ISSN: 2149-2018

Applied Medical Research, 2021
VOL 8, NO. 2, PAGE 1 – 6
DOI: doi.org/10.47363/AMR/2021(8)210

RESEARCH ARTICLE

Open Access

Abdominal Tuberculosis, Cancer and Granulomatous Disease: A Clinical Review

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ABSTRACT

Background: Tuberculosis is one of the top 10 causes of death worldwide caused by mycobacteria tuberculosis. Specifically, abdominal tuberculosis represents the 6th most frequent form of extra-pulmonary tuberculosis. Human infection with ycobacteria is a potent trigger of granuloma formation. Tuberculoid granulomas are also typically highly organized structures that could be associated with cancer.

Objectives: The aim of this review was to highlight the tuberculosis epidemiology and the difference between developed and undeveloped countries; to describe theefectsofatimelyidentificationofgranulomatousdiseasethatmayaltertheclinicalcourseandrespectiveprognosisofthepatientsandstandoutperitoneal or/and abdominal tuberculosis as a rare entity seen in the literature.

Methods: The inclusion criteria were any peer-reviewed observational or interventional human studies or case reports describing granulomas and abdominal tuberculosis, from 1 January 2018 to 31 December 2019. We searched PubMed, using combined keywords for tuberculosis (TB) and peritoneal tuberculosis in the search queries. To stipulate, we used ("tuberculosis" OR "abdominal tuberculosis" OR "peritoneal tuberculosis") and ("generalized lymphadenopathy" OR "peritoneal disease" OR "cancer"). We also searched World Health Organization about the tuberculosis data and respective guidelines.

Discussion and Conclusions: This review highlights the importance of the patient's epidemiology. Comparing to Portugal, the TB incidence in developing countries was higher. It also highlights the great mimicker that simulates many diseases, and its peritoneal variant can clinically behave like a different abdominal pathology, and the risk of misdiagnosis in patients with generalized lymphadenopathy, peritoneal disease, and cancer. TB and cancer share many similarities in symptoms and radiology and laboratory results. True diagnosis with and correct follow-up can decrease patient morbidity and deaths. Abdominal tuberculosis is not a common form of extrapulmonary tuberculosis, however, should be considered in developing countries. There are also a lot of diagnostic procedures for TB in the literature, but none of them is completely specific or sensitive. It is very important to be multidisciplinary with professional inputs from all related fields to achieve the best outcomes of diagnosis and treatment for the patients.

ARTICLE HISTORY

Received September 18, 2021
Accepted September 24, 2021
Published October 23, 2021

KEYWORDS

Tuberculosis, Granuloma, Abdominal Tuberculosis, Peritoneal Disease

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Introduction

Tuberculosis (TB) is a communicable disease, one of the top 10 causes of death worldwide caused by Mycobacterium tuberculosis, which typically affects the lungs (pulmonary TB). The principal route of spread is through airborne route, through inhalation of infected aerosolized droplets. The other modes of spread can be contiguous involvement from adjacent tuberculous lymphadenopathy or primary involvement of extrapulmonary organ, result from hematogenous or lymphogenous dissemination (extrapulmonary TB) [1].

Mycobacterium tuberculosis is a non-spore forming, non-motile, gram-positive, alcohol and acid-fast bacillus, obligate-aerobic, facultative, catalase negative and intracellular bacteria [2]. It has several lipids in the cell wall, including mycolic acid, cord factor and Wax-D, that contribute to resistance to several antibiotics.

Primary tuberculosis manifestations are promoted by the first contact of Mycobacterium organism with a host. This primary TB is usually localized to the middle portion of the lungs, known

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as the Ghon focus of primary TB. In most infected patients, the Ghon focus enters a state of latency. Latent tuberculosis could be reactivated after immunosuppression in the host. Following first exposure, some people would develop an active disease. That cases are referred to as primary progressive tuberculosis. Primary progressive tuberculosis is seen in malnourished people, individuals on long-term steroid use, people with immunosuppression, and children. Secondary tuberculosis usually occurs with latent tuberculosis infection's reactivation. Also, the secondary tuberculosis lesions are in the lung apices.

