm yellowish-white	Positive
3	≥ 1 core tissue with > 2 mm yellowish-white	Positive

Table 3 Sites of tuberculosis with cheesy material

Ref.	No. of patients	Presentation	Site of tuberculosis	Procedure
Yeat *et al*[26]	1	Pontomedullary junction, ring-enhancing lobulated lesion	Brainstem	Suboccipital craniotomy
Gopakumar *et al*[27]	1	Retropharyngeal cold abscess	Cervical lymphad-enitis	Surgical exploration of the parapharyngeal space by needle aspiration
Ng *et al*[28]	1	Right adnexal mass	Abdominopelvic	Exploratory laparotomy
Lakhey *et al*[29]	122		Lymphadenopathy	Fine-needle aspiration cytology
Sahoo *et al*[30]	1	Pain in the left foot	Talus bone	Debridement and curettage of the lesion



DOI: 10.12998/wjcc.v11.i10.2181

Figure 2 Cheesy macroscopic on-site evaluation (green arrow). A: The core of the first two passes was cheesy; B: The third one was also cheesy but a little bloody.

Worldwide, the most commonly used molecular test for the diagnosis of TB is Xpert MTB/RIF, approved by the World Health Organization in 2013. When performed directly in specimens, it can detect the DNA of the MT complex in biopsies and the rifampicin (RIF) resistance conferred by the *rpoB* gene mutation detected by nested real-time PCR within 2 h. This test is generally available in less than 24 h[3,9]. Thus, over the last decade, these molecular tests have played an essential role in controlling TB [3].

Even if these tools are more commonly performed, their use for the diagnosis of extrapulmonary TB, especially pancreatic, has not been well studied. In the Panic review, including 166 patients, PCR confirmed the diagnosis in only 9.6% *vs* 59.6% for histology[2]. However, in recent studies, PCR is increasingly used to detect TB rapidly with a higher positive rate (43%-67%)[4,33].

In cases of the human immunodeficiency virus (HIV)- positive patients with AIDS, TB is an extremely common opportunistic infection[12]. The success rate of FNA under computed tomography scan or ultrasound guidance in diagnosing pancreatic TB was 50.0% in the Jenney review for non-HIV-infected patients (37 cases). However, this reported success rate was much lower than the 85.7% rate in HIV-infected cases in the systemic review of Meesir, which reflects the operator-dependent nature of the procedure[11,12].

In Morocco, the correct diagnosis of TB is based on histopathology, whereas bacteriology testing is uncommonly used to confirm TB. In a Moroccan cross-sectional study including 262 patients with cervical lymph nodes, Xpert tests confirmed the diagnosis of TB in 47.3%[34].

Table 4 Doses of antitubercular therapy

Drugs	Doses (mg/kg/d)	Duration (mo)
Rifampin	10 (8-12)	6
Isoniazid	5 (4-6)	6
Pyrazinamide	25 (20-30)	2
Ethambutol	15 (15-20)	2

The study of Mechal, including 714 patients with pulmonary or extrapulmonary TB, analyzed all the samples using GeneXpert MTB/RIF. Its sensitivity and specificity were almost the same in both groups: 79.3% and 90.3% for pulmonary TB *vs* 78.2% and 90.4% for extrapulmonary TB, respectively[35]. Therefore, GeneXpert MTB/RIF can be considered the test of choice for diagnosing extrapulmonary TB because of its high sensitivity and specificity[35].

TREATMENT

Treatment of pancreatic TB, as the other localization, is based on antitubercular therapy (ATT) using 3 or 4 drugs given for 6–12 mo: isoniazid, rifampin, pyrazinamide, and ethambutol (Table 4)[15].

According to the initial finding, follow-up is based on clinical improvement, weight, radiology, or endoscopy. Moreover, performing the liver function test is crucial for detecting the hepatotoxicity of ATT. In pancreatic TB, EUS may also be a good modality for follow-up[33]. These tools allow us to decide the duration of ATT, even for pancreatic TB, which is usually 6 or 9 mo, depending on the country. Otherwise, it is suggested to search for other immunosuppression like diabetes and HIV in these patients[15].

In the presence of a pancreatic abscess, percutaneous or EUS-aspiration should be performed to make the correct diagnosis and avoid unnecessary surgery. Some patients, even under ATT, can develop pruritus with cholestatic symptoms or severe cholangitis, and a biliary stent will be placed[10].

CONCLUSION

Isolated pancreatic tuberculosis is an extremely rare site of abdominal TB, often misdiagnosed as pancreatic carcinoma. Nevertheless, a EUS with pancreatic FNA/FNB is important to confirm the diagnosis. A calcified lesion with a cheesy core in MOSE must be suggestive of tuberculosis and leads to the request of the GeneXpert, which can detect MT deoxyribonucleic acid and resistance to rifampicin. A decent diagnostic strategy is crucial to prevent unnecessary surgical resection and provide conservative management with antitubercular therapy.

To our knowledge, this is the first review relating the correlation between cheesy core and tuberculosis and the importance of MOSE in diagnosing this rare disease, a subject to which the authors wish to draw attention.

FOOTNOTES

Author contributions: Delsa H collected the literature; Delsa H and Bellahammou K wrote the manuscript, and Okasha HH and Ghalim F revised the paper; All authors read and validated the final version of the manuscript.

Conflict-of-interest statement: All authors declare that they have no conflicts of interest.

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S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

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