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Latent tuberculosis in patients with Crohn's disease in a university hospital in Northeastern Brazil: a retrospective study

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HIGHLIGHTS

- Latent tuberculosis in patients with Crohn's disease it's serious public health problem globally.
- The authors analyzed 235 medical record regarding the clinical and epidemiological characteristics of the studied patients classified as having ILTB, 34%.
- Profile of the participants in this study it's aligns with findings previously established in the literature.

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ABSTRACT – Background – Among chronic condition problems, tuberculosis still represents a serious public health problem globally. **Objective** – To investigate latent tuberculosis infection in patients with Crohn's disease. Retrospective, descriptive cross-sectional study of quantitative analysis. **Methods** – The research was conducted on diagnosed cases of Crohn's disease at the University Hospital located in a city in Northeastern Brazil. All cases of patients with Crohn's disease undergoing isoniazid or rifampicin therapy for latent tuberculosis (LTBI) were included in the study. The data obtained were subsequently subjected to statistical analysis using the Statistical Package for the Social Sciences (SPSS) program. **Results** – We analyzed 235 medical records, and it was observed that 56% were male, with a mean age of 42.7. Among these, 54% declared themselves as brown, 31% had completed high school, and 47% were residents of the city of Teresina. Regarding the clinical and epidemiological characteristics of the studied patients classified as having ILTB, 34% of the medical records were diagnosed by tuberculin test, 48.51% were investigated by x-ray examination, and the recent location affected the colon with 27%. **Conclusion** – Overall, the health profile of the participants in this study aligns with findings previously established in the literature, particularly studies conducted in other Brazilian states, as well as in other developing countries.

Keywords – Latent tuberculosis; Crohn's disease; tuberculin test; epidemiology.

INTRODUCTION

Among chronic diseases, tuberculosis (TB) remains a significant public health concern worldwide, as stated by the World Health Organization (WHO). Its resurgence is linked to various factors, including immune-mediated diseases such as inflammatory bowel diseases, including Crohn's disease⁽¹⁾.

The use of immunosuppressive therapy that blocks tumor necrosis factor alpha (TNF- α) increases the risk of developing infectious diseases, particularly TB. This underscores the need for intensified prevention and control measures, especially among population groups at higher risk⁽²⁾.

Latent tuberculosis infection (LTBI) occurs when a person is infected with the tuberculosis bacillus but does not show clinical signs of active disease, remaining healthy for years despite being infected. It is estimated that one-quarter of the world's population is infected with *Mycobacterium tuberculosis*, but not all infected individuals will develop the disease. However, under conditions of altered immune response, there is a risk of bacillary reactivation⁽¹⁾.

In 2015, the World Health Organization (WHO) published the End TB Strategy, which sets forth goals aimed at ending tuberculosis as a public health threat by 2035. To achieve this objective, strategies were outlined, including increased efforts in the investigation, diagnosis, and treatment of LTBI, particularly among children under 5 years of age, contacts of TB patients, and individuals living with HIV⁽³⁾.

Among the most vulnerable populations are those with chronic inflammatory diseases, who are at a heightened risk of developing TB. Therefore, one preventive measure involves actively investigating and providing prophylactic treatment for LTBI in these groups of individuals⁽⁴⁾. This is particularly relevant for individuals with Crohn's disease, in which the immune response is compromised either due to the disease itself or because of immunosuppressive medications. Consequently, it becomes crucial to investigate LTBI in this context.

The significance of this study lies in the epidemiological understanding of latent LTBI among patients with Crohn's disease undergoing clinical follow-up at a teaching hospital. This understanding will facilitate the development of strategies to enhance care for

such patient groups and, subsequently, aid in the implementation of interventions tailored to address the specific needs of these patients. Furthermore, the results of this study can serve as a foundation for further research endeavors aiming to delve deeper into this topic and foster advancements in tuberculosis management among patients at increased risk of acquiring the disease.

