Lung ultrasound (LUS) in pulmonary tuberculosis: correlation with chest CT and X-ray findings

Federico Giannelli1 · Diletta Cozzi1 · Edoardo Cavigli1 · Irene Campolmi2 · Francesca Rinaldi2 · Susanna Giachè2 · Pier Giorgio Rogasi2 · Vittorio Miele1 · Maurizio Bartolucci3

Abstract

Aims The aim is to describe lung ultrasound (LUS) findings in a cohort of patients with suspected pulmonary tuberculosis (PTB) and compare them with computed tomography (CT) and chest x-ray (CXR) findings in order to evaluate the potentiality of LUS in TB diagnosis.

Methods In this prospective study, 82 subjects with suspected TB were enrolled after being evaluated with CXR and chest CT. LUS was performed by blinded radiologists within 3 days after admission. A semiquantitative index was used: score 1 (lesions that extend for about 1–15% of the affected zone), score 2 (15–40%) and score 3 (40–100%).

Results Microbiological analysis confirmed TB diagnosis in 58/82 (70.7%). CT was positive in all patients, LUS in 79/82 (96.3%) CXR in 78/82 (95.1%) and adding LUS and CXR in 100%. In PTB patients we found a great number of lungs zones with micronodules and with total findings than non-TPB patients (p < 0.05). Overall LUS sensitivity was 80%, greater for micronodules (82%) and nodules (95%), lower for consolidation with air bronchogram (72%) and cavitations (33%). We reported 5 complicated pleural effusion at LUS, only 1 in CT. CXR overall sensitivity was 81%. Adding CXR and LUS findings we reported a sensitivity of 90%.

Conclusions LUS could be considered a valid, non-invasive and cost-effective diagnostic tool especially in world regions where CT were not available, also in addiction with CXR.

Trial registration This study was approved by the Ethics Committee of our University Hospital (rif. CEAVC 14,816).

Keywords Chest radiograph · Computed tomography · Lung ultrasound · Tuberculosis

Abbreviations

TB Tuberculosis
CXR Chest x-ray
CT Computed tomography
PTB Pulmonary tuberculosis
LUS Lung ultrasound
WHO World health organization
COPD Chronic obstructive pulmonary disease
BAL Bronchoalveolar lavage

Introduction

Nowadays, tuberculosis (TB) is the leading cause of death from a single infectious agent, greater even than HIV/AIDS. In 2018, TB infected 10 million people, causing an estimated 1.2 million deaths among HIV-negative people, with an additional 251,000 deaths in HIV-positive ones [1]. Worldwide TB has different epidemiology: low and middle-income countries, such as the regions of sub-Saharan Africa and South-East Asia, are affected with the highest infection rates [1]. To stop the global TB epidemic, in 2014 World Health Organization (WHO) defined the “End TB Strategy”, underlining the need to develop diagnostic methods, as well as improve treatment and prevention strategies, to ensure an earlier and correct diagnosis. In the diagnosis and management of TB, imaging plays a fundamental role in the evaluation of disease extension, response to therapy and during follow-up [2–4]. Chest X-ray (CXR) has always been one of the main methods of imaging in the diagnosis of TB.
Nevertheless, this technique has high sensitivity but poor specificity [5]. Based on the data reported in some studies, the radiological diagnosis of pulmonary TB (PTB) is initially correct in only 49% of the cases (34% for primary and 59% for post-primary PTB) with CXR that may be normal or show only mild or non-specific findings in patients with active disease [6]. Furthermore, CXR can be negative especially in the earliest stages of the disease [7]. Computed tomography (CT) is the gold standard for its higher sensitivity than CXR in the detection and characterization of pulmonary findings [6]. CT is also helpful in the evaluation of pleural complications and may show signs of pleural disease misdiagnosed on plain radiographs [8]. However, CT and CXR have several disadvantages: the main limitations are radiation exposure, poor access to high-quality radiologic equipment and expert interpretation, limited access in rural areas and prohibitive costs for low-middle-income countries [5]. Nowadays, Lung Ultrasound (LUS) is considered a valid tool in the diagnosis of many lung pathologies: the three main applications are interstitial, alveolar and pleural syndromes [9]. LUS has several advantages compared to radiologic techniques used in TB diagnosis: in fact, LUS is mainly a safe, portable and cost-effective imaging modality. Ultrasound is more available than other radiological equipment and it does not involve exposure to ionizing radiation, permitting use even with pregnant women and children. Many studies have shown a higher sensitivity of LUS compared to CXR and comparable to CT for pulmonary consolidation: in critically ill patients, more than 98% of consolidations caused by pneumonia reach the pleura and can be well studied by LUS as well [10, 11]. To the best of our knowledge, there are some studies about specific LUS findings in PTB and there are not any comparative studies between different imaging techniques [12–16]. This study aims to compare LUS, CXR and CT findings in suspected PTB to validate the ecographical approach in these patients.