More than 80% of patients with TB manifest pulmonary findings with classical symptoms of productive cough with or without hemoptysis, fever, night sweats and weight loss [2]. For extrapulmonary disease, symptoms depend on the affected area.

The World Health Organization (WHO) considers that about a quarter of the world's population (1.8 billion people), are infected with Mycobacterium tuberculosis [1,3]. Africa, Asia, Eastern Europe, and Latin and Central America have a high burden of tuberculosis. Most TB in 2018 were in regions of South-East Asia (44%), Africa (24%) and the Western Pacific (18%), with smaller percentages in the Eastern Mediterranean (8%), Europe (3%) and the Americas (3%). Especially in Portugal, TB incidence is low (20/100000 people) [1,4]. Risk factors include immunosuppression, poverty, malnutrition, occupational factors and living in endemic areas.

Most people who develop TB can have onward transmission curtailed and be cured with a prompt diagnosis and treatment with antibiotics. Global targets and milestones for reductions in the burden of TB disease have been set as part of the WHO's End TB Strategy [1]. The work-up generally begins with a chest radiograph, often manifests with abnormalities in the upper lung zones, including fibronodular infiltrates and cavities with thick and lack of air-fluid levels [2]. Diagnostic tests for TB disease include tuberculin skin testing (Mantoux test); Interferon Release Assays (IGRA) and confirmatory tests, such as, Acid Fast Staining-Ziehl-Neelsen smear microscopy, culture-based methods, nucleic acid amplification (Polymerase Chain Reaction) and gene-based tests. Without treatment, the mortality rate is high. Active disease requires a combination of drugs, including 6 months of isoniazid plus rifampicin, initially supplemented by 2 months of ethambutol and pyrazinamide. However, there is an increasing number of multidrug-resistant TB.

In 2016, the national vaccination program had moved the Bacille Calmette-Guérin (BCG) vaccine from universal to restricted risk groups, as well as with most European countries [5,3]. The BCG vaccination, a milestone of tuberculosis control, began following initial pilot studies in the former Czechoslovakia (1961–1972) and Sweden (1975) and since 1974 has been included in the WHO Expanded Programme on Immunization. It is the only vaccine that reduces the risk of severe forms of tuberculosis in childhood, preventing its spread, but its efficacy against pulmonary forms in adults is variable [5]. The distinctive vaccine strains created by several laboratories are not homogeneous in their genetic components, casting doubt on whether they maintain the look-alike immunogenicity [6] Concurrently, it does not prevent primary infection and, it does not prevent reactivation of latent pulmonary infection [5].

Moreover, human infection with mycobacteria is a potent trigger of granuloma formation. Tuberculoid granulomas were thought to be a result of protective cell-mediated, typically highly organized structures consisting of central necrosis surrounded by lymphocytes and fibrocytes that could be associated with cancer [2]. Noncaseating granulomas are associated with several noninfectious or infectious conditions, including tuberculosis, which is usually a diagnosis of exclusion. Thus, abdominal tuberculosis develops from invasion of pathogenic bacteria, triggering damaging granulomatous inflammation. Such invasion and inflammation can lead to bleeding, ulceration, and perforation. Among other things, pathologic involvement of the gastrointestinal vasculature and inflammatory damage of the gastrointestinal tract occurs. The gastrointestinal vasculature observed under the microscope, shows granulomatous inflammation within the arterial wall and thrombosis with the arterial lumen. Therefore, ischemia may exacerbate the gastrointestinal damage initiated by this localized granulomatous inflammation [7].