The objective of the study was to assess the prevalence of LTBI among patients with Crohn's disease undergoing treatment at a tertiary hospital in the Northeast region of Brazil. Additionally, the study aimed to characterize patients with Crohn's disease and evaluate the clinical features of latent tuberculosis, including the presence of symptoms and prescribed treatment. It also sought to assess the screening for latent tuberculosis using the tuberculin test (TT), with a cutoff point of measurement ≥ 5 mm and/or findings on chest x-ray suggestive of prior TB infection without active infection. Furthermore, the study aimed to evaluate the outcome of chemoprophylaxis among Crohn's disease patients diagnosed with latent tuberculosis.

OBJECTIVE

This study to evaluate the prevalence of ILTB among patients with Crohn's disease accompanied in a tertiary hospital in the Northeast region of Brazil.

METHODS

Research design

This is a retrospective, descriptive cross-sectional study of quantitative analysis.

Data collection period

The research was carried out in diagnosed cases of Crohn's disease at the University Hospital of the Federal University of Piauí (HU-PI) in Teresina, State of Piauí, from January 2005 to December 2019. The management of medical records was performed in the premises of the institution, according to variables such as: gender, ethnicity, schooling, age group, and clinical-epidemiological characteristics with emphasis on: history of contagion, previous history of TB treatment, presence of vaccination scar (BCG),

respiratory symptoms, tuberculin test (PT), chest x-ray, presence of striations, nodular alterations and pleural thickening and others. The variables related to Crohn's disease included sociodemographic data such as gender, race/color, age, municipality of residence and the federated unit, clinical data such as disease behavior whether inflammatory, penetrating or stenotic), age of diagnosis and location according to the Montreal classification (L1, L2, L3, L4, L1 + L4, L2 + L4, L3 + L4, L4 + "p").

Selection criteria

All cases of patients with Crohn's disease undergoing therapy with isoniazid or rifampicin for latent tuberculosis treated at the research hospital were included. All cases whose situation is a change of diagnosis are excluded.

Data processing and analysis

All cases of patients with Crohn's disease with ILTB diagnosed in HU-UFPI were evaluated, accordingly with report of a working group at the 2005 Montreal World Congress of Gastroenterology. The data were tabulated and organized in spreadsheets

in Microsoft Excel 2016 software and statistically analyzed in the Statistical Package for the Social Sciences program, Version 26.

For qualitative variables, relative and absolute frequencies were used. For quantitative variables, mean and standard deviation were utilized. To test the association between variables, Fisher's Exact Test and Mann-Whitney U Test were employed, with a confidence interval (CI) of 95%.

The project was approved by the Research Ethics Committee under opinion number 4,006,555, following Resolution 466/12 of the National Health Council.

RESULTS

A total of 235 medical records of patients with Crohn's disease undergoing clinical follow-up at HU-UFPI during the study period were analyzed. Considering the patient population included, the majority were male, comprising 132 (56.4%) patients, with a mean age of 42.8 years, predominantly in the age range of 20 to 59 years (TABLE 1).

Regarding self-reported skin color, there was a

TABLE 1. Sociodemographic data of patients with Crohn's disease. Teresina, Piauí. 2021.

	N (%)	IC-95%	Mean (CI-95%)	DP
Sex				
Female	102 (43.6)	(37.3–50.0)		
Male	132 (56.4)	(50.0–62.7)		
Age Group (current)				
Adult (20–59 years)	207 (88.1)	(83.5–91.8)	42.80 (40.95–44.64)	14.35
Elderly (≥60 years)	28 (11.9)	(8.2–16.5)		
Age group				
Young people (≤19 years)	23 (9.8)	(6.5–14.1)	34.47 (32.66–36.28)	14.10
Adult (20–59 years)	200 (85.1)	(80.1–89.2)		
Elderly (≥60 years)	12 (5.1)	(2.8–8.5)		
Race/Color				
White	29 (13.8)	(9.6–19.0)		
Negress	6 (2.9)	(1.2–5.8)		
Brown	172 (81.9)	(76.3–86.7)		
Yellow	3 (1.4)	(0.4–3.8)		
Municipality of Residence				
Teresina	138 (60.3)	(53.8–66.4)		
Interior of Piauí	90 (39.3)	(33.1–45.7)		
Other State	1 (0.4)	(0.0–2.0)		
Schooling				
Unliterate	15 (6.6)	(3.9–10.4)		
Complete Elementary School	80 (35.4)	(29.4–41.8)		
Complete High School	93 (41.2)	(34.9–47.6)		
Complete Higher Education	38 (16.8)	(12.4–22.1)		