Materials and methods

Patients’ selection and TB diagnosis

This is a prospective monocentric study involving patients selected from September 2017 to February 2020 in our university hospital, which is a regional referral centre for infective diseases. The study was approved by our Ethics Committee (rif. CEAVC 14816). Inclusion criteria were age > 18 years, clinical and epidemiological suspect of PTB, CT and CXR imaging available at baseline, ability to maintain seated and supine positions (for LUS exam). Exclusion criteria were missing CT or CXR baseline imaging, LUS contraindications (subcutaneous emphysema, skin diseases, such as thoracic burns or wound). An accurate anamnecsis and physical examinations were performed after the admission. All patients enrolled in the study underwent HIV 1–2 testing. Other risk factors for TB, such as smoking habits, chronic obstructive pulmonary disease (COPD), presence of active cancer, immunosuppressive therapy, type II diabetes mellitus and homelessness, were also investigated. Diagnosis of PTB was based on clinical findings (dyspnea, fever, loss of weight, persistent cough for more than 2 weeks), positive CT scan images suggestive for pulmonary TB and microbiological identification through microscopy, culture or nucleic acid amplification test. Depending on clinical features, we collected sputum, bronco alveolar lavage (BAL), pleural liquid or trans bronchial biopsy for microbiological analysis.

Imaging

Patients with suspected PTB performed CXR and chest CT scan in the emergency department. CXR was obtained as digital radiographs in the X-Ray room (DigitalDiagnost 4.1.x, Philips Medical System) or with the same portable X-Ray unit (FDR Go PLUS-Fujifilm). Only a small number of patients were scanned with two projection (postero-anterior e latero-lateral); most were scanned in supine position with anteroposterior projection, so we decided to not evaluate the lateral view for all patients. Chest CT was obtained using a 128-slice multidetector CT (Brilliance 128 iCT SP, Philips Medical System). Patients were scanned in supine position with a crania-caudal acquisition, with suspended breath; slice thickness was 1 mm, and images were reconstructed with B70 lung filter.

LUS was performed within 5 days after CXR and CT exams. The exam was performed by a radiologist blinded about the patient’s radiological and clinical status, using a 5–3.5 MHz convex or 7.5 MHz linear probe (ESAOTE MyLab Class C advance). The chest was explored posteriorly in a seated position and anteriorly in a supine one. Examinations were performed taking longitudinal scans starting anteriorly from the parasternal zone and posteriorly from the paravertebral/posterior axillary to analyze every intercostal space. The examination of the lung apexes was performed by applying the probe vertically between the clavicle and the trapezius muscle anteriorly and directly on the cranial part of the trapezius muscle on the back. The whole surface of the chest explorable with US was thus analyzed. Ecographic and radiological images were collected and were reviewed by a thoracic radiologyst for the presence of consolidation areas with or without air-bronchogram (AB), cavitations, micronodules (at LUS and CXR) or tree-in-bud consolidations areas with or without air-bronchogram (AB), cavitations, micronodules (at LUS and CXR) or tree-in-bud (at CT), nodules > 4 mm diameter, ground-glass opacity (at CT e CXR) or white-lung (at LUS), interlobular septal thickening (at CT and CXR) or B-lines with 5–7 mm distance at LUS, pleural effusion, pleural irregularities (Figs. 1, 2).
The ultrasound signs correspond quite exactly to the CT findings. In fact with LUS it is possible to describe (1) consolidations with evidence or less of dynamic air bronchogram within them; (2) the subpleural micronodules as small parenchymal lesions visible at the level of the pleural interface that appear compatible with the endoalveolar/centrolobular dissemination of disease, (described in CT findings as tree-in-bud alterations); (3) larger nodules as a collection of confluent lesions or small pseudonodular thickenings; (4) pleural thickenings; (5) also the B-lines at a distance of 5–7 mm appear corresponding to interlobular septa thickening which are observed in an interstitial syndrome. Moreover, white lung indicates the presence of numerous closely spaced B-lines such as