Abdominal tuberculosis represents the 6th most frequent form of extra-pulmonary tuberculosis, after lymphatic, military, bone, joint, genitourinary, and meningeal tuberculosis. This continues to represent a diagnostic challenge to clinicians [8,14]. It could be present with involvement of the peritoneum, esophagus, stomach, intestinal tract, hepatobiliary tree, pancreas, perianal area, and lymph nodes [10]. The most common forms of disease include involvement of the peritoneum, intestine, and/or liver. Infection of the peritoneum is usually secondary to hematogenous spread of tubercles from a pulmonary focus [7]. The rising prevalence of abdominal TB is thought to be secondary to the increasing prevalence of immunocompromised states, as well as of increased migration into endemic regions [10]. Presentations of abdominal TB are multi-site, then specific diagnosis requires a high index of suspicion, imaging modalities, various laboratory findings and histologic exclusion of malignancy. The diagnosis of abdominal TB is usually made by adequate radiological and histopathological studies and a wide range of imaging techniques is available for sampling and diagnosis [8]. The biopsy methods consist of image-guided percutaneous biopsy, endoscopic GI mucosal biopsy, endoscopic ultrasound guided biopsy, and surgical (laparoscopic or open) biopsy. Peritoneal TB is divided toward three types: (a) the wet ascitic type is more common and is associated with large amounts of free or loculated fluid in the abdomen; due to increased protein content of the inflammatory exudate, the ascites is usually of high density. Peritoneal intensification is mostly present; (b) the fixed fibrotic type, less common, is characterized by omentum and mesentery involvements, by matted bowel loops on imaging or by the presence of loculated ascites; and (c) the dry plastic type is characterized by fibrous peritoneal reaction, peritoneal nodules, and presence of adhesions [7,9-11]. Abdominal TB is generally responsive to medical treatment alone, so early diagnosis can prevent unnecessary surgical intervention [12]. All diagnosed cases of gastrointestinal TB should receive at least 6 months of anti-tuberculous therapy which includes initial two months of therapy with isoniazid, rifampicin, pyrazinamide, and ethambutol thrice weekly [10].

The aim of this clinical review was to highlight the tuberculosis epidemiology and the difference between developed and undeveloped countries; to describe the effects of a timely identification of granulomatous disease that may alter the clinical course and respective prognosis of the patients and stand out peritoneal or/and abdominal tuberculosis as a rare entity seen in the literature.

Methods

The inclusion criteria were any peer-reviewed observational or interventional human studies or case reports describing granulomas and abdominal tuberculosis, from 1 January 2018 to 31 December 2019. We searched PubMed/MEDLINE and Google Scholar, using combined keywords for tuberculosis (TB) and peritoneal tuberculosis in the search queries. To stipulate, we used ("tuberculosis" OR "abdominal tuberculosis" OR "peritoneal tuberculosis") and ("generalized lymphadenopathy"OR "peritoneal disease" OR "cancer"). We also searched World Health Organization about the tuberculosis data and respective guidelines. We excluded article in non-English-language.

Discussion

The multiple vaccination policies are mainly related to different opinions on vaccine efficacy and local variations in the epidemiology of TB. The decrease in incidence between the 1980s and 1990s led most Western European countries to modify their strategy. According to a study carried out in Ireland, a country that still maintains a universal vaccination scheme, indicates that the selective vaccination strategy, although having less economic impact, is less effective. In this way, concentrating vaccination on risk groups, if resources can also be concentrated on more effective diagnosis and treatment. However, there are important ethical aspects, such as the increase in TB cases with the change of paradigm. So, in February 2016, Portugal entered the list of European countries that only vaccinate at-risk groups. This decision comes from the proposal of the General Directorate of Health (DGS), the change being justified by the good levels of TB control and a decrease in its incidence in recent years [6]. In 2018, the incidence was 17.5 cases per 100,000 inhabitants, which places Portugal as a country with a low incidence [4]. According to DGS, the reduction in incidence over the years allowed the fulfillment of control criteria recommended by WHO and a consequent change in the vaccine paradigm [6]. Despite this favorable evolution, large urban centers, namely, the region of Lisbon, Oporto, Setubal, and Algarve have higher incidences, between 20 to 30 cases per 100,000 inhabitants in 2018 [4,6] and the TB incidence in undeveloped countries [figure 1 and figure 2].

