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The Role of Computed Tomography in the Diagnosis of Pediatric Pulmonary Tuberculosis

Çocukluk Çağı Akciğer Tüberkülozu Tanısında Bilgisayarlı Tomografinin Yeri

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Abstract

Objective: The objective of this study is to define specific computed tomography (CT) findings in the diagnosis of pediatric pulmonary tuberculosis.

Material and Methods: Fifty-seven pediatric patients with suspicion of tuberculosis were involved in this study. Thoracic CT images were reviewed by two radiologists in consensus. Seventeen patients were diagnosed with culture (gastric lavage, pleural fluid, biopsy or bronchoalveolar lavage specimens) and 20 patients were clinically diagnosed with tuberculosis. The criteria evaluated were lymph node enlargement (> 1 cm), calcified lymph nodes, consolidation, cavitation, tree-in-bud opacity, pleural effusion, pleural thickening, empyema and atelectasis. The differences between tuberculosis patients (group A) and non-tuberculosis patients (group B) were analyzed using Fisher exact test.

Results: Lymph node enlargement (> 1 cm) was significantly higher in group A (27/37) than group B (5/20) (p< 0.01). Consolidation was significantly more frequently encountered in group B (11/20) compared with group A (7/37; p< 0.01). The sensitivity and spesifity of lymph node enlargement with a maximal diameter of > 1 cm were 73% and 75%, respectively. In group A, pleural effusion was present in 43.2% (n= 16) of the patients, atelectasis in 40.5% (n= 15), pleural thickening and consolidation each in 18.9% (n= 7), tree-in-bud opacification in 16.2% (n= 6), and calcified lymph nodes in 13.5% (n= 5). In group B, pleural effusion was present in 40% (n= 8) of the patients, atelectasis in 35% (n= 7), pleural thickening and empyema each in 20% (n= 4), and tree-in-bud opacification in 15% (n= 3). These differences were not significant.

Öz

Giriş: Bu çalışmanın amacı, çocukluk çağı akciğer tüberkülozu tanısında spesifik bilgisayarlı tomografi (BT) bulgularını tanımlamaktır.

Gereç ve Yöntemler: Çalışmaya tüberküloz şüphesi olan 57 çocuk hasta dahil edildi. Toraks BT görüntüleri iki radyolog tarafından değerlendirildi. On yedi hasta kültür pozitifliği ile (mide açlık suyu, plevral sıvı, biyopsi veya bronkoalveoler lavaj örnekleri), 20 hasta ise klinik olarak tüberküloz tanısı aldı. Değerlendirilen kriterler lenf nodu büyümesi (> 1 cm), kalsifiye lenf nodları, konsolidasyon, kavitasyon, bronşiyal dallarda belirginleşme, plevral efüzyon, plevral kalınlaşma, ampiyem ve atelektazi olarak belirlendi. Tüberküloz hastaları (grup A) ve tüberküloz olmayan hastalar (grup B) arasındaki farklar Fisher exact testi kullanılarak analiz edildi.

Bulgular: Lenf nodu büyümesi (> 1 cm), grup B'ye (5/20) kıyasla grup A'da (27/37) anlamlı olarak daha fazla bulundu (p< 0.01). B grubunda konsolidasyon (11/20), grup A'ya (7/37) kıyasla anlamlı olarak daha sık görüldü (p< 0.01). En büyük çapı > 1 cm olan lenf nodu büyümesinin duyarlılık ve özgüllüğü sırasıyla %73 ve %75 idi. Grup A'daki hastaların %43.2 (n= 16)'sinde plevral efüzyon, %40.5 (n= 15)'inde atelektazi, %18.9 (n= 7)'unda plevral kalınlaşma, %16.2 (n= 6)'sinde bronşiyal dallarda belirginleşme, %18.9 (n= 7)'unda konsolidasyon ve %13.5 (n= 5)'inde kalsifiye lenf nodları mevcuttu. B grubundaki hastaların ise %40 (n= 8)'ında plevral efüzyon, %35 (n= 7)'inde atelektazi, %20 (n= 4)'sinde plevral kalınlaşma, %20 (n= 4)'sinde ampiyem ve %15 (n= 3)'inde bronşiyal dallarda belirginleşme mevcuttu. Bu farklılıklar anlamlı değildi.

