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Research Article

Gastrointestinal Tuberculosis in Peru: A Comparative Study of Clinical Characteristics, Drug Resistance and Performance Diagnostic in Two Health Centers

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Abstract

Background: Gastrointestinal tuberculosis (GTB) can have diverse manifestations and is the 10-20% of the tuberculosis worldwide.

Objective: To evaluate the frequency of GTB diagnosis in two health centers highlighting several clinical characteristics, drug resistance, and yield diagnosis of sputum smear.

Methods: A cross-sectional study was conducted in Archbishop Loayza (ALNH) and Hipolito Unanue (HUNH) National Hospitals in Peru. We included patients with and without treatment, with diagnosed of pulmonary TB, and apparently healthy of the TB Control Program. We use the conventional sputum smear and Ogawa-Kudoh culture following the standard guidelines. Also, analyzing drug resistance was carried out with several methods.

Results: We analyzed 43580 patients in total. In ALNH of 400, only 24 (6%) patients presented EPTB. We determined that 37.5% (9 patients, 55 ± 20.4 years) had GTB. All these were from Lima's downtown. The 15% were male and MDR-TB was isolated in one. The occupations more frequently were freelancers-workers, hawkers, and mechanics (each 5%). In HUNH, 836 patients were gastric samples analyzed for EPTB where 42 (5%) had a positive result (42 ± 30.4 years), and 33 (78.6%) had no prior treatment. More than > 50% of cases in the UHNH occurred in <35 years, while in the ALNH ~50% occurred in patient > 55 years. The sputa smear had a poor correlation (κ = 0.24) and a low sensitivity (30%) and high specificity (96.6%) compared with culture.

Conclusion: Our findings suggest that the GTB affected mainly mechanics, hawkers, and freelancer-workers, mainly affected young people < 35 years where > 75% had no previous treatment. Also, the overall yield diagnostic of the sputum smear is poor.

Keywords: *Gastric Cancer; Tuberculosis; Diagnosis; Multidrug-Resistant TB; Extensively Drug-Resistant TB; Peru*

Abbreviations

TB: Tuberculosis; GTB: Gastrointestinal Tuberculosis; MDR-TB: Multidrug-Resistant TB; XDR-TB: Extensively Drug-Resistant TB; DALY: Disability-Adjusted Life-Years

Introduction

For causing nearly 2.4 disability-adjusted life-years (DALY) per year, Tuberculosis (TB) is one of the main public health problems globally. Since 1990, TB has gone from position 12 to position 18 for 2015 of the main causes of global DALY's for both sexes [1].

The reduction of TB worldwide has been attributed to global technological progress. The World Health Organization (WHO) points out that since the year 2000 it has been reduced to 1.5% of the incidence of TB globally. However, the trends are more complicated than it seems. Many countries still have TB as one of their main health problems, which causes high mortality rates. Hence, *Mycobacterium tuberculosis* has become the infectious agent that causes most deaths, even above the Human Immunodeficiency Virus (HIV) and malaria [2].

The TB is not exclusively pulmonary, although it mainly affects the lungs causing 1.8 million deaths annually. For the infection of *M. tuberculosis* to develop in the gastrointestinal tract, there must be frequently a swallowing of the bacilli. This swallowing plus other factors (immunological, nutritional, and changes in the milieu) allow the development of gastrointestinal TB (GTB), an uncommon disease among abdominal TB [3].

Peru is a developing country with high rates of TB and multidrug-resistant TB (MDR-TB). Tuberculosis's incidence in Peru is of 87.6 per 100,000 inhabitants and occupies the fifteenth place as cause of death in the general population. In this country, where economic resources have apparently been insufficiently allocated to fight to TB, there is a little evidence on extrapulmonary TB (EPTB) even in recent reports [4-8]. Here, we present a comparative evaluation of the frequency of GTB diagnosis in two health centers in Lima, Peru. Further, we highlight several clinical characteristics, risk factors, drug resistance, and yield diagnosis of sputa smear for TB.