![Consolidations imaging at LUS and CT. A Consolidation with air bronchogram. B Consolidation without air bronchogram. C Consolidation with cavitation seen from the anterior portion of the left pulmonary apex.](image-url)
to form a globally white image due to the close proximity of the hyperreflective tails of the B-lines: it has been described how this phenomenon corresponds to a partial alveolar filling which is highlighted in CT as areas of ground glass opacity. Finally, pleural effusions in intended both as small para-pneumonial effusions and both more conspicuous simple, corpuscular or complicated effusions in the posterior part of pleural space.
Lung air cavitations that we were able to highlight in our study deserve a separate mention: in fact, we were able to demonstrate the presence of a thin air's sickle with a slightly convex margin towards the pleural surface in the context of pulmonary consolidation like a single large air interface which represents the outermost air surface of the cavitation.

Each pulmonary alteration was spatially localized in superior/middle/inferior, anterior/posterior, left/right. In particular, the upper zone extends from apices to lower border of 2nd rib anteriorly, the middle zone extends from the lower border of 2nd rib to lower border of 4th rib and lower zone extends from the lower border of 4th rib to lung bases; the limit between anterior and posterior was considered to be the middle axillary line, so we divided each lung in 3 antero-lateral and 3 poster-lateral zones. At CXR we weren’t able to evaluate anterior and posterior regions with only a supine projection, so we localized CXR without considering anterior/posterior. A semiquantitative index was used: score 1 (lesions that extend for about 1–15% of the affected zone), score 2 (15–40%) and score 3 (40–100%).

**Statistical analysis**

Data were analyzed using STATA/MP (version 14 STATA Corp. College Station, TX). Epidemiological, clinical and demographic features were analyzed by adequate descriptive statistics. Continuous variables were expressed with median and interquartile range, categorical variables as proportions. Differences between groups were assayed using the Wilcoxon Ranks Test or Chi Square Test. The diagnostic accuracy of each echographic sign was assessed and sensitivity of LUS versus CT (gold standard) was calculated. \( p \) values < 0.05 were considered statistically significant.

**Results**

**Patients’ characteristics**

Eighty-two patients (51 males, 31 females) with suspicion of PTB were enrolled in this study. Table 1 shows patients' epidemiological and anamnestic features (Table 1). Italian patients were 28 (34.1%) and 54 (65.9%) had foreign origin: in particular from South America (35%), Asia (27%), Eastern Europe (24%) and Sub-Saharan African regions (15%). All patients were investigated for possible risk factors for PTB, which was confirmed in 58 patients with a prevalence of 70.7%. Regarding anamnestic features, there are not any statistical significance between PTB and non-PTB patients.

**Imaging findings**

CT showed pathological findings in all 82 patients (100%); instead LUS demonstrated pathological imaging in 79/82 (96.3%), of which 56/58 (96.6%) PTB ones. CXR showed pathological findings in 78/82 (95.1%) (Table 2). Analyzing CT data, it can be seen that there were a higher number of affected lung regions, with more cavitations and pleural effusion in PTB patients than in non-PTB ones. It has to be noted the small number of ground-glass opacities detected in
PTB patients than in non-PTB, although the small number of cases cannot determine a statistically significant difference (Table 3). At CXR, the CT data regarding the cavitations' distribution were confirmed, while data of pleural effusion were not significant (due to the small number of patients and score of effusions detected in both groups). At LUS, a statistical significance was found in greater detection of regions involved a higher score of micronodules (Table 3). Similarly to CT and CXR, also using LUS the total number and overall score of all the lesions analyzed was statistically greater in PTB patients rather than non-PTB patients. In CT, the major percentage of lesions are located in the superior zones (typical areas of post-primary TB), mainly posterior with statistically significant data both for score and number of lesions \( (p \text{ value } 0.0003) \). Same results were obtained with LUS, with statistically significant scores for lesions located in the anterior-middle zone and for the antero-inferior region \( (p \text{ values } 0.03 \text{ and } 0.004 \text{ respectively}) \) (Table 4). Finally, we compared parenchymal findings highlighted on CT and LUS of all 82 patients included in the study. We collected a total of 426 different lesions in the 12 zones analyzed on CT and 342 different parenchymal lesions in the 12 zones analyzed at LUS, with an overall sensitivity of LUS of 80%. We did not see a statistically significant difference in the two methods although LUS sensitivity appeared quite heterogeneous ranging from 100% of the ground-glass opacity/white lung