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Conclusion: Lymph node enlargement could be the only abnormal finding of pediatric tuberculosis on thoracic CT images. Other imaging findings are not specific for tuberculosis.

Keywords: Computed tomography, pediatric, pulmonary, tuberculosis

Sonuç: Toraks BT görüntülerinde çocukluk çağı tüberkülozunun tek anormal bulgusu lenf nodu büyümesi olabilir. Diğer görüntüleme bulguları tüberküloz için spesifik değildir.

Anahtar Kelimeler: Bilgisayarlı tomografi, pediatrik, pulmoner, tüberküloz

Introduction

Tuberculosis (TB) is an airborne infectious disease caused by *Mycobacterium tuberculosis* and is a major health problem among children, particularly in developing countries with poor public health facilities. The incidence of infection has been decreasing gradually in developed countries. However, as a result of increased international travel and immigration, childhood TB cases underwent a rise even in developed countries. Differences in the pathophysiologic and immunologic responses of TB in children make the diagnosis more challenging than in adults (1). Especially if patients present with ambigious complaints and symptoms, the long delay in applying the appropriate therapy causes infected patients to serve as a reservoir from which new cases of the disease will emerge. The definitive diagnosis of TB is established by identifying *M. tuberculosis*, however tuberculosis has a paucibacillary behaviour, particularly in children. Therefore, samples obtained from sputum (if possible) or gastric lavage frequently yield negative results when seeded in culture or analyzed on direct smear examination (2,3). Additional methods for identifying the disease in daily practice include tuberculin skin test (TST) and radiological imaging modalites such as chest radiographs (CXR) and thoracic computed tomography (tCT). A meticulous interrogation of contact history with a contaminant patient is always helpful (4).

In the early stages of TB, irrespective of other indicators, signs may be missing or obscure on CXR. For those cases, tCT can be performed to demonstrate pathological changes which are unremarkeble or hardly interpretable on CXR (5). This study aimed to investigate the usefulness of the tCT in the diagnosis of pediatric pulmonary TB by detecting parenchymal lung lesions and lymph node enlargement which are unremarkable on CXR. This study also intented to demonstrate the difference between tCT findings of TB-patients and non-TB patients.

Materials and Methods

This study was performed in collaboration with the Clinics of Radiology and Pediatrics in our hospital. The patients who were referred to the Pediatric Infectious Disease Clinic with the diagnosis of TB were evaluated retrospectively for a period of six years, in terms of their final-diagnosis, age, sex, vaccination status, history of exposure to a patient with active TB, TST positivity, laboratory findings, results of culture tests and radiological findings. Clinical findings suggestive of TB consisted of intermittent/sustained fever, loss of appetite, developmental delay, cachexia, excessive sweating, apathy, persisting cough for more than two weeks despite antibiotherapy, wheezing, stridor, dyspnea, tachypnea, hemoptysis, and exacerbation of recurrent pneumonia, bronchitis and bronchiectasis due to lymphadenopathy pressure (6). In total, 57 pediatric patients who had undergone tCT scan with the suspicion of TB were involved in this study. tCT images were reviewed by two radiologists and interpretations were made by consensus.

Children who had been previously treated for TB, who had any immunosuppressive medical conditions (e.g. human immunodeficiency virüs infection, malignancy) and who have been taking immunosuppressive drugs were excluded from the study.

Culture positivity was detected in 17 of 57 patients from gastric lavage, pleural fluid, biopsy or bronchoalveolar lavage specimens and it was accepted as pulmonary tuberculosis. After the expert meetings where laboratory findings, clinical and radiological indicators including tCT were carefully evaluated, 20 out of 40 culture negative patients were diagnosed with tuberculosis. As a result, the patients were divided into two groups based on the presence or abscence of pulmonary TB.

Criteria evaluated were lymph node enlargement (> 1 cm), calcified lymph nodes, consolidation, cavitation, tree-in-bud opacity, pleural effusion, pleural thickening, empyema and atelectasis. The differences between TB patients (group A) and non-TB patients (group B) were analyzed using Fisher exact test.