Materials and Methods

Health centers characteristics

The cross-sectional comparative study was conducted in two health centers in Lima, Peru during 2015. The first was a tertiary-care hospital (the Archbishop Loayza National Hospital - ALNH), and the other was a Center of Excellence to diagnose of TB in the Hipolito Unanue National Hospital (HUNH), both in Lima's downtown [5]. Both institutions have the TB Control Program (PCT) as a policy of comprehensive TB care. The main difference between these two health centers is the specialty of HUNH in the diagnosis of TB. Both hospitals follow the national quality standard procedures and are subject to evaluation under the protocols of the National Institute of Health (Abbreviated in Spanish as INS) and the Ministry of Health of Peru.

Patients and specimens

All PCT and outpatient-clinics patients attended during 2015 were included, and patients with suspected GTB diagnosis were considered as a study sample. We included patients with previous treatment, without treatment, with previously diagnosed with Pulmonary TB (PTB), and apparently "healthy" admitted in the doctor's office. All extrapulmonary samples were gastric aspirates and gastric juice. The average of the sample volume was 4 ± 1.5 ml and these were processed before 4 hours after the sampling. The process of obtaining the sample, the microbiological and molecular analysis, and the emission of the results complied with the Standardized Operational Procedure (SOP) of the hospitals [5,9,10].

TB diagnostic and drug resistance diagnosis

We use the conventional method of sputum analysis following the recommendation of the regional guide [6]. We analyzed the acid-fast bacilli smear (AFB) with the Ziehl Neelsen stain and then were analyzed by bright-field microscopy. In both hospitals, we performed the culture on Ogawa-Kudoh agar (Merck, Darmstadt, Germany) following the international quality requirements [10].

Analyzing drug resistance was carried out mainly with Genotype® MTBDRplus (Hain Life Science, Nehren, Germany) and BACTEC MGIT 960® (Becton Dickinson, Sparks, MD, US) in each hospital by the availability of supplies and equipment. Moreover, all positive specimens (including strains and extrapulmonary-samples stored) were referred to the INS where these studies were re-performed and MODS (Microscopic Observation Drug Susceptibility), GeneXpert® (Cepheid, Sunnyvale, CA, US), among others, were also used.

Data analysis

All these results of both hospitals were codified from the Hospital's data storage system (in MS-Excel 2010, Redmond, US) and GESTOS (ALNH only) to the data matrix (in EPIDAT v4.1, Xunta de Galicia, Spain). We used descriptive statistics, non-parametric correlation, Non-paired T-student, and chi-square between the variables of the study, considering a 95% confidence interval and a value of $p < 0.05$ as statistically significant. The statistical analysis was performed with IBM SPSS v21.0 (Armonk, USA) and BloxPlotR [11] for Windows.

Results

Twenty-six thousand six hundred and thirty-six patients were analyzed during 2015 in the ALNH, of which 799 (3%) had a positive AFB smear. When we selected one sample per patient, we obtained only 400 (1.5%) cases with positive sputum smears in total. These patients came from Lima and other regions of Peru, and their mean age was 40 ± 18.3 years (CI95%: 38.1 - 41.7). The 249 (62.3%) men did not show significant differences with the 151 (37.7%) women ($p = 0.448$).

The PTB was mainly diagnosed (94%) and only 24 (6%) patients presented EPTB. In the EPTB, we determined that 37.5% (9 patients) had GTB. All these patients were from Lima's downtown (15%) and whose average age was 55 ± 20.4 years (range: 28-79 years). Fifteen percent of patients with GTB were male, and MDR-TB was isolated in one (Figure 1).

