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대한영상의학회지

Chest Radiographs and CT Findings during Healthcare Workers' Tuberculosis Screening Using Interferon-Gamma Release Assay: Retrospective Observational Study

인터페론-감마 분비 검사를 이용한 의료 종사자의 결핵 스크리닝에서 흉부 X선 사진 및 CT 소견: 후향적 관찰 연구

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Purpose To investigate the incidence of tuberculosis (TB) in healthcare workers (HCWs) with positive interferon-gamma release assay (IGRA) results based on chest X-ray (CXR) and CT findings and determine the role of imaging in the diagnosis of TB.
Materials and Methods Among 1976 hospital personnel screened for TB using IGRA, IGRA-positive subjects were retrospectively investigated. Clustered nodular and/or linear streaky opacities in the upper lung zone were considered positive on CXR. The CT findings were classified as active, indeterminate, inactive, or normal. The active or indeterminate class was considered CT-positive.
Results IGRA was positive in 255 subjects (12.9%). CXR and CT were performed in 249 (99.2%) and 113 subjects (45.0%), respectively. CXR- and CT-positive findings were found in 7 of 249 (2.8%) and 9 of 113 (8.0%) patients, respectively. Among the nine CT-positive subjects, active and indeterminate TB findings were found in 6 (5.3%) and 3 (2.7%) patients, respectively. Microbiological tests, including acid-fast bacilli staining, culture, and polymerase chain re-

action for TB, were negative in all nine CT-positive subjects. Empirical anti-TB medications were administered to 9 CT-positive subjects, and 3 of these nine subjects were CXR-negative for pulmonary TB.

Conclusion CT helped diagnose asymptomatic TB in IGRA-positive HCWs.

Index terms Thorax; X-Rays; Tomography, X Ray Computed; Tuberculosis; Interferon Gamma Release Tests

INTRODUCTION

Latent tuberculosis infection (LTBI) is persistent immune state with small number of viable *Mycobacterium tuberculosis* bacilli resided without evidence of clinically manifested active TB (1). Without treatment, 10% of persons with LTBI will develop TB disease (2). By increasing the trend of patients with reduced immunity due to aging and medical advancement, treatment guidelines for latent TB have been strengthened to avoid progression of active TB in persons with LTBI (3). Because healthcare workers are at increased risk of acquiring TB than the general population, TB blood test to diagnose TB infection was proposed as effective occupational protection strategies (2, 4). Although there are no clear consensus guidelines about the use of imaging modalities in this setting, chest X-ray (CXR) or chest CT can reveal the presence of image findings of active or inactive TB in persons with TB infection and lead to appropriate treatment of health care personnel (4). With the recent advancement of CT technique, chest CT has been widely used for the diagnosis of pulmonary TB due to its superior sensitivity to CXR (5). To our knowledge, there was no study about the use of chest CT in healthcare personnel with positive interferon-gamma release assay (IGRA) results and diagnosis of latent or active TB. The aim of this study was to investigate the incidence of TB based on CXR and CT findings in healthcare workers with positive IGRA results, and to determine the role of imaging in diagnosis and treatment of pulmonary TB.

MATERIALS AND METHODS

Our Institutional Review Board approved this retrospective observational study, and requirement for informed consent was waived (IRB No. 20-2018-3).

STUDY SUBJECTS

Among 1976 hospital personnel screened for TB infection with IGRAs from January 2015 to December 2017, IGRA-positive subjects were retrospectively included. Clinical information including age, sex, history of TB was investigated by the review of electronic medical records. For IGRA-positive subjects, consequent radiologic examinations, microbiological tests including acid-fast bacilli (AFB) stain, sputum culture, and TB polymerase chain reaction (PCR), and the use of anti-TB medications were recorded.