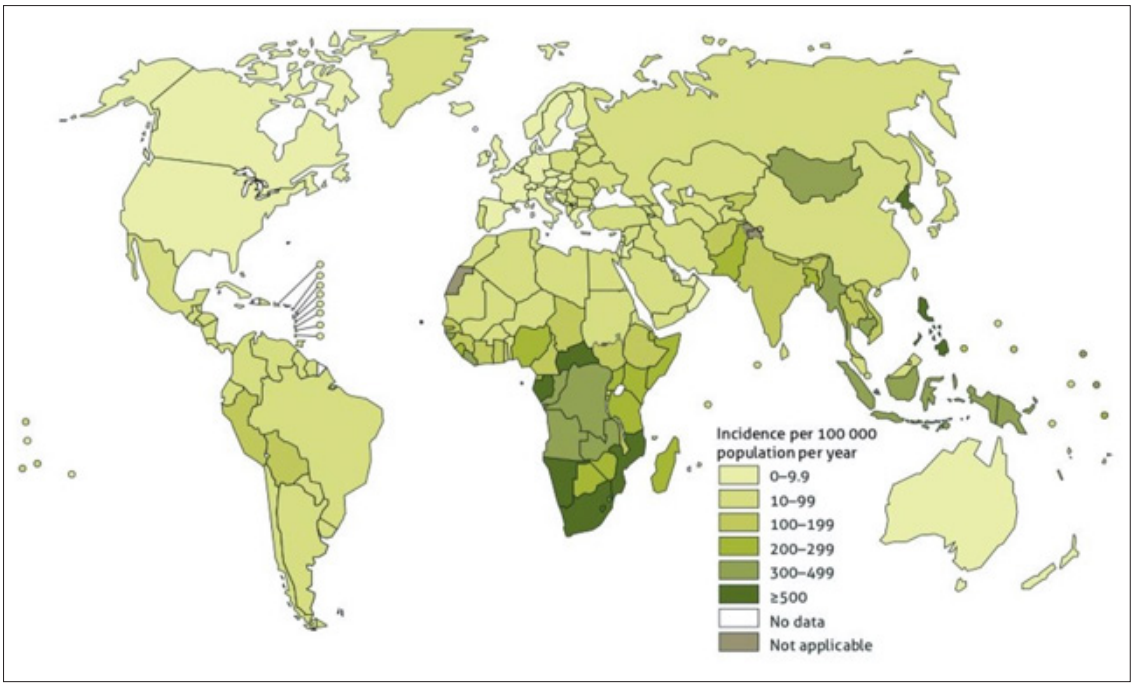

Figure 1: Global incidence of TB in 2018 by country. From Global Tuberculosis Report 2018, World Health Organization 2018

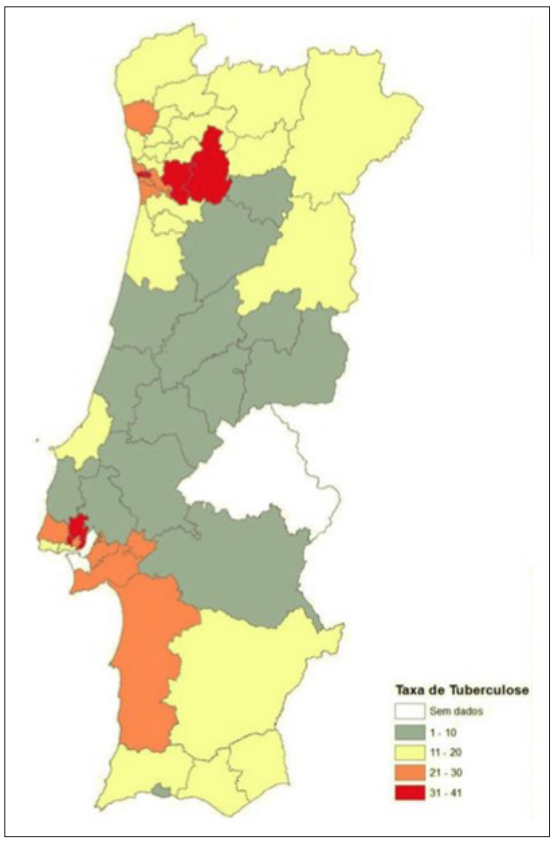

Figure 2: Portuguese TB incidence in 2018. Lisbon has the highest incidence rate according to DGS

This clinical review alerts the importance of the patient's epidemiology and to the highest incidence in undeveloped countries. Besides, increasing population migration, usage of more potent immunosuppressant therapy and the acquired immunodeficiency syndrome (AIDS) epidemic has contributed to a resurgence of this disease in regions where it had previously been largely controlled [10,13].