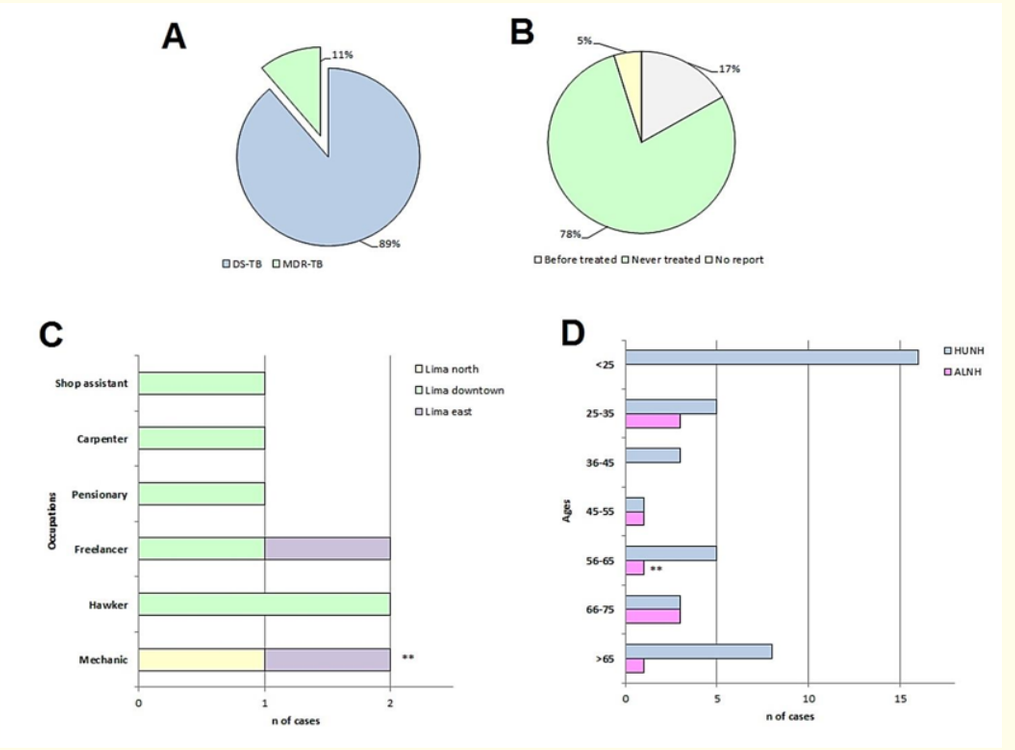

Figure 1: *Clinical characteristics and risk factors of gastric Tuberculosis (GTB) in Peruvian patients from two health care centers. A. Distribution of drug-resistance TB isolates from the Archbishop Loayza National Hospital (ALNH). B. Distribution of treatment history (before treated, never treated, and not report) of patients with presumptive diagnosis of GTB from the Hipolito Unanue National Hospital (HUNH). C. Occupations of patients with gastric tuberculosis of the ALNH by Lima's district of origin. D. GTB Patient distribution to age group. ** indicates patient with Multidrug-Resistant Tuberculosis (MDR-TB) isolate. Abbreviations: DS-TB: Drug-Sensitive Tuberculosis.*

For the ALNH, the occupation of patients with GTB were available, where 2 (5%) were freelancers, 2 (5%) were hawkers (in Spanish called "Ambulante," defined as informal workers who market products on the street [12,13]), 2 (5%) mechanics, and the remaining 7.5% consisted of a pensionary, a carpenter, and a shop assistant.

Instead, 2015 at HUNH, 16944 patients were analyzed. The average age of the 492 men (35 ± 30.1 years, CI95%: 32.6 to 38) showed significant differences with the 344 (41.2%) women (33 ± 34 years, CI95%: 29.1 to 36.2) (p = 0.008).

Eight hundred thirty-six (4.9%) were gastric samples analyzed for EPTB and 42 (5%) had a positive result. Fourteen (1.7%) samples were positive in both AFB smear and culture, and 28 (3.3%) were positive only in *M. tuberculosis* culture. In addition, 15 (1.8%) samples presented culture contamination. Seven (0.8%) patients with GTB had a treatment, 33 (3.9%) had no prior treatment, and 2 (0.24%) had no history (Figure 1). The mean age of all patients with GTB was 42 ± 30.4 years (CI95%: 39.2 to 45.5). Seven (0.84%) of the 15 contaminated cultures came from patients without previous treatment and were mostly males (8 patients, 0.9%) who did not show significant differences (p = 0.358). All contaminated cultures had AFB negative smear.