Statistical Analysis

Mean, standard deviation, frequency and ratio of the relevant values were calculated to achieve descriptive statistics of the data in our study. Student's t-test was used for the analyses of the constant variables, as the parametric test and ki-square test were used for the analyses of caterogical variables. Fisher exact test was used when it was not suitable for the ki-square test. SPSS (Statistical Package for Social Sciences) for Windows 19.0 programme was utilized. The results were presented as mean ± standard deviation (SD), percentage (%), and range (min-max). Confident interval of 95% and p value of < 0.05 were assessed for statistical significance.

Results

Fifty-seven pediatric patients who underwent tCT scan with the suspicion of TB were involved. The mean age was 99.1± 58.2 months (1-192 months). 38.6% (n= 22) of the patients were female, 61.4% (n= 35) were male. 64.9% (n= 37) of the patients were diagnosed with tuberculosis (group A). The distribution of patients by gender were shown in Table 1. 28.1% (n= 16) were considered as having bacterial pneumonia and 1.8% (n= 1) had pneumatocele secondary to previous infection (Figure 1). 5.3% (n= 3) of the patients who had been referred to our hospital with suspicion of TB were considered as healthy. Of the 37 patients in group A, 54% (n= 20) were diagnosed with primary pulmonary tuberculosis, 5.4% (n= 2) with progressive primary pulmonary tuberculosis and 40.5% (n= 15) with tuberculosis pleurisy (Figure 2).

In group A, 48.6% (n= 18) of the patients had one or more BCG vaccinations. On the other hand in group B, 70% (n= 14) of the patients had been vaccinated once or more than once. The correlation between the number of the patients in group A or B and their vaccination status was not statistically significant (p= 0.121).

In group A, 43.2% of the patients (n= 16) had an in-door history of exposure to a patient with active tuberculosis and 18.9% had an out-door history of exposure. The correlation between the history of exposure and the diagnosis of TB was highly significant (p= 0.01).

Table 1. The distribution of patients by gender

	Total	Female n (%)	Male n (%)
TB-patients (Group A)	37	15 (40.5)	22 (59.5)
non-TB patients (Group B)	20	7 (35)	13 (65)
Total	57	22 (38.6)	35 (61.4)

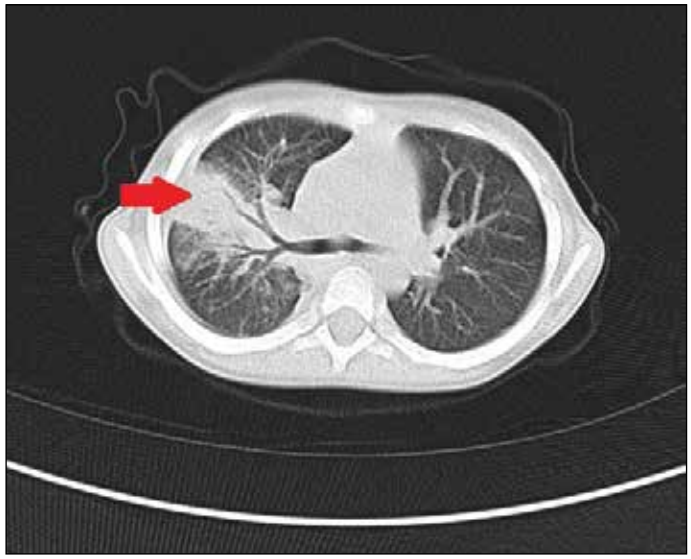

Figure 1. Thoracic CT scan of a patient with pneumonia shows air space consolidation of right upper lobe posterior segment.

