



Tuberculosis in a Cross-Border Hospital During Covid-19: Does a Pandemic Modifies Another Pandemic?

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Abstract

Due to the COVID-19 pandemic, borders were closed in March 2020 to alleviate the health crisis and prevent further transmission and impact at the international level. This not only had economic consequences, but in border cities such as Melilla (Spain) the implications were also social. Under this situation, humanitarian settlements were created for people who could not return to their places of origin in Morocco. Both the risks of tuberculosis outbreaks in the settlements and the fact of being locked up in this Spanish city that usually has important relations with Morocco made the profile of tuberculosis patients treated in the hospital different.

Objective: To analyze sociodemographic and clinical characteristics of inpatients diagnosed of TB from January of 2019 to March 2021, focusing on the differences between pre-COVID-19 and COVID-19 periods.

Methods: Descriptive study of characteristics by review of clinical records of the patients diagnosed of tuberculosis during the study period.

Results: There were a total of 31 patients diagnosed of tuberculosis, mainly from Berber etnia and being affected by the pulmonary form. The proportion of migrants living in settlements was high (22%) and there was an important lost of follow up because of the population characteristics. The only difference between pre-COVID-19 and COVID-19 periods was nationality, decreasing Moroccan population due to the lock down in the second one.

Conclusion: The social reality of a cross-border city during COVID-19 pandemic has important healthcare implications, and the risk of outbreaks such as tuberculosis in improvised settlements has to be highlighted.

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Introduction

Tuberculosis (TB) is an infectious disease caused by a group of microorganisms belonging to the genus *Mycobacterium*, called M. Tuberculosis Complex (MTBC). This group actually comprises four species that cause human TB cases: *M. tuberculosis*, *M. bovis* (including BCG), *M. africanum* and *M. microti* [1,2]. It is transmitted by air, spreading from person to person through tiny droplets released from the coughs or sneezes of an infected person [3,4]. Although it is mainly a pulmonary pathogen, it can affect any other body location (abdomen, glands, bones and nervous system). The pulmonary form is the most contagious type [5].

Nowadays, the disease possess a worldwide distribution with a significant number of affected people [6]. The diagnostic complexity and the long-term treatment make this infectious disease one of the leading causes of death in the world [7,8]. In Europe, the TB incidence rate is 28 cases per 100,000 inhabitants [9], whereas this rate is lower (9.39 cases per 100,000 people) in Spain, with a progressive decline in recent years [10]. Nevertheless, the rate in the Spanish autonomous city of Melilla stands at 9.43 per 100,000 people, slightly higher than the national rate [11].

The especial epidemiological status of Melilla requires an assessment of the geographic surroundings. This Spanish city is located in the North of Morocco, on the shores of the Mediterranean Sea, so it is continuously receiving a large floating population; it is estimated that about 10.000 to 30.000 people cross the Spanish border every day (unofficial data), being the Moroccan Nador province (that surrounds Melilla) the main emigration focus. According to the Moroccan Epidemiological and Public Health Bulletin of 2017, the incidence of TB in that country was 91/100.000 inhabitants, ten times higher than the one above mentioned for Spain [12].

The total number of patients diagnosed of TB every year in Melilla Hospital is variable since it does not depend only on our population. Cases attending the hospital for diagnosis and/or treatment are official residents from Melilla but also individuals living in Morocco as well as those living in the Center for the Temporary Stay of Immigrants (CETI) but coming from different countries (especially, from sub-Saharan Africa, the Middle East and North African ones). Thus, it is obvious the epidemiological complexity of Melilla.

After the declaration of COVID-19 pandemic by the WHO at 11th of March of 2020 [13], international borders were close and lock-down restrictions imposed, so the border crossing from the Moroccan population to Melilla was also interrupted. Many people got trapped in the Spanish city, unable to return to Morocco and several temporary settlements had to be established (CETI, hotels and, even the bullring of Melilla). These settlements represented many public health concerns due to the risk of outbreaks inside them.

The objective of this study has been the analysis of sociodemographic and clinical characteristics as well as other associated features of inpatients diagnosed of TB from January of 2019 in our hospital, focusing on the differences between the previous period to COVID-19 pandemic and the beginning of this.

Methods

We collected all the clinical records from patients diagnosed of TB who were hospitalized in our hospital of Melilla, the only

referral hospital in this area, between January 2019 and March 2021. We analyzed epidemiological and clinical as well as TB-related features, such as risk factors, origin, diagnostic method, treatment and drugs resistance. Individuals diagnosed before March 2020 were considered the “pre-pandemic” patients, whereas those diagnosed since then represented the “pandemic” ones.