| Table 3 Number of findings in each zone considered with CT, CXR and LUS in both PTB and non-PTB patients |
|---------------------------------|-----|-----|-----|-----|-----|
|                                | PTB | Non–PTB | p value | PTB medium score | Non–PTB medium score | p value |
| CT                              |     |       |       |                |                  |         |
| Consolidations with AB          | 20  | 12    | 0.65  | 0.89           | 1.04             | 0.82    |
| Consolidations without AB       | 61  | 23    | 0.63  | 1.93           | 1.67             | 0.54    |
| Cavitations                     | 42  | 6     | 0.001 | 1.37           | 0.71             | 0.05    |
| Micronodules (<4 mm)            | 106 | 25    | 0.25  | 3.77           | 1.08             | 0.02    |
| Nodules (> 4 mm)                | 34  | 8     | 0.22  | 1.19           | 0.42             | 0.06    |
| GGO                             | 3   | 14    | 0.1   | 0.05           | 1.04             | 0.14    |
| Interlobular septal thickening  | 27  | 0     | 0.11  | 0.91           | 0                | 0.17    |
| Pleural effusion                | 30  | 4     | 0.04  | 1.25           | 0.33             | 0.05    |
| Pleural thickening              | 9   | 2     | 0.57  | 0.16           | 0.08             | 0.57    |
| Total findings                  | 332 | 94    | 0.01  | 12.77          | 6.71             | 0.0003  |
| CXR                             |     |       |       |                |                  |         |
| Consolidations with AB          | 14  | 6     | 0.98  | 0.53           | 0.50             | 0.93    |
| Consolidations without AB       | 62  | 24    | 0.72  | 2.04           | 1.83             | 0.68    |
| Cavitations                     | 23  | 4     | 0.03  | 0.89           | 0.42             | 0.08    |
| Micronodules (<4 mm)            | 53  | 8     | 0.06  | 1.7            | 0.33             | 0.02    |
| Nodules (> 4 mm)                | 35  | 3     | 0.008 | 1.0            | 0.17             | 0.01    |
| GGO                             | 1   | 12    | 0.09  | 0.02           | 0.71             | 0.06    |
| Interlobular septal thickening  | 6   | 0     | 0.32  | 0.11           | 0                | 0.32    |
| Pleural effusion                | 15  | 1     | 0.03  | 0.51           | 0.04             | 0.02    |
| Pleural thickening              | 1   | 0     | 0.32  | 0              | 0                | –       |
| Total findings                  | 254 | 58    | 0.025 | 7.30           | 4.04             | 0.0007  |
| LUS                             |     |       |       |                |                  |         |
| Consolidations with AB          | 13  | 10    | 0.50  | 0.56           | 0.75             | 0.71    |
| Consolidations without AB       | 51  | 16    | 0.36  | 1.79           | 1.08             | 0.12    |
| Cavitations                     | 12  | 4     | 0.66  | 0.39           | 0.21             | 0.32    |
| Micronodules (<4 mm)            | 95  | 12    | 0.01  | 3.02           | 0.67             | 0.01    |
| Nodules (> 4 mm)                | 31  | 9     | 0.43  | 0.84           | 0.38             | 0.11    |
| White lung                      | 16  | 1     | 0.28  | 0.70           | 0.04             | 0.26    |
| B-lines 5–7 mm distance         | 17  | 4     | 0.10  | 0.32           | 1.29             | 0.93    |
| Pleural effusion                | 35  | 8     | 0.15  | 1.32           | 0.5              | 0.06    |
| Pleural thickening              | 5   | 3     | 0.68  | 0.09           | 0.17             | 0.47    |
| Total findings                  | 275 | 67    | 0.001 | 10.33          | 4.58             | 0.0001  |

Medium score with statistical correlation \( (p \text{ value significant if } <0.05) \)

GGO ground-glass opacities
to 33% of the cavitations (Table 5). We also compared CT and LUS by zones to understand which region it is more difficult to be studied with ultrasound: the least explorable zones where we have obtained a lower sensitivity with LUS are the Posterior-Superior, the Anterior-Inferior and also the Superior-Anterior zones (Table 5). In order to compare CT and LUS data with CXR ones, we had to merge anterior and posterior zone lesions described at CT and LUS to make the two data-set comparable in 3 zones (Superior, Middle and Inferior). We have chosen the highest score value for the anterior or posterior zone that we have merged. We obtain an overall sensitivity for CXR of 81%, substantially overlapping the sensitivity of LUS (80%). Instead, the overall sensitivity of information obtained with CXR + LUS is 90%.