Tuberculosis is one of the major health worldwide problems especially in developing countries, where the disease is endemic.

Abdominal TB is relatively rare, but it is recognized to be increasing in both developing and developed countries and should always be considered in developing countries [3,14]. It is predominantly a disease of young adults with a slight male predominance and the mean age of patients is between 30–40 years. Besides, abdominal TB accounts for 0.1% to 0.7% of tuberculosis cases and is one of the common sites of extra-pulmonary involvement (10%) [3,14].

Peritoneal TB is the most common presentation of abdominal TB, and it is particularly difficult to distinguish from peritoneal carcinomatosis because of the similarities in clinical manifestations and laboratory results [7,12]. It can occur because of reactivation of bacilli in the peritoneal space or mesenteric lymph nodes [2,9]. Patients may present with subacute symptoms of abdominal or pelvic pain, low-grade fever, diarrhea or constipation, and weight loss, anorexia, and malaise [2,7,8,10,12]. Patients with peritoneal TB manifest a progressive abdominal distention from abdominal pain and ascites. Some patients could also have small intestine obstruction caused by adhesions may also [13]. On physical examination, diffuse abdominal tenderness, doughy abdomen, hepatosplenomegaly, and ascites (the predominant finding) may also be present. Laboratory tests are non-specific, although normochromic, normocytic anemia, thrombocytosis, monocytosis, and elevated erythrocyte sedimentation rate are characteristic [2,7]. The most useful diagnostic method for peritoneal TB is analysis of peritoneal fluid. It is usually straw colored with cell counts between 500 and 1500 cells/mm3, predominantly lymphocytes. High (> 33 IU/L) ascitic adenosine deaminase activity (ADA) level (that is increased in tuberculous ascitic fluid because of the stimulation of T cells by the mycobacterial antigens) and low serum ascitic albumin gradient (< 1.1) have a sensitivity of 97% and specificity of 100% [7]. Ascitic fluid total protein levels >25 g/L is seen in almost all the patients. Elevation of CA-125 has been documented in peritoneal TB. Risk factors for peritoneal TB include states of immunosuppression (most prominently HIV infection/AIDS or malignancy), diabetes mellitus, renal failure requiring dialysis, cirrhosis or alcoholic liver disease and malnutrition [7-9]]. People living in endemic regions have also the greatest risk of infection [2].

Peritoneal tuberculosis can mimic malignancy or cancer recurrence and pose a diagnostic challenge. During infection, the peritoneum becomes thick, hyperemic, and less shiny. Both visceral and parietal peritoneal layers are studded with multiple tuberculous nodules. Ascites is a secondarily signal of the proteinaceous fluid exudates from the tubercles. Approximately 90% of patients with peritoneal TB suffer from ascites and about 20-40% of patients present with an acute abdomen and need surgical management [14]. The typical histopathologic findings are the chronic granulomatous inflammatory reaction made up of activated epithelioid macrophages surrounded by, plasma cells and Langerhans multinucleated giant cells and a collar of lymphocytes, fibrosis and central caseous necrosis. Also, on computerized tomographic (CT) imaging, the ascitic fluid has high attenuation values. The peritoneum is commonly thickened and nodular. Thickened mesentery (>15 mm) with mesenteric lymph nodes is seen in most cases. US is superior to CT in revealing the multiple, fine, mobile septations characteristically found in TBP, while CT cloud highlight the peritoneal, mesenteric, or omental involvement. The presence of a smooth peritoneum with minimal thickening and pronounced enhancement on CT suggests pTB, whereas nodular implants and irregular peritoneal thickening suggests carcinomatosis [15]. Laparoscopy is the diagnostic tool of choice in patients with suspected pTB [7,9,13]. Not only does it allow inspection of the peritoneum, but also offers the option of obtaining specimens for histology. Peritoneal carcinomatosis may occasionally mimic the laparoscopic features of pTB, hence the importance of biopsy [15]. Special stains, such as the Ziehl-Neelsen stain, can identify the presence of the bacillus, but this finding is rare [7,12]. For example, to allow for the detection of mycobacteria in stained smears, presence of at least 5000 bacilli/mL of specimen is required, whereas for positive culture as few as 10 organisms might be sufficient for the diagnosis.