The qualitative variables were expressed in frequencies while quantitative variables were described by the average and standard deviation. Student t test was used in paired samples to contrast continuous variables; comparison of proportions was performed by Chi-square test. In all cases, the contrasts were done bilaterally and significance was set at a $p < 0.05$. The statistical analysis was carried out using the SPSS 17.0.0 program (SPSS, Inc., Chicago, IL, USA).

Institutional review board/ethics committee approval was obtained for the analysis of anonymous routine clinical data of patients.

Results

Epidemiological characteristics of the study participants

A total of 31 patients were diagnosed of TB at the Regional Hospital of Melilla (autonomous city of Spain), in the period between January of 2019 and March of 2021. The median age of the infected population was 29.7 ± 3.5 years old. Most of the patients were from Morocco (51.6%) and Spain (41.9%), and only one patient was Cameroonian (3.2%). Predominant ethnicity was Berber one (93.5%). Regardless of their origin, 20 patients lived in Melilla (64.5%), 9 out of 31 lived in several cities of Morocco (29.0%), and one of them usually resided in Alicante (eastern Spain). Among patients living in Melilla, three of them had recently visited Morocco, the same as seen for the patient living in Alicante. Most the patients (83.9%) lived with other relatives, and only three patients out of total (9.7%) lived alone (the rest two cases were unknown for this variable). Three patients (9.7%) were internals in Center for Temporary Stay of Immigrants (CETI) whereas one (3.2%) out of the total cohort had stayed in the bullring of Melilla used as provisional reception facility for immigrants since April of 2020. In addition, other three patients (9.7%) were unaccompanied foreign minors (MENA), with a total of 7 (22,6%) living in settlements and facilities. Education level is unknown for all of them, except one patient with incomplete primary school.

Most of cases (25 out of 31, 80.6%) had not had any other prior respiratory disease, but 4 of them (12.9%) suffered from asthma and another patient had previously been diagnosed of pulmonary tuberculosis and was in treatment. Furthermore, one patient had presented a latent tuberculosis infection and another one more (3.2%) an infection by Human Immunodeficiency Virus (HIV). Moreover, six patients (19.4%) were suffering diabetes mellitus type 2. Regarding habits, six patients (19.4%) were self-defined as current smokers, three of them also defined as drug users (9.7% out of the total cohort of 31 patients).

The majority (90.3%) of the diagnosis recorded during the study period was of pulmonary tuberculosis, in many cases accompanied by a pleural spilling, a ganglionic tuberculosis, a visceral splenic, an abdominal tuberculosis or miliary tuberculosis with dissemination (3.2% for all of each). Only one patient (3.2%) had received the Bacillus Calmette-Guérin (BCG) vaccine, ten out of the total cases (32.2%) possessed a positive result on either Mantoux or QuantiFERON test, but 24 and 20 patients,

respectively, had none of these tests done though. In addition, the diagnosis of tuberculosis was done with a sputum smear microscopy and a culture in solid Löwenstein–Jensen medium, giving a positive result in each of the tests for 13 patients (41.9%), 9 cases of them (29.0%) positive for both ones. Regarding genetic diagnosis of tuberculosis by means of Xpert MTB/Rif[®], 14 patients (45.2%) were diagnosed so (a newborn from a gastric fluid sample). Strikingly, we have to mention one case (3.2%) of a confirmed *Mycobacterium bovis* infection.

Finally, all the patients were treated with conventional antituberculosis drugs. However, one case (3.2%) showed resistance to Rifampin (RIF) and another one (3.2%) was resistant to isoniazid (INH). All the patients were treated with the four

antituberculosis drugs combination Rimstar[®] (150 mg of RIF, 75 mg of INH, 400 mg of pyrazinamide and 275 mg of ethambutol hydrochloride) as first option but 17 (54,8%) were lost in follow up (included the one of RIF resistance). The rest of them were treated with the combination for two months followed by 4 months therapy of Rifinah[®] (300 mg of RIF + 150 mg of INH) and the first combination associated to levofloxacin for six months for the one with INH resistance. Adverse drug reactions were found in 8 patients (25.8%), with a wide range of symptoms (gastro intestinal symptoms, gout attack, hepatic toxicity, conjunctivitis, etc.). One patient (3.2%) died by the illness, and in the pre pandemic period 9 (69.2%) patients lost follow-up compared to 8 (44.4%) of them in the pandemic year.