In both institutions, range of patients with a presumptive diagnosis of GTB ranged from neonates (25 days old) to old people (95 years) (Figure 2). The mean ages men and women of both hospitals had significant differences (p = 0.032). By age groups > 50% of cases in the UHNH occurred in < 35 years, while in the ALNH ~50% occurred in patients > 55 years (Figure 1d). We did see a significant difference between patients with GTB between hospitals (p = 0.034).

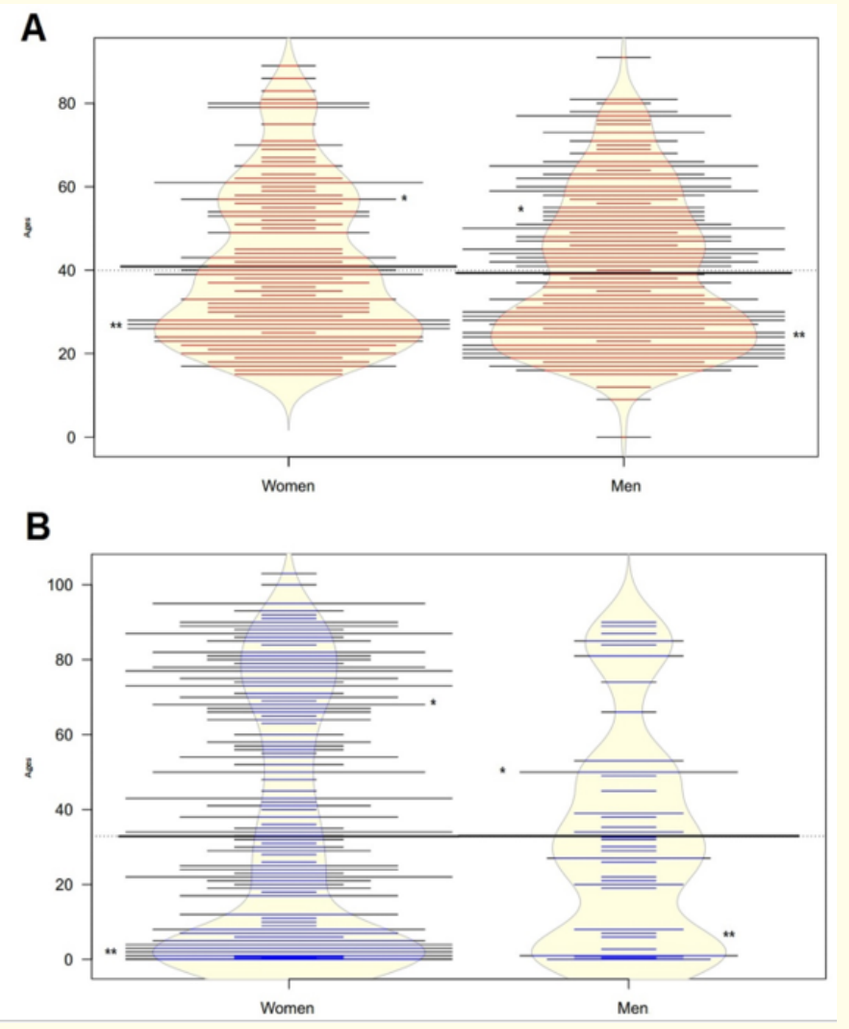

Figure 2: *Age distribution by sex of all patients with a presumptive diagnosis of Tuberculosis of Hipolito Unanue National Hospital (A) and Archbishop Loayza National Hospital (B). The mean ages men and women of ALNH (37.5 and 35 respectively) and HUNH (29 and 22 respectively) had significant differences (p = 0.032). The 3rd quartile (marked with *) and 1st quartile (marked with **) are shown in the figure. Data in Bean plot.*

We determined a correlation between GTB and sex, affected significantly more men (p = 0.045). However, we did not find any difference and correlations between the GTB with the occupation (p = 0.826), nor with the sex (p = 0.212), nor with the patient's place of origin (p = 0.748).