CHEST CT IMAGE ACQUISITION

CT scans were performed with the use of a 128-channel CT scanner (Ingenuity, Philips Medical Systems, Best, the Netherlands) or a 64-channel MDCT (Brilliance; Philips Medical Systems, Cleveland, OH, USA). For contrast-enhanced chest CT scans, 80 to 120 mL of iopamidol (Iopamiro 300; Bracco, Milan, Italy) was administered intravenously at a rate of 2.5 mL/s. Data acquisition was performed in the cranio-caudal direction with a detector collimation of 64 × 0.625 mm, section collimation of 64 × 0.625 mm, and gantry rotation time of 0.5 seconds, a pitch of 1.0 or 0.515, and 120 kv (peak). Effective milliampere-second (mAs) for routine chest CT scans ranged between 150 and 200, using an automatic tube current modulation technique. For low dose CT protocol, reference tube current was 25 mAs or 50 mA. The CT raw data was reconstructed with a slice thickness of 2.5 mm and an increment of 2.5 mm, using a sharp reconstructing algorithm. Resultant images were transferred to a picture archiving and communication system (PACS) for image analysis.

ESTIMATION OF RADIATION DOSE

Dose length product (DLP) values were recorded as displayed on the CT exam information for each CT scan. The effective dose was calculated from DLP values and a conversion coefficient of 0.017.

CLASSIFICATION OF RADIOLOGIC ACTIVITY OF TB

Consolidation or cavitary nodules or clustered nodular and/or linear streaky opacities in upper lung fields on CXR were defined as positive for TB, which included active and indeterminate activity. Fibronodular scarring with calcified nodules were considered as inactive lesions for TB (6). To determine the image-based activity of TB, CT findings were classified into 4 categories by the consensus readings of two thoracic radiologists: active, indeterminate, inactive, and normal. Multiple clustered centrilobular nodules or cavitary consolidation were defined as active; small nonspecific ill-defined nodules and/or minimal reticulation as indeterminate; fibroatelectasis or calcified nodules as inactive TB (7, 8). In both CXR and CT, active and indeterminate activities were classified as positive, and inactive and normal findings were classified as negative.

RESULTS

IGRA positive TB infection was found in 255 subjects (12.9%). Demographic information of

Table 1. Demographic Description of Study Subjects with Positive Interferon-Gamma Release Assay Results and Radiologic Examinations

Variables	Chest Radiograph Only (*n* = 138)	Chest CT (*n* = 113)	Total (*n* = 251)
Female	92 (66.7)	63 (55.8)	155 (61.8)
Male	46 (33.3)	50 (44.2)	96 (38.2)
Age, years	43.5 ± 10.9 (22–64)	45.0 ± 11.2 (21–64)	44.2 ± 11.1 (21–64)
History of tuberculosis	7 (0.7)	4 (3.5)	11 (4.4)

Values are number (%) or means ± standard deviation (minimum value – maximum value).

study subjects was described in Table 1. Mean age was 44 years (range; 21–64). Radiologic examinations were performed in 251 subjects. CXR and CT scan was performed in 249 subjects (99.2%) and 113 (45.0%), respectively. Two subjects underwent CT without CXR. LDCT scans were performed in 77 subjects (61.1%). Contrast enhanced chest CT was performed in 2 subjects (0.2%). Total dose-length product (DLP) was 210.33 ± 182.57 mGy·cm (range: 75.6–747.4). Consequent effective dose was 4.89 ± 4.32 mSv (range: 1.96–16.85).