All the characteristics are summarized in **Table 1**.

Table 1: Main characteristics of the patients infected by TB diagnosed in our centre. The pre-pandemic cohort refers to patients diagnosed between Jan 1, 2019 and February 29, of 2020, and pandemic one from March of 2020.

		Pre-pandemic	Pandemic		
Nº of patients		13 (41.9)	18 (58.1)		31
Demographic characteristics					
Age (years)		29.3 ± 7.0	30 ± 3.8	NS	29.7 ± 3.5
Sex (male)		7 (53.8)	13 (72.2)	NS	20 (64.5)
Origin	Cameroonian	1 (7.7)	0	0.004	1 (3.2)
	Moroccan	11 (84.6)	5 (27.8)		16 (51.6)
	Spanish	1 (7.7)	12 (66.7)		13 (41.9)
	Unknown	0	1 (5.6)		1 (3.2)
Bereber ethnicity		12 (92.3)	17 (94.4)	NS	29 (93.5)
City of residence	Alicante (Spain)	1 (7.7)	0	NS	1 (3.2)
	Melilla (Spain)	7 (53.8)	13 (72.2)		20 (64.5)
	Morocco (different cities)	5 (38.5)	4 (22.2)		9 (29.0)
	Unknown	0	1 (5.6)		1 (3.2)
CETI		1 (7.7)	2 (11.1)	NS	3 (9.7)
Provisional stay at bullring of Melilla		0	1 (5.6)	NS	1 (3.2)
MENA		1 (7.7)	2 (11.1)	NS	3 (9.7)
Living with relatives		10 (76.9)	16 (88.9)	NS	26 (83.9)
Smokers		1 (7.7)	5 (27.8)	NS	6 (19.4)
Drug users smoke		0	3 (16.7)	NS	3 (9.7)
Comorbidities and prior health conditions					
Prior respiratory disease		1 (7.7)	5 (27.8)	NS	6 (19.4)
Prior latent TB infection		1 (7.7)	0	NS	1 (3.2)
Concomitant HIV infection		1 (7.7)	0	NS	1 (3.2)
Concomitant COVID-19 infection		0	1 (5.6)	NS	1 (3.2)
Diabetes mellitus type-2		3 (23.1)	3 (16.7)	NS	6 (19.4)
Previous BCG vaccine		1 (7.7)	0	NS	1 (3.2)
TB diagnosis					
Positive Mantoux test		1 (7.7)	4 (22.2)	NS	5 (16.1)
Positive QuantiFERON test		3 (23.1)	2 (11.1)	NS	5 (16.1)
Sputum smear microscopy		4 (30.8)	9 (50.0)	NS	13 (41.9)
Growth on Lowenstein medium		6 (46.2)	7 (38.9)	NS	13 (41.9)
Positive Xpert MTB/Rif [®] result		6 (46.2)	8 (44.4)	NS	14 (45.2)
Pulmonary form		10 (76.9)	18 (100)	0.032	28 (90.3)

The quantitative variable (age) is expressed as average \pm standard deviation, and the qualitative variables as n (%).

Abbreviations: BCG: Bacillus Calmette-Guérin; Center for Temporary Stay of Immigrants; INH: Isoniazide; HIV: Human Immunodeficiency Virus; MENA: Unaccompanied Foreign Minors; NS: Non-Significant; RIF: Rifampicin; TB: Tuberculosis.

Differential characteristics of tuberculosis diagnoses before and after COVID-19 pandemic

Eighteen out of 31 cases (58.1%) were diagnosed of tuberculosis in our hospital from the beginning of the COVID-19 pandemic (March of 2020), whereas 13 out of the total diagnoses (41.9%) were before (from January of 2019 to February of 2020). A significant difference regarding origin was found out before and after the start of the pandemic ($p=0.004$): Most of the patients were from Morocco (84.6%) before March of 2020, but only 5 (27.8%) were Moroccan after that date. On the contrary, Spanish was the predominant nationality (66.7%) after beginning the pandemic.

The presentation of TB significantly varied between the two periods studied ($p=0.032$): All the TB diagnosed once started the pandemic were a pulmonary one (100%), but this presentation was also predominant (76.9%) during the period before.

The rest of characteristics were not significantly different between both periods (Table 1).