Source: HU/UFPI.

predominance of individuals identified as “pardos”, or brown (mixed race), with 172 (81.9%) cases. Regarding educational level, the most significant number of patients had completed high school, with 93 (41.2%) individuals. Furthermore, the most frequent place of residence was the city of Teresina, with 138 (60.3%) of the cases. TABLE 1 presents the sociodemographic data of the patients in this study.

The clinical characteristics of the studied patients classified as having Crohn's disease are described in TABLE 2. The average time between the onset of symptoms and the first consultation was 1,413.90 days, and between the first consultation and the diagnosis confirmation was 1,616.38 days.

There were similar data regarding the initial and recent behavior of Crohn's disease with 67.9% and 52.7% with non-stenotic /non-penetrating disease, respectively, regarding the initial location 317 patients were affected in the colon, and the recent location affected in the colon and terminal ileum/colon with 26.7%. Almost all patients underwent diagnostic investigation by x-ray and most of them by PPD test. Latent TB was reported in 13.5% of patients and TB diagnosis in 4.9%. Only one patient died as an outcome of TB (TABLE 2).

TABLE 3 shows the characterization of tuberculosis investigation in patients with Crohn's disease. Almost a quarter of the patients studied had respiratory symptoms at the time of the consultation, and only two patients reported a previous history of TB and close contact with people with TB.

Regarding the outcome of chemoprophylaxis, TABLE 4 describes the cases of patients with Crohn's disease who had latent-ILT tuberculosis from 2005 to 2019, 93.3% of the cases that underwent treatment with isoniazid for 6 months evolved in the healing process, without complications or abandonment during treatment. There was only one case corresponding to 6.7% that underwent treatment with rifampicin in a more extended period of 12 months, being performed with isoniazid with change to follow in the course of treatment to have an adverse effect as an increase in hepatic transaminases.

DISCUSSION

The epidemiology of tuberculosis is variable. The

incidence of this disease is higher in Pakistan, Turkey, and West Africa, with a sick population composed mainly of young adults and women, findings compatible with our study. However, in studies carried out in China, Singapore, and the United Kingdom, there is a report of greater involvement of men⁽⁵⁾.

To understand the epidemiological profile of the group, the average age of 42.7 (± 14.3) years was obtained. Similar to our data, a study conducted in the municipality of Criciúma/SC presented an average age for Crohn's disease of 35.72 (± 10.86)⁽⁶⁾. Females were the most affected according to the present study, in line with epidemiological data from other Brazilian states, including studies conducted in the states of Mato Grosso⁽⁷⁾, Mato Grosso do Sul⁽⁸⁾, and Rio Grande do Sul⁽⁹⁾.

The epidemiological profile of the present study, concerning race and education, resulted in most patients being identified as mixed race (54.2%) and white (11%), with completed high school education (31%), representing a population with a level of education equivalent to elementary school. These results may be explained by the characteristics of the location where the study was conducted. The predominance of mixed-race and white individuals may reflect the ethnographic distribution in the state of Piauí, which has approximately 239,605 mixed-race residents and 107,063 white residents⁽¹⁰⁾.