Finally, the distribution of sputum smear and culture results are shown in table 1. Their diagnostic values indicate a poor correlation between the two tests (κ = 0.24, CI95%: 0.02 to 0.45). The AFB smear gave a sensitivity of 30% (CI 95%: 18.1 to 45.4) and specificity of 96.6% (CI 95%: 82.8 to 99.4) for GTB diagnosis. In addition, this test gave a positive predictive value (PPV) of 92.3% (CI 95%: 66.7 to 98.6), a negative predictive value (NPV) of 50% (CI 95%: 37.3 to 62.7) and a precision value of 58% (CI 95%: 46.2 to 68.9).

Sputum smear (AFB result)	TB culture							
	HUNH (n = 57)*						ALNH (n = 9)	
	Negative	COL	1+	2+	3+	Contaminated	DS-TB	MDR-TB
Negative	-	20 (35.1)	5 (8.8)	3 (5.3)	-	15 (26.3)	-	-
Paucibacillary¶	-	1 (1.8)	1 (1.8)	-	-	-	-	-
1+	1 (1.8)	1 (1.8)	2 (3.5)	2 (3.5)	-	-	2 (22.2)	-
2+	-	-	-	1 (1.8)	1 (1.8)	-	4 (44.4)	-
3+	-	-	-	-	4 (7)	-	2 (22.2)	1 (11.1)

Table 1: *Distribution of sputum smears results and culture of gastric samples in the Hipolito Unanue National Hospital (HUNH) and Archbishop Loayza National Hospital (ALNH). The interaction between results in the HUNH showed a proportion of false positives and negatives of 3.4% and 70%, respectively. In ALNH there were no paucibacillary results and the only Multidrug-Resistant Tuberculosis (MDR-TB) isolate presented 3+ in the sputum smear. Data in n(%).*

Include 42 samples and 15 undiagnosed contaminated cultures. ¶Number of Acid-fast bacilli (AFB) per 100x fields. Abbreviations: AFB: acid-fast bacilli smear, COL: Tuberculosis colonies on Ogawa agar, , DS-TB: Drug-Sensitive Tuberculosis, MDR-TB: Multidrug-Resistant Tuberculosis.*

Discussion

We detected a seven-fold increase in the frequency of GTB in the ALNH compared to the HUNH. In the ALNH, the GTB affected mainly mechanics, hawkers, and freelancer-workers over 55 years, while in the HUNH affected young people less than 35 years where more than 75% had no previous treatment against *M. tuberculosis.* Our findings also suggest that when the sputum smear had 3+ the culture had a many colonies developed on the medium, but when the results of the sputa smear were lowered the results of the culture were heterogeneous.

The main strength of the study is that we conducted the first study on GTB in two Peruvian health centers, comparing their frequency, clinical characteristics, and diagnoses. During the past decades, there have been isolated reports on GTB that have been presented as a thesis and separate projects [14-16]. Here, we have included some clinical characteristics available, such as resistance to drugs and occupations, as important factors to understand the GTB and it aetiology.

As in our study of 43 580 patients, GTB is 10 - 20% of the total TB worldwide. However, the regional and national prevalence is underestimated, since there has been a geographic variability between population groups, and also because the GTB is often not diagnosed, is dismissed or is asymptomatic in patients with PTB [17]. The previous retrospective study of the ALNH determined 28 patients with GTB per year, while another study showed that ~54% of children with PTB had a gastrointestinal localization [15,25]. Our results indicate that the GTB affects more males, but that the age varies according to the population studied, affecting up to 30% of those < 35 years (Figure 1).

In some countries where EPTB has increased, such as Uruguay, GTB rates have increased in frequency due to the high proportion of patients in immunosuppressive states (with HIV/AIDS, solid-organ transplant, immunosuppressive treatment), low socioeconomic status, and migratory changes [18]. These risk factors and others even complex generate, in part, variability in the prevalence of GTB.