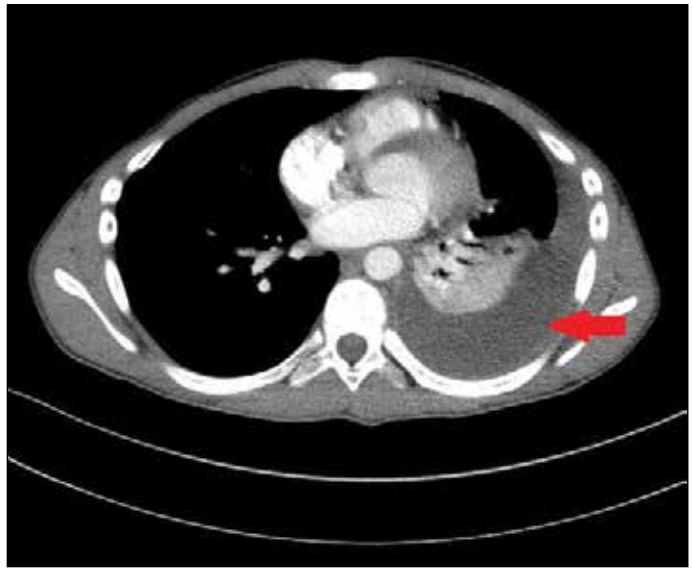

Figure 2. Contrast-enhanced thoracic CT scan of a tuberculosis patient shows left sided pleural effusion associated with compression atelectasis.

TST was positive in 37.8% of patients in group A and 5% in patients in group B. The number of positive TST was significantly higher in group A patients (p= 0.012). Pathological CT findings in TB-patients (group A) and non-TB patients (group B) were shown in Table 2. The most common finding in patients with TB was 73% (n= 27) lymph node enlargement (> 1 cm), while the least common finding was cavitation with 10.8% (n= 4). Lymph node enlargement (> 1 cm) was significantly higher in group A (27/37) than in group B (5/20; p< 0.01) (Figures 3,4). The sensitivity and spesifity of lymph node enlargement with a maximal diameter of > 1 cm were 73% and 75%, respectively. The anatomical distrubition of the enlarged lymph nodes observed on tCT examinations of group A patients were as follows: 27% (n= 10) had paratracheal; 21.6% (n= 8) had paratracheal and subcarinal; 13.5% (n= 5) had paratracheal, subcarinal and prevascular; 10.8% (n= 4) had paratracheal and prevascular; 5.4% (n= 2) had right paratracheal; 5.4% (n= 2) had hilar; 2.7% (n= 1) had subcarinal; 2.7% (n= 1) had subcarinal and prevascular; 2.7% (n= 1) had subcarinal and hilar; 2.7% (n= 1) had paratracheal, subcarinal and hilar localized enlarged lymph nodes.

Consolidation was significantly more frequently encountered in group B (11/20) compared with group A (7/37; p< 0.01). In group A, pleural effusion was present in 43.2% (n=16) of the patients, atelectasis in 40.5% (n= 15), pleural thickening in 19% (n= 7) and tree-in-bud opacification in 16.2% (n= 6). In group B, pleural effusion was present in 40% (n= 8) of the patients, atelectasis in 35% (n= 7), pleural thickening and

Table 2. Pathological CT findings in tuberculosis-patients (group A) and non-tuberculosis patients (group B)

	Group A (n= 37)	Group B (n= 20)	Total (n= 57)	p
Lymph node enlargement	27 (73%)	5 (25%)	32 (56%)	< 0.01
Consolidation	7 (18%)	11 (55%)	18 (32%)	< 0.01
Pleural effusion	16 (43%)	8 (40%)	24 (42%)	> 0.05
Atelectasis	15 (40%)	7 (35%)	22 (39%)	> 0.05
Pleural thickening	7 (19%)	4 (20%)	11 (19%)	> 0.05
Tree-in-bud opacification	6 (16%)	3 (15%)	9 (16%)	> 0.05
Calcified lymph nodes	5 (13%)	0 (0%)	5 (9%)	< 0.05
Empyema	0 (0%)	4 (20%)	4 (7%)	> 0.05

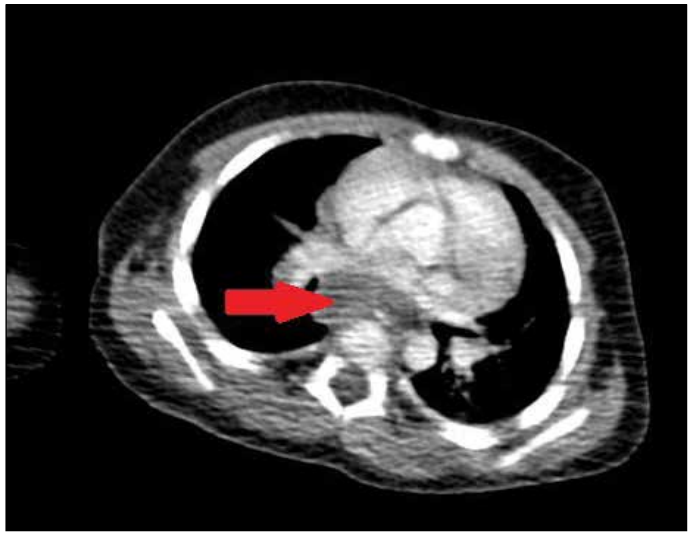

Figure 3. Contrast-enhanced thoracic CT scan of a tuberculosis patient shows subcarinal lymphadenopathy.