In turn, the urban origin characteristic of patients with TB and CD was demonstrated in this study, with 47% of patients living in urban areas. Similarly, in a study conducted in South American countries, 90.5% of the population was urban and 9.5% rural⁽¹¹⁾. Corroborating the finding of this study, a study conducted with 252 patients in Piauí showed that 86.1% of the patients lived in urban areas, while only 14% lived in the countryside when the disease was diagnosed⁽¹²⁾.

This finding is consistent with the fact that individuals from urban areas are more exposed to environmental factors, such as poor eating habits, high carbohydrate diet and low in fruits, smoking, Western lifestyle, industrialization of these regions, use of contraceptives, and IINES^(11,12) (Industrially Important Nutritional Elements).

Regarding the rate of latent TB diagnosis found in the present study, it is considered low when compared to studies in similar contexts conducted in Spain

TABLE 2. Characterization of the clinical and investigation profile of patients with Crohn's disease. Teresina, Piauí. 2021.

	N (%)	IC-95%	Mean (CI-95%)	DP
Clinical Profile				
Time between symptom onset-first consultation (days)			1413.90 (1195.76-1632.04)	1634.2
first consultation-diagnosis (days)			1616.38 (867.06-2365.71)	5277.4
Crohn's Disease Location [Initial Location]				
L1	54 (24.2)	(18.9–30.1)		
L2	70 (31.4)	(25.6–37.7)		
L3	71 (31.8)	(26.0–38.2)		
L4	9 (4.0)	(2.0–7.2)		
L1.L4	6 (2.7)	(1.1–5.5)		
L2.L4	3 (1.3)	(0.4–3.5)		
L3.L4	3 (1.3)	(0.4–3.5)		
L1.L2	3 (1.3)	(0.4–3.5)		
Disease in remission	4 (1.8)	(0.6–4.2)		
Crohn's disease location [most recent location]				
L1	36 (16.8)	(12.3–22.3)		
L2	59 (27.6)	(21.9–33.8)		
L3	59 (27.6)	(21.9–33.8)		
L4	13 (6.1)	(3.4–9.9)		
L1.L4	5 (2.3)	(0.9–5.0)		
L2.L4	3 (1.4)	(0.4–3.7)		
L3.L4	2 (0.9)	(0.2–3.0)		
L2.L3	1 (0.5)	(0.1–2.2)		
Remission Disease	36 (16.8)	(12.3–22.3)		
Crohn's disease behavior [initial behavior]				
B1	146 (67.9)	(61.5–73.9)		
B2	25 (11.6)	(7.9–16.4)		
B3	38 (17.7)	(13.0–23.2)		
B1,B3	1 (0.5)	(0.1–2.2)		
B2,B3	3 (1.4)	(0.4–3.7)		
Disease in remission	2 (0.9)	(0.2–3.0)		
Crohn's disease behavior [most recent behavior]				
B1	109 (52.7)	(45.9–59.4)		
B2	23 (11.1)	(7.4–15.9)		
B3	39 (18.8)	(14.0–24.6)		
B2,B3	3 (1.4)	(0.4–3.8)		
Disease in remission	33 (15.9)	(11.4–21.4)		
RESEARCH DATA				
RX TB Investigation				
No	1 (0.6)	(0.1–3.0)		
Yes	154 (99.4)	(97.0–99.9)		
PPD TB Investigation				
No	10 (9.9)	(5.2–16.9)		
Yes	91 (90.1)	(83.1–94.8)		
			2.42 (1.26–3.57)	5.97
Diagnosis of latent TB				
No	96 (86.5)	(79.2–91.9)		
Yes	15 (13.5)	(8.1–20.8)		
Latent TB treatment				
No	89 (85.6)	(77.9–91.3)		
Yes	15 (14.4)	(8.7–22.1)		
Diagnosis of TB disease				
No	77 (95.1)	(88.7–98.3)		
Yes	5 (4.9)	(1.7–11.3)		
Treatment of TB disease				
No	68 (93.2)	(85.6–97.3)		
Yes	5 (6.8)	(2.7–14.4)		

TB: tuberculosis. Source: HU/UFPJ.