**Discussion**

The results of this study are promising and LUS could be a reliable method for the diagnosis of PTB. We have seen pathological findings in 79/82 (96.3%) and only in 3 patients we didn’t detect any alteration: one of these patients had

| Lesions detected with CT and LUS for each zone in PTB e no-PTB patients and medium score with statistical correlation |
|--------------------------------------------------|
| PTB | Non-PTB | p value | PTB medium score | Non-PTB medium score | p value |
|---|---|---|---|---|---|
| CT parenchymal findings | | | | | |
| Posterior–superior | 57 | 6 | 0.0003 | 2.14 | 0.42 | 0.0003 |
| Posterior–middle | 61 | 24 | 0.80 | 2.04 | 1.71 | 0.57 |
| Posterior–inferior | 31 | 19 | 0.22 | 1.0 | 1.29 | 0.47 |
| Anterior–superior | 59 | 15 | 0.10 | 2.09 | 0.83 | 0.01 |
| Anterior–middle | 72 | 22 | 0.15 | 2.39 | 1.50 | 0.06 |
| Anterior–inferior | 22 | 5 | 0.23 | 0.63 | 0.29 | 0.17 |
| LUS parenchymal findings | | | | | |
| Posterior–superior | 38 | 5 | 0.004 | 1.32 | 0.29 | 0.001 |
| Posterior–middle | 49 | 16 | 0.47 | 1.68 | 1.08 | 0.23 |
| Posterior–inferior | 31 | 10 | 0.48 | 0.89 | 0.58 | 0.34 |
| Anterior–superior | 43 | 12 | 0.28 | 1.42 | 0.58 | 0.03 |
| Anterior–middle | 65 | 17 | 0.08 | 2.00 | 1.08 | 0.03 |
| Anterior–inferior | 18 | 0 | 0.001 | 0.56 | 0.0 | 0.004 |

**Table 4**

**Table 5** Number of lesions detected at CT and LUS in all 82 patients and in different thoracic regions and medium score with statistical correlation. Sensitivity of LUS compared with CT (gold standard)
only a very small area of central ground glass opacity (to be referred to alveolar hemorrhage of non-tuberculous origin), another one had only large cavitation with surrounding thickening that did not reach the pleura in the posterior segment of the Superior Upper Lobe behind the scapula and the last one had only a small thickening at the center of the lung parenchyma. Even with CXR we weren’t able to highlight findings in 4 patients; however, in all those four patients we were able to highlight pathological findings at LUS so, by adding LUS and CXR, we were able to detect pathological findings in all 82 patients analyzed. Although the two populations are similar in clinical, epidemiological and anamnestic features and CT signs, there is a greater disease severity and lesions extension (both in CXR, LUS and CT) in PTB patients than in non-PTB ones. From this data, we can assume that the detection of multiple and diffuse micronodules at LUS (in the presence of clinical-epidemiological features), allows us to presume with good confidence the diagnosis of PTB.

Regarding lesions distribution, we have seen that TB patients had a higher distribution of lesions in the Posterior-Superior and Anterior-Superior zones; moreover, statistical correlation was also seen in the Antero-Inferior zone in relation to the failure of detecting lesions in no-PTB patients. In addition to the fact that the total number of lesions in Anterior-Inferior zone is poor, as it is not characteristic of TB lesions, this data may appear partly distorted by the fact that this region appears more difficult to explore in women due to adipose and dense glandular tissue which obscure partially the visualization of the pleural surface. Comparing LUS to CT by zones, was evident that we obtain a lower sensitivity of LUS in Posterior-Superior zone due to the presence of the scapula which limits the visualization of the pleural interface with a sensitivity of 68% (compared to the overall sensitivity of 80%). Two other zones with lower sensitivity than average turned out to be the Anterior-Inferior due to the presence of the breast in women, and the Anterior-Superior maybe due to the presence of the clavicle and to a not always easy access in the supraclavicular fossa.