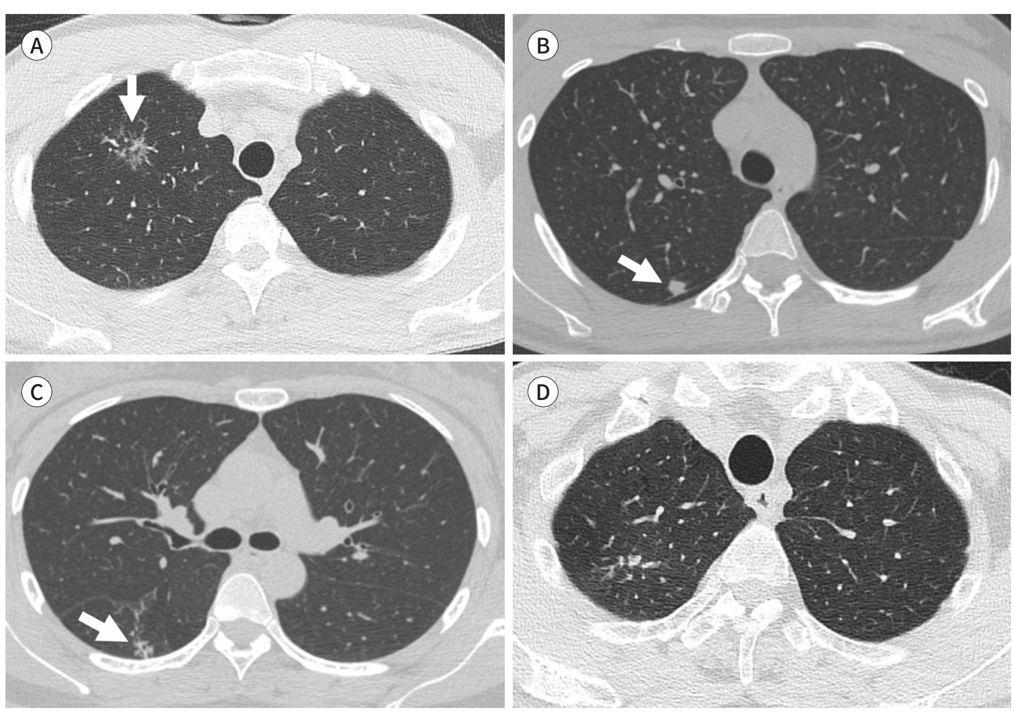
Table 2 demonstrates the image findings of TB on CXRs or CT scans in subjects with positive IGRA results. CT-positive subjects for TB were 9 of 113 (8.0%), 6 of them showed active TB

Table 2. Diagnoses of TB Based on Chest Radiograph and Chest CT Findings in Healthcare Workers with Positive Interferon-Gamma Release Assay Results

	TB Findings on Chest CT					Total
	Active	Indeterminate	Inactive	Normal	N/A	
TB findings on chest radiographs						
Positive	4 (1.6)	2 (0.8)	1 (0.4)	0	0	7 (2.8)
Inactive	0	0	6 (2.4)	0	10 (4.0)	16 (6.4)
Normal	2 (0.8)	1 (0.4)	10 (4.0)	85 (33.9)	128 (51.0)	226 (90.0)
N/A	0	0	0	2 (0.8)	0	2 (0.8)
Total	6 (2.4)	3 (1.2)	17 (6.8)	87 (34.7)	138 (55.0)	251 (100)

Values are number (%).
N/A = not available, TB = tuberculosis

Fig. 1. Chest CT findings according to the activity of TB.
A, B. Chest CT findings suggestive of active TB; clustered micronodules (A, arrow) and a small noncalcified nodule (B, arrow) in the right upper lobe.
C, D. Chest CT findings with indeterminate activity of TB; ill-defined nodules with equivocal fibrotic changes (arrow) in the right lower lobe superior segment (C) and right upper lobe apical segment (D).
TB = tuberculosis



(5.3%), and 3 of them showed indeterminate activity of TB (2.7%). CT findings with active TB included clustered micronodules or centrilobular nodules in 4 subjects, and a noncalcified nodule of 1–3 cm in 2 subjects. CT findings with indeterminate activity included clustered ill-defined nodules with mild or equivocal fibrotic changes in 2 subjects, and apical pleural thickening and subpleural nodules in 1 subject. CT findings with inactive TB included variable range of calcified nodules and fibrotic changes in all 17 subjects. Fig. 1 shows examples of CT findings according to the activity of TB.

Microbiological tests including AFB stain, culture, and PCR for TB were negative in all 9 CT-positive subjects. Empirical anti-TB medications were administered in all 9 subjects with CT-positive TB findings, and 3 of these 9 subjects were CXR-negative for TB (Figs. 2, 3). Three of the nine subjects had a follow-up CT scan after treatment and the suspected lesions de-

Fig. 2. A 57-year-old male with positive interferon-gamma release assay.
A. Chest radiography is considered as negative.
B, C. Low-dose chest CT shows clustered tiny centrilobular nodules in both upper lobes (arrows), suggesting active pulmonary tuberculosis.