TABLE 3. Characterization of tuberculosis investigation of patients with Crohn's disease. Teresina, Piauí. 2021.

	Tuberculosis investigation	
	No N (%)	Yes N (%)
Pleural thickening	66 (94.3)	4 (5.7)
Respiratory Symptoms	30 (76.9)	9 (23.1)
Previous History of TB Treatment	69 (97.2)	2 (2.8)
Close contact with person with TB	65 (97.0)	2 (3.0)
Nodules >5 mm	55 (93.2)	4 (6.8)
Cavitations	59 (95.2)	3 (4.8)
Condensation	52 (89.7)	6 (10.3)
Fibrotic stretch marks	50 (96.2)	2 (3.8)

TB: tuberculosis. Source: HU/UFPI.

TABLE 4. Chemoprophylaxis of *iltb*-positive cases in patients with Crohn's disease, Piauí 2021.

	N (%)	IC-95%	Mean (CI-95%)	DP
Treatment (medicine)				
Isoniazid 300 mg	14 (93.3)	(72.8–99.3)		
Rifampin	1 (6.7)	(0.7–27.2)		
Treatment time			935.64 (904.39–966.89)	243.17

Source: HU/UFPI.

(10.9%)⁽¹³⁾ and Korea (10.06%)⁽¹⁴⁾. In countries with intermediate and high TB loads, high rates of latent TB are common in patients with Crohn's disease.

Although the participants of the present study already make use of the indicated drug treatment, the low prevalence should be analyzed with caution since the history of latent TB increases the risk of developing active TB.

Regarding the Montreal Classification⁽¹⁵⁾, the patients in this study mostly had disease located in the colon region (31%) and in the terminal ileum, 31% of the patients. Regarding behavior, the highest frequency was non-stenotic/non-penetrating (inflammatory) (47%), although when added to the penetrating and stenotic behaviors (complicated forms), the total was 28%.

A study conducted in Piauí with 74 patients with CD showed that similarly, the majority had the disease located in the ileum/colon (36.6%) and exhibited non-stenotic and non-penetrating behavior (42.3%)⁽¹⁶⁾. Other studies conducted in Rio Grande

do Sul, the Northeast region⁽¹²⁾, and Mato Grosso, showed more significant involvement of the disease in the colon and terminal ileum region.

In the present study, the majority (14%) of the patients were in remission, as expected in those using biologics. A different rate was found in a study conducted with 116 patients with CD using infliximab, in which remission was found in 83.7% of the evaluated patients⁽¹⁷⁾.

According to the European Consensus on prevention, diagnosis, and management of opportunistic infections in patients with inflammatory bowel disease, TB should be managed through clinical and epidemiological history, physical examination, chest x-ray, and tuberculin skin test⁽¹⁸⁾.

Although the participants of the present study already make use of the indicated drug treatment, the low prevalence should be analyzed with caution since a history of latent TB increases the risk of developing active TB⁽¹⁹⁾.

There is significant concern regarding the diag-

nostic validity of PPD for the diagnosis of latent *M. tuberculosis* virus infection due to its low specificity in individuals vaccinated with BCG and low sensitivity in patients with immune-mediated inflammatory diseases. To improve the accuracy of skin tests, new techniques have been experimentally tested⁽¹⁸⁾.

Chest radiographs have a sensitivity of 59–82% and a specificity of 52–63% for active TB. In addition, chest x-rays only demonstrate abnormal strata in 10–20% of patients with ILTB. The present study presents some limitations because it was conducted in a single center and with a small sample of patients, in addition to the lack of some data in medical records. A prospective evaluation of these patients may provide a better amount of data on risk factors and the development of active TB.