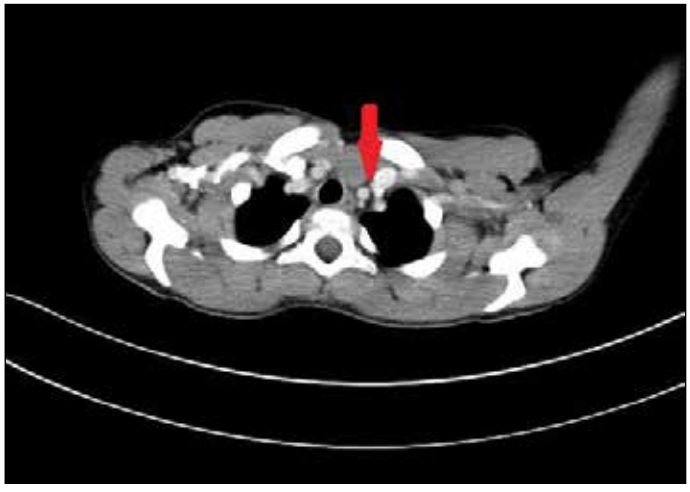

Figure 4. Contrast-enhanced thoracic CT scan of a tuberculosis patient shows prevascular lymphadenopathy.

empyema each in 20% (n= 4), and tree-in-bud opacification in 15% (n= 3). These differences were not significant. Calcified lymph nodes observed 13.5% (n= 5) in group A, but none of the group B patients had calcified lymph nodes on their thoracic scannings. This difference was significant (p< 0.05).

In group A, cavitation, consolidation and tree-in-bud sign were demonstrated significantly higher on CT examination of the patients with confirmed TB (culture positive) (23.5%, 41.2% and 29.4% respectively) than of the patients diagnosed with TB after consensus of expert meetings (5%, 0% and 0% respectively) (p< 0.05).

The total culture positivity rates of the samples were 45.9% (n= 17). Culture positive result was 37.9% (n= 11) in gastric aspirate, 66.7% (n= 4) in pleural fluid, 100% (n= 1) in biopsy specimen and 100% (n= 1) in bronchoalveolar lavage specimen. No statistically significant difference was found in the positivity rates between samples since the sample numbers were not equal or close to each other (p> 0.05).

Discussion

TB is an infectious disease caused by *M. tuberculosis* and is a major cause of morbidity and mortality, particularly in developing countries (7,8). Children represent one of the high-risk groups, carry a huge burden of TB and need immediate attention in view of the longer life span. In 2017, 10 million people fell ill with TB and 1.6 million died from the disease. It is presumed aproximately one million children became ill with TB and 230.000 children died of TB (9).

When compared with TB in adults, children are at much higher risk of progression to active disease. They tend to develop severe or extrapulmonary forms of the TB which is probably related to the immaturity of the immune response (10). For this reason, rapid identification and effective treatment is the first priority.

Unfortunately, diagnostic difficulties constitute the most challenging aspect of childhood TB management. The major

concern for establishing the definitive diagnosis of TB is based on the paucibacillary behaviour of the disease in children. Obtaining sufficient amounts of sputum (which is generally swallowed by children rather than expectorated) is an impediment. Samples may be collected by performing early morning gastric lavage. It is a difficult technique which require hospitalization, achieving a yield of 30-40% and up to 80% in young infants and in cases with advanced endobronchial disease (11,12). Consequently, only in a limited number of children acid fast bacilli (AFB) can be identified. For this reason, when TB is suspected, CXR and TST are utilized in clinical practice in order to initiate the relevant treatment. A detailed contact screening is indispensable for a complete evaluation for TB. If CXR are normal, the diagnosis of tuberculosis can not be excluded. CXR has low sensitivity and specifity in recognizing paratracheal and subcarinal lymphadenopathies (13). TST has limits in the diagnosis of TB and in distinguishing latent and active forms (14,15). As for tCT, it may provide an early-diagnosis and thereby an appropriate treatment for infected children.