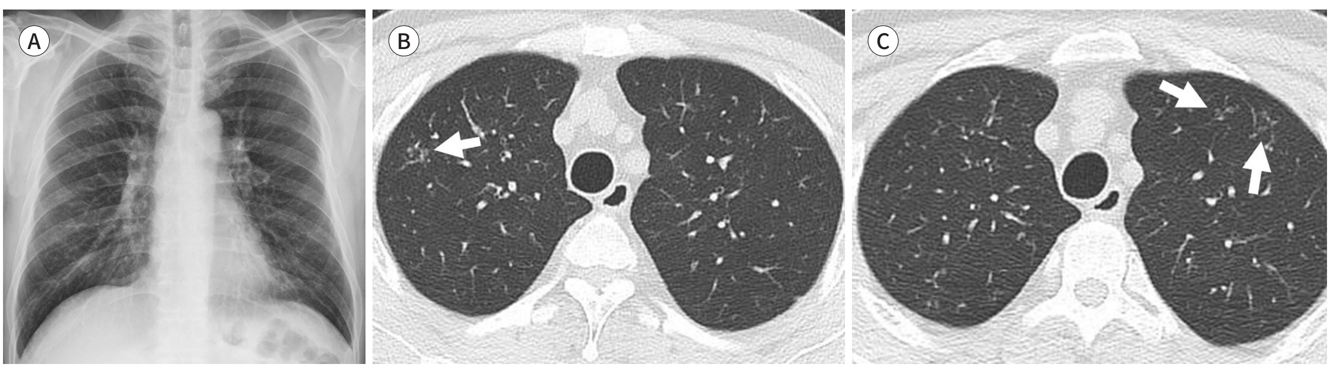


Fig. 3. A 58-year-old male with positive interferon-gamma release assay.
A. Chest radiograph was determined as negative.
B, C. Chest CT axial (B) and coronal (C) images show tiny ill-defined nodules and minimal reticulations (arrows) in the right upper lobe apex classified as indeterminate.