CONCLUSION

At the end of this study, it was possible to identify the clinical and epidemiological profile of patients with Crohn's disease monitored at the university hospital in the state of Piauí, as well as the importance of a careful investigation regarding the opportunistic diseases such as latent tuberculosis and or latent disease, whose results of the present study coincide with those previously established by the literature, studies conducted in other Brazilian states, or other developing countries.

Although tuberculosis is an endemic disease in Brazil, Crohn's disease remains underdiagnosed due to its diverse clinical presentation. Distinguishing it from other pathologies continues to be a significant diagnostic challenge.

It is reinforced that, in view of the patient with intestinal disease, tuberculosis should be investigated and treated on time in the sample evaluated in the current study. It was observed that there is a significant percentage of 154% to 91% respectively within

the investigation process for both imaging (x-ray) and tuberculin test (PPD) and a low identification of ILTB cases as a 15% response. This is justified by the non-performance of the PPD examination by patients once the examination is performed after scheduling through outpatient regulation, in addition to the waiting time for the result, which is part of the diagnostic methodology.

This work contributed to expanding knowledge about Crohn's disease and implementing strategies to improve the investigation of tuberculosis and/or latent disease diagnosis in the state but it suggests further studies on the topic.

Authors' contribution

The study corresponds to the product of Melo IV's master's dissertation, under the guidance of Campelo V, Santos MO contributed to data collection, Sousa KAA analyzed and interpreted the data, Abi-Chacra EA developed the data collection instrument, Araújo TME performed the final manuscript review, Lima MM conducted the epidemiological investigation, Parente JML, provided institutional support. The authors participated in the study conception, analysis and interpretation of data, writing, review approval of the final manuscript version. And declared themselves responsible for all aspects of the study, ensuring its accuracy and integrity.

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RESUMO – Objetivo – Investigar a infecção latente por tuberculose (ILT) em pacientes com doença de Crohn no período de janeiro de 2005 a dezembro de 2019. **Métodos** – Estudo retrospectivo, descritivo transversal realizado nos casos diagnosticados de doença de Crohn do hospital universitário em uma cidade do nordeste brasileiro. Foram incluídos todos os casos de pacientes com doença de Crohn em terapia com isoniazida ou rifampicina para tuberculose latente que fazem acompanhamento no HU-UFPI. Os dados sobre doença de Crohn e tuberculose latente foram obtidos do banco de dados que foi solicitado ao HU-UFPI após aprovação da proposta de pesquisa no Comitê de Ética e Pesquisa da UFPI. Foram identificados todos os casos de pacientes com doença de Crohn com ILTB diagnosticados no HU-UFPI. Os dados foram analisados estatisticamente no programa *Statistical Package for the Social Sciences-SPSS*. **Resultados** – Foram analisados 235 prontuários, observou-se que 56% eram do sexo masculino, com a média de idade 42,7. 54% se declaravam pardos, 31% tinham o ensino médio completo e 47% residentes na cidade de Teresina. As características clínico-epidemiológicas dos pacientes estudados classificados como portadores de ILTB. 34% dos prontuários tinham diagnóstico pela prova tuberculínica, 48,51% foram investigados através do exame de raio x. Houve dados semelhantes em relação ao comportamento inicial e recente da doença de Crohn sendo 62% e 47% com a doença não estenosante/não penetrante, respectivamente, ao que se refere a localização inicial 31% acometido no cólon e íleo terminal/cólon, e a localização recente acometido no cólon com 27%. **Conclusão** – Em síntese observou-se que, o perfil de saúde dos participantes do presente estudo assemelha-se com os resultados previamente estabelecidos pela literatura, como estudos realizados em outros estados brasileiros e outros países em desenvolvimento. Esse trabalho contribuiu para ampliar o conhecimento sobre a doença de Crohn, bem como propor estratégias na melhoria da investigação do diagnóstico de tuberculose latente e ou doença, porém sugere novos estudos nesta temática em questão.

Palavras-chave – Tuberculose latente; doença de Crohn; teste tuberculínico; epidemiologia.

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