Discussion and conclusion

We have carried out a descriptive analysis of patients diagnosed of tuberculosis and hospitalized in the Hospital of Melilla (Spain), between January 2019 and March 2021. This series report a predominance of males (64.5%) of Berber ethnicity (93.5%). This can be related to multiple factors. On one hand, only patients diagnosed during hospital admission have been included, but not those who were diagnosed on an outpatient basis and had regular follow-up in clinics. On the other hand, the Berber population has a greater relationship with Morocco due to cultural similarities and previous origins, with families living on either side of the border and can be considered as visiting friends and relatives. Furthermore, as it has been marked, there is a male predominance and all the patients living in settlements (CETI, bullring or MENA in centers for minors) were male. This is probably related with the sort of illegal entry to the city used by immigrants by scaling the high, razor wired fence that separates both countries that requires an extraordinary physical condition and strength [14,15].

The percentage of patients born outside of Spain in the cohort is 54.8%, higher than the rest of the country, where the percentage stands at 32.3% [10]. Likely to the Spanish cohort, the highest number of foreign people diagnosed of TB in Melilla correspond to people born in Morocco [10], so this reflects the social reality of this border. The rest of non-Spanish patients were from Africa. Tuberculosis is known to be related to poverty [16,17] and Melilla border is one of the most inequality borders in the world as it is the South frontier of Europe with Africa [18].

A high percentage (22%) of the study patients lived in settlements, with the consequent Public Health problems, such as the difficulty of quarantining in the event of COVID-19 contagion or other risks of outbreaks in crowding conditions like tuberculosis [19,20]. In this situation, the study of close contacts in the case of the one diagnosed of TB could not be completely done.

Regarding the risk factors, a high percentage of patients (19.4%) had a history of type 2 diabetes mellitus, a well-recognized trigger for the development of the active form of tuberculosis [21,22], although in countries with a low prevalence

such as Spain, systematic screening is not recommended in this population [23].

The most widely used diagnostic method was sputum smear microscopy and a culture in solid Löwenstein–Jensen medium followed by Xpert MTB/Rif®. The latter is currently recommended as an initial diagnostic test by the WHO due to its high sensitivity and specificity associated with the speed of results and same time identification of mutations associated with RIF resistance, being the genotypic test of choice [16,24]. In the case of patients in the pandemic period, 8 were diagnosed by Xpert (44.4%) but it should be noted that in another 8 patients (44.4%) this test was not performed because the equipment had been used since the beginning of the pandemic for the diagnosis of COVID-19 to the detriment of the diagnosis of TB. In the case of the patient with resistance to RIF, due to technical reasons only a solid medium culture could be performed, so when the result of the resistance study was received the patient had already lost follow-up after returning to Morocco.

During the pandemic period, 22.2% of the cohort patients had a Mantoux test realized as outpatients, but none of them had received chemoprophylaxis probably because of healthcare system collapse related to COVID-19 pandemic waves and the need of relegating chronic diseases to a background despite health workers effort [25,26].

In our series, there was only one patient coinfecting by TB and COVID-19, who was also a resident of one of the most overcrowded settlements, the CETI. The transmission mechanisms of both diseases are similar: airborne pathologies in which close contacts are the greatest risk factor for contagion [3,27,28] and an outbreak in the CETI could have dramatic consequences. Furthermore, the fact of having a previous pulmonary pathology as TB makes COVID-19 infection have a worse prognosis as Tamuzi and colleagues have noted [28].

Although a strong relationship between HIV infection and TB has been described, in our cohort only one case was observed, which was not significant [30,31], but we cannot ignore it because in the context of the COVID-19 pandemic, the progress in control of these other two pandemics (HIV, TB) is threatened [32,33] and the risk of mortality is shown to be increased mainly in advanced disease and multimorbidity patients [34,35].

Regarding to comparison between both periods, the only difference was related to nationality where the patients came from, being Spanish most of them in the pandemic period. As the border closed in March 2020 (and it is still so at the time of writing this article), Moroccans could not come to the hospital to be treated. Because of this reason, the lost of follow-up was greater in the first period, as many patients came to Melilla to be diagnosed but then went back to their country to continue treatment and care. Also there were differences in the mean of presentation, in spite of being the pulmonary form the most frequent, before the border's close there were more extrapulmonary manifestations as there were more outsider patients with a more advanced disease.

Conclusion

With this study it can be remarked the social reality lived in an unique border before and during COVID-19 pandemic with

important healthcare implications, and a high risk of overlapping pandemics mainly in improvised settlements where overcrowd, poverty and diseases increase migrants suffering.

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