Another point to be emphasized is the fact that the disease burden in children can be considered as a appropriate measure of the current communication of the disease within a population. Because TB in children reflects mostly recent infection, rather than re-activation (16).

The probability of transmission depends on the number of aerosolised respiratory droplets expelled by an infectious case, the persistence and proximity of exposure, and the infectiousness of the source (2). Immune status associated with host genetics, vaccination and age, underlying conditions that impair immune competence (e.g. malnutrition, cancer, immunosupressive therapy, HIV infection, end-stage renal disease, diabetes). Also poverty, poor housing, overcrowded urban settings determine the outcome of infection (3,17).

In adults and children alike, the initial primary TB infection is mostly clinically asymptomatic and remain completely unnoticed. In about 5% of affected individuals, immunity is insufficient and within a year primary TB evolves into a condition known as progressive primary infection. In over 90% of individuals, however, the immune system is adequate and limits the multiplication of the bacilli, resulting in local scar tissue with or without calcification. If immune mechanisms wane, in about 5% of the affected individuals, endogenous reactivation of dormant bacilli occurs in following years after the initial infection, a condition called as postprimary TB (18). Occasionally, it is caused by re-infection with exogenous bacilli. Most TB cases in children are related to primary infection (19). Mediastinal or hilar lymphadenopathy with a focal parenchimal lesion is the most common finding to be detected by radiologic examinations. Parenchimal lesions show no predilection for any lung segments (20). Other presentations of primary TB include miliary TB, tuberculous pleurisy and tracheo-bronchial TB. Although lymph node enlargement or parenchymal abnormality are generally present in children with pulmonary TB, it is not always feasible to demonstrate it on CXR. The development of CT technology has enabled to reduce the required radiation dose, achieved shorter acquisition times, especially for children and provided higher levels of spatial resolution for defining anatomical structures. So, a tCT scan can be performed to reveal the lymphadenopathy or the parenchimal abnormality related to TB. On tCT, enlarged nodes seeded with tubercle bacilli characteristically show central low attenuation, representing caseous necrosis, and peripheral rim enhancement, which represents inflammatory hypervascularity in granulomatous tissue (21).

In the study of Gomez et al. including 22 pediatric patients with TST positivity, it is reported that 63% of the patients with normal CXR had pathological lymph nodes on tCT images (22). In a study of Kim et al. including 41 pediatric patients, it is suggested that for 22% of the patients with TB the diagnosis could have been achieved only by respecting the tCT findings. Additionally, for 37% of the patients, treatment protocol had to be changed due to CT findings (23,24).

Tree-in-bud opacification may be observed on tCT images of children with pulmonary TB. It is an important radiological finding that is mostly encountered in adult pulmonary TB and reflect the endobronchogenic spread of the infection by filling bronchioles with inflammatory exudate. Tree-in-bud infiltrates may show lobar or segmental distribution and are considered as a reliable determinant of the activation of the disease (25). It is also noted that when tree-in-bud sign is present, the chance of identfying the organism on microbiologic smears and cultures increases significantly. It is worth mentioning though, tree-in-bud opacification is characteristic but not pathognomonic for active TB. In the present study, 16.2% of the patients in group A and 15% of the of the patients in group B had tree-in-bud infiltrates, revealing that there was no significant relationship between these two groups. On the other hand, tree-in-bud sign was demonstrated significantly higher on CT examination of the patients with confirmed TB (culture positive) than of the patients diagnosed with TB after consensus of expert meetings; which was suggestive for endobronchial spread of the organism and consistent with other studies.

Consolidation is the result of dense exudative material filling the alveoli, which may be observed on CT scans of TB-patients. These foci of consolidation has a high load of bacilli. According to the study of Peng et al. including 46 pediatric patients, there was no significant difference between the patients with TB and the patients with pneumonia in terms of consolidation on CT images (26). Consolidation is not spesific

in the diagnosis of tuberculosis. However, with non-resolving pneumonia after 4 weeks of relevant therapy, TB should be taken into the differential list (26). In the present study, consolidation was significantly more frequently encountered in group B compared with group A.