The overall LUS sensitivity of 80% was found to be lower than the values described in other US studies of pulmonary infectious diseases [10, 17, 18]. This happens in our opinion for two reasons: first of all because in our study we searched systematically for all lung lesions and we made an exact comparison by lung zones between the three methodical, instead of reporting the number of patients with any lung lesion despite to lesion number or the zone they were located. Another reason is certainly that TB lesions are often localized, in a higher percentage than other infectious diseases, in the Posterior-Superior regions where many lesions do not appear visible at LUS due to the presence of the scapula. Sensitivity was found to be slightly different depending on the lesions examined (Table 5). The highest sensitivity was obtained for the ground-glass opacity/white lung even if this data was not fully reliable due to the mismatch of these findings in many regions and different patients. We have found regions of white lung at the margins of pulmonary consolidations, corresponding to small areas of perilesional ground-glass not always reported on CT, or as regions of pulmonary consolidations that reach the pleura only as partial alveolar filling (therefore with a image of the peripheral white lung).

Pleural effusions deserve a separate discussion. As described extensively in the literature, also our study confirms that LUS is more sensitive than CT in identifying pleural diseases (33 pleural effusion at LUS with 5 of them complicated versus 22 pleural effusion at CT with one of them complicated) [19, 20]. In 2 of our patients with mild and non-specific lung lesions at CT, it was LUS that suggest a high suspicion of PTB due to the high number of corpuscles and fibrinopurulent stratifications in the pleural space (Fig. 3).

The most interesting data comes from the fact that combining CXR and LUS we obtain a sensitivity that reaches 90% compared to CT. CXR and LUS can detect different findings, in such a complementary way: LUS can better identify micronodules, interlobular septal thickening, pleural thickening and effusions. These findings are visible at the pleural interface while in a methodical such as CXR, more panoramic and less sensitive for smaller lesions, they appear more difficult to identify. On the other hand, CXR is more sensitive for consolidations, nodules and cavitations [21–24]. The greater panoramic view of CXR has made it possible to detect even those exclusively central densities that do not reach the pleura, while for cavitations the CXR has shown a much lower sensitivity than the CT (58%), however higher than the sensitivity demonstrated by the LUS (33%).

Our study showed had some limitations. As widely known, ultrasound examination of the chest does not identify the deepest lesions, or it can determine them only through the observation of superficial manifestations not always present. Moreover, LUS is an operator-dependent technique, and the observed findings may change based on the experience of the operator. Although, to the best of our knowledge, there is no comparative data in the literature related to the diagnosis of PTB between CT and LUS, even if it was performed on a limited number of patients. Another important limitation is the difficulty of making a confident radiological diagnosis in patients with a similar clinical-epidemiological feature. The two populations in the study were very homogeneous and the differential diagnosis was difficult also in CT. Another limit of the study was the impossibility of obtaining CXR lateral view to fully compare plain radiograph with CT and LUS without forcing us to merge CT and ultrasound findings to allow comparability.
Nevertheless, LUS examination has some important advantages: it is easier to learn, more available, safer and cheaper compared to the classic radiological techniques. Considering its low costs, LUS may be an important diagnostic tool, especially in developing countries where the incidence of PTB is higher and the delay in diagnosis represents a critical point in disease control. Furthermore, LUS does not require patient transport nor the presence of expensive CT machines in dedicated spaces, nor dedicated technicians.

Fig. 3 Pleural effusion: comparison between LUS (A, B), CT (C) and CXR (D) images in the same patient. A simple bilateral effusion in CT, detected only in the right pleural space at CXR in supine position, reveals to be a bilateral pleural effusion at LUS with fibrinopurulent stratification (A, B)

Conclusions

In conclusion, LUS is an effective method in highlighting parenchymal lesions in TB patients with good sensitivity. Therefore, its use is to be encouraged if there is no CT availability or the patient is not suitable for CT itself. Combining LUS with CXR allows for further improvement of every single methodical sensitivity. LUS could also be
useful in closely monitoring the patient to evaluate any change in the parenchymal findings. Differential diagnosis between TB and other infectious pulmonary diseases keeps being difficult also with CT scan; anyway, LUS subpleural micronodules visualization could allow a confident radiological diagnosis.

**Author contributions** FG, DC and EC: data collection, manuscript writing, images collection; IC, FR, SG: patients’ selection and data analysis; PGR, VM and MB: idealization, supervision and final approval. All authors read and approve the final manuscript.

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**Availability of data and materials** The dataset used and analysed during the current study are available from the corresponding author on reasonable request.

**Declarations**

**Conflict of interest** The authors declare that they not have competing interests.

**Ethical approval and consent to participate** This study was approved by the Ethics Committee of our University Hospital (rif. CEAVC 14816).

**Consent for publication** Informed consent was obtained from all individual participants included in the study. Patients signed informed consent regarding publishing their data and photographs. All procedures in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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