As it was shown, its diagnosis is still difficult because of unstable presentation and insidious nature, low percentage of positive microscopy for acid-fast bacilli (AFB) and the time delay of up to several weeks for a positive TB culture. If typical caseation

was not seen, staining for AFB would be negative and isolation of mycobacterium is a cumbersome-time consuming process. In agreement, the WHO policy recommendation stipules that "neither interferon-gamma release assays (IGRA) nor the tuberculin skin test (TST) should be used for the diagnosis of active TB disease in low and middle-income countries" [1,3]. On the other hand, a positive result cannot distinguish between latent and active infection, and negative TST or IGRA does not exclude active tuberculosis infection [9]. IGRAs alone are insufficient in diagnosing peritoneal TB [9]. It limits their utility in diagnosis of active abdominal TB [13]. Other technological advancement has been the introduction of rapid amplification-based tests for detecting specific regions of bacterial DNA or RNA. The polymerase chain reaction (PCR) is a technique that uses nucleic acid amplification to detect bacteria in body tissues and is especially useful when AFB test is negative. Reports suggest that the performance of the various PCR tests is reasonably good with sensitivity reaching up to 95% in smear-positive patients [12]. The pharmaceutical treatment of abdominal TB recommends a conventional anti-tuberculous therapy for at least 6 months including an initial 2 months of rifampicin, isoniazid, pyrazinamide, and ethambutol [7]. Complications of abdominal TB include ulcer, perforation, adhesion, fistula formation, obstruction, stenosis, and bleeding. Therefore, the importance of establishing early diagnosis lies in the fact that the management of the disease is entirely different from other pathologies and a delay in the diagnosis and treatment of peritoneal tuberculosis may lead to worse clinical outcome [10].

Conclusions

This review highlights the importance of the patient's epidemiology. Comparing to Portugal, the TB incidence in developing countries was higher. It also highlights the great mimicker that simulates many diseases, and its peritoneal variant can clinically behave like a different abdominal pathology, and the risk of misdiagnosis in patients with generalized lymphadenopathy, peritoneal disease, and cancer, particularly in young patients. TB and cancer share many similarities in symptoms and radiology and laboratory results.

Peritoneal tuberculosis is not a common form of extrapulmonary tuberculosis, however, should be considered in developing countries. The main pathologic mechanism involves the activation of localized tuberculous focus in the peritoneum.

Peritoneal tuberculosis can often mimic peritoneal carcinomatosis and it should be considered in differential diagnosis. True diagnosis and then a correct and careful follow-up can decrease patient morbidity and mortality. This old disease may be fatal within just 5 years in more than 50% of cases and clinicians should start the treatment as soon as possible.

Its diagnosis is frequently difficult with significant variability in symptom onset, duration, and presentation. Additionally, the patients who have peritoneal tuberculosis also have other comorbidities like cirrhosis, renal failure, diabetes mellitus or malignancy.

There are several procedures for diagnosing TB, but none is sensitive or specific.

To finalize, it is very important to be multidisciplinary with professional inputs from all related fields to achieve the best outcomes of diagnosis and treatment for the patients.

Global estimated TB incidence rate in 2018. U have higher rates, according to the WHO.

Portuguese TB incidence in 2018. Lisbon has the highest incidence according to DGS.

Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Disclosure Statemnent

All authors have no personal conflicts of interest or financial relationships relevant to this publication to disclose.

Funding Sources

No funding was received.

Autor Contributions

Filipa Lucas: article concept, draft of the manuscript and critical review. João Gigante and Soraia Silva: critical review.

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