Cavities are the radiological hallmark of reactivation TB. Therefore, cavitation is a rare finding in pediatric pulmonary TB compared to adult pulmonary TB. When cavitation is present, the possibility of having positive culture results and of identifying the organism on direct smear increases significantly, because the most common complication of the cavitation is endobronchial spread. On CT images, cavitation was detected in 15% of the pediatric TB patients in the study of Acar et al. (27). When we examined the CT images of our patient group, we did not find cavitation.

Hilar or mediastinal lymph node enlargement is the most common finding on CT examination of the patients with TB, but uncommon in reactivation TB (28). Some authors suggested that pathological lymph nodes usually range between 5 mm and 10 mm, while some considered larger than 10 mm as pathological (29,30). In the present study, lymphadenopathies larger than 10 mm on tCT were considered as pathological lymph nodes. In a study of Kim et al. comparing conventional CXR and tCT findings of the 2-12 months old patients with pulmonary TB, it is noted that CT is markedly superior to conventional CXR in demonstrating lymphadenopathies and parenchimal lesions (31). It is also reported that centrally necrotic lymph node enlargement was the most common finding on CT examination. In our study, the most common location of lymphadenopathy was paratracheal and subcarinal stations, respectively.

Gomez et al. reported that 63% of the TST positive asymptomatic patients with culture negativity and normal CXR findings had pathological lymph nodes on their tCT images which were localized mostly in the paratracheal region (32). Peng et al suggested that calcified and caseous necrotic lymph nodes are characteristic for TB (26). We found that lymphadenopathy was present in 91.9% of the group A patients. In 73% of the group A patients, lymph node enlargement with a maximal diameter of >1 cm was observed. Although only 13.5% of the group A patients had calcified lymph nodes, when it was present it was interpreted as a spesific finding for TB (specifity %100). The anatomical distrubition of the enlarged lymph nodes was mostly paratracheal and subcarinal, which was consistent with the literature.

Clinically asymptomatic children with a positive TST and normal CXR may have enlarged hilar or mediastinal lymph nodes on tCT (30). However the natural behaviour of TB suggests that moderate enlargement may be related to the primary TB infection and if serial radiological examinations performed, it was reported that in 40% of cases enlarged lymph nodes resolved spontaneously in the first six months and in 30% in the first year (33). For this reason, the debate over the use of tCT still continues and many authors advise performing tCT, only on symptomatic children or if the impact area of the disease or complications were being questioned (22).

In patients with TB, atelectasis is caused by external compression of the bronchial lumen due to enlarged lymph nodes or endobronchial spread of the infection. Acar et al. detected 14% of the 77 pediatric patients with confirmed pulmonary tuberculosis had atelectasis on tCT. Atelectasis was mainly located at the lateral segment of the middle lob and at the anterior segment of the upper lobe (27). In our study, atelectasis was present in 24.3% of the group A patients and in 36% of the group B patients. So, it is assumed that atelectasis is not a useful finding in the diagnosis of tuberculosis.

Conclusion

Delayed diagnosis of TB in children are usually because of failure to detect hilar/mediastinal lymphadenopathy and possible concomitant parenchymal abnormality on CXR. On tCT images, pulmonary hilar lymphadenopathy could be the only abnormal finding of pediatric TB. In addition to its contribution for diagnosing TB, tCT provides further information in the management of TB, especially by evaluating the disease activity and when it is a complicated form of TB.

Ethics Committe Approval: University of Health Sciences, Sisli Hamidiye Etfal Training and Research Hospital, Regional Ethical Review Board (Registration number: 2010/1007).

Informed Consent: Due to the retrospective design of the study, informed consent was not obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – EAK, ND; Design – EAK, ND, SME; Supervision - ND; Materials – EAK, DA; Data Collection and/or Processing - EAK, ND, OYU; Analysis and/or Interpretation: EAK, ND, EOK; Literature Review - EAK, EEA; Writing - EAK, ND, EEA; Critical Review - ND, SME.

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