Our analysis indicates that the occupation did not have a significant relationship with the GTB. However, this possible risk factor must be carefully evaluated. We determined that ~67% of GTB affected mechanics, freelancer-workers, and hawkers, finding the only case of MDR-TB in these occupational groups. There is evidence for the high relation of certain occupations with TB [19,20]. This evidence suggests the epidemiological importance of some occupations with TB. For example, the Hawkers that we included in the study are dedicated

to street food sales (Figure S3) and therefore must be "healthy" to have the authorization of Food Handling following Peruvian guidelines [13,21]. The Peruvian's high incidence of MDR-TB and the possibility that these workers may have PTB and EPTB require the intervention of health institutions to assess the degree of infection, promote prevention and control actions, as they have been reported previously diseases transmitted by these routes [12,22-24].

Figure S3: *Street food vending and typical Peruvian breakfast. The sale of food on the street is usual in Lima, Peru. The workers have certain breakfast/dinner (A and B) and other foods (D) stands. For both, there is no robust microbiological control of the food sold (C), but of the vendors who undergo the diagnosis of TB through the sputum smear, although sometimes their sensitivity is poor.*

Drug-resistance plays a distinctive and a key role among people with TB. The TB's drug-resistance has been related to the capacity to generate resistance to the main agents (MDR-TB, first-line agents: isoniazid and rifampin; and XDR-TB, resistant to isoniazid and rifampin plus any of the fluoroquinolones and at least one second-line injectable agent) with varied rates thoughtfulness worldwide [7]. In this study, we determined one case with MDR-TB in a Mechanic of Lima, which presented GTB after PTB. Two considerations on this case. First, in none of the previous reports on GTB in Peru has drug resistance been determined with molecular tests [2,4-6,14-16,25]. Second,

since GTB is unusual and its clinical approach is uncommon, we are sure that its clinical diagnosis is confused with other diseases [7,17]. In addition, the follow-up or retrospective analysis of the cases that have been identified to date does not present adequate information on their characteristics of drug resistance, risk factors, and prognosis.

Faced with this conception of the implications of TB treatment, > 75% of the GTB's patients enrolled in this study had no previous treatment history. The importance of TB diagnosis in new patients lies in its correct health intervention and treatment support. A good deal of tuberculosis control programs are not adequate for the sociocultural reality, which is why tuberculosis has a high incidence and mortality rates in many countries, such as Peru.

We have recently reported the low performance of sputa smear in subjects > 65 years [26]. Our findings on the performance of microscopy in the diagnosis of GTB also demonstrate inconsistencies in the results compared to culture. These findings not only detail a sensitivity ~30%, a diagnostic accuracy of 58% (95% CI: 46.2 to 68.9), and an alarming proportion of false negatives (70%, 95% CI: 54.6 to 81.9), but show 1.8% of contaminated cultures. These findings indicate that both microbiological methods are not sufficient for the diagnosis of GTB, but they are useful in the control of treatment against *M. tuberculosis.*

Limitation of the Study

This study has limitations. We did not analyze all the clinical characteristics in both GTB patients in both health cares. Due to the limited collection and poor quality of data collected in each hospital, the data were not homogeneous and depended on a large extent on medical judgment and their interests in the management and follow-up of each patient. We did not have access to drug-resistance and occupational data in the HUNH, while in the ALNH we did not have data on patients' treatment history. Another limitation was that we did not identify *Mycobacterium bovis* in patients with GTB in both hospitals. *M. bovis* has been described as a rare cause of GTB in developed countries, while in low-and-middle-income countries and high incidence of TB it is likely that some patients with GTB may have been infected by *M. bovis* through milk and derived products [7,15]. Further investigation is also required to determinate the frequency of *M. bovis* in GTB and if these species are related to particular risk factors. Finally, we focus on GTB in general terms, consequently we do not perform an exhaustive search to know the specific location in each patient [6,7].

Conclusion

In summary, this is the first study to compare the diagnosis of GTB in two Peruvian health centers. Our findings suggest that the GTB affected mainly mechanics, hawkers, and freelancer-workers older than 55 years, while, and also affected young people < 35 years where more than 75% had no previous TB treatment. We have also identified that a sputum smear with 3+ had most colonies in the culture and that the overall yield diagnostic of the sputum smear is poor.

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Author Contributions

All the authors contributed to this paper.

Conflict of Interest Statement

There are no potential conflicts of interest.

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