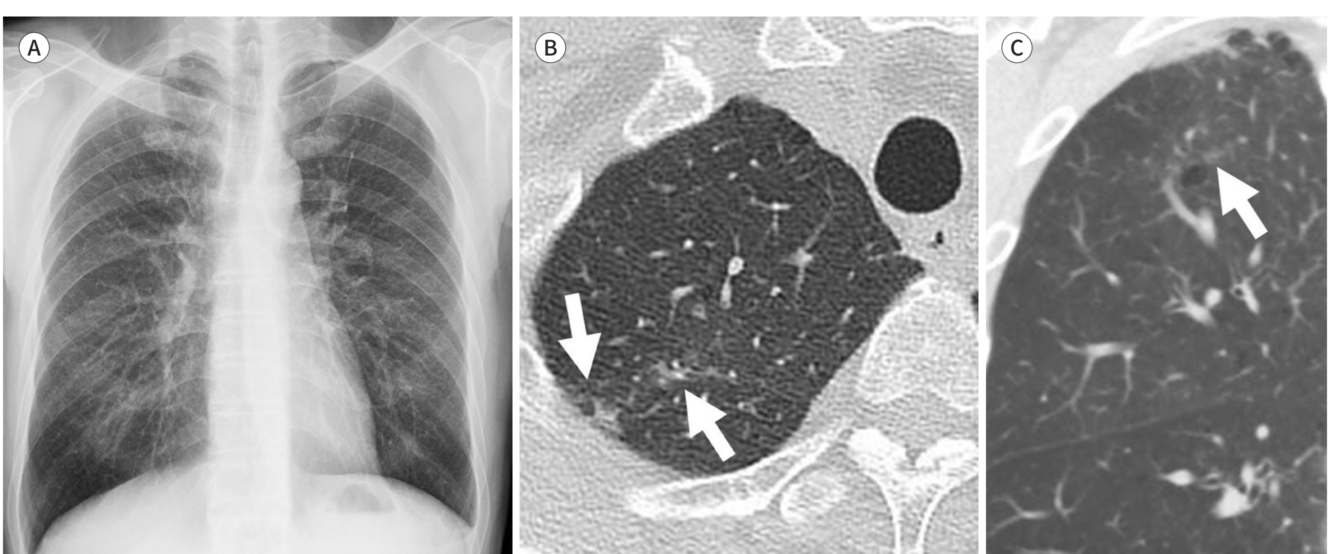
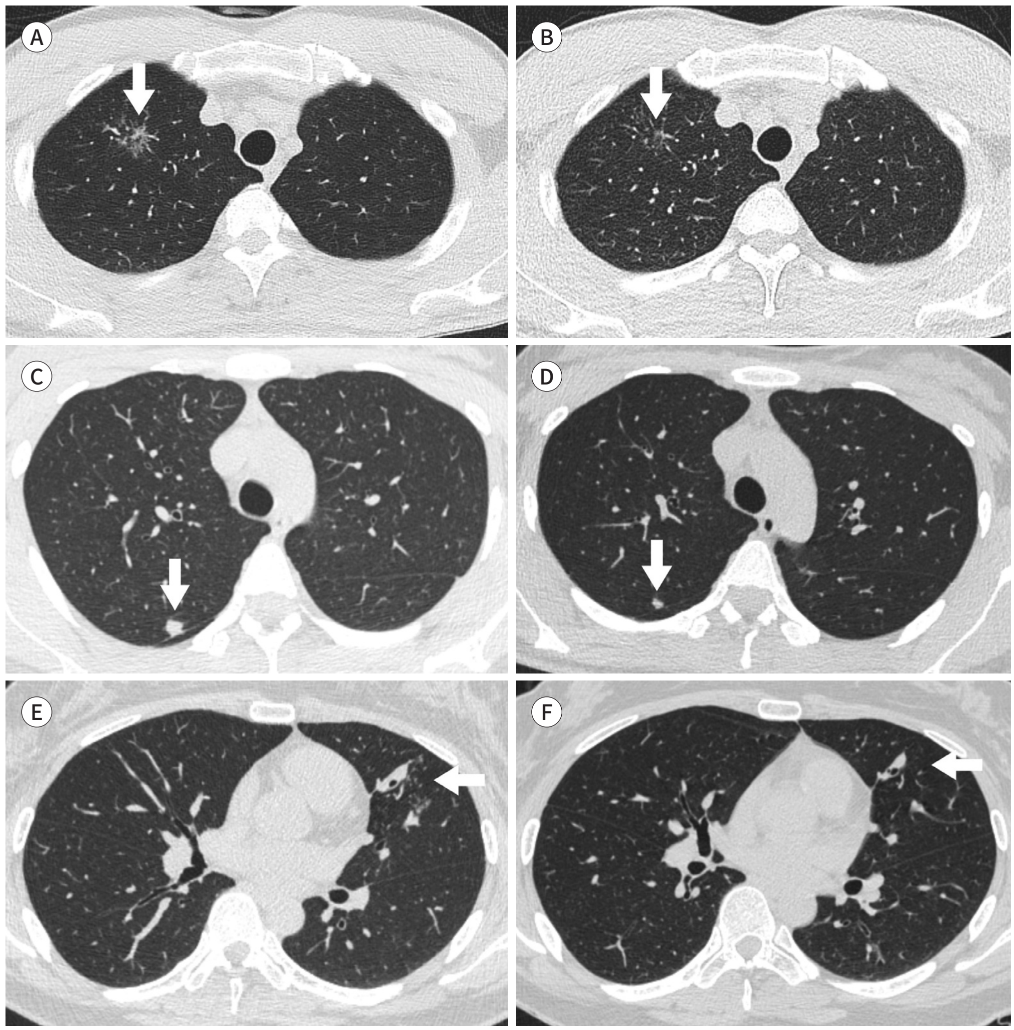


Fig. 4. CT scans before and after empirical treatment of tuberculosis in positive interferon-gamma release assay subjects.
A, B. A 35-year-old male showing clustered micronodules in the right upper lobe (arrows).
C, D. A 26-year-old female showing a small noncalcified nodule in the right upper lobe (arrows).
E, F. A 35-year-old female showing centrilobular nodules with focal bronchiectasis and atelectasis in lingular division of left upper lobe (arrows).



creased in size or extent (Fig. 4).

Of all 255 IGRA-positive subjects, 41 subjects (16.1%) received preventive treatment for LTBI. The proportion of subjects receiving LTBI treatment was 30.7% (32/104) in the CT-negative group and 16.5% (40/242) in the CXR-negative group. The development of active TB was observed after 1 year in one subject in the CXR-negative group without CT evaluation.

DISCUSSION

In this retrospective observational study, we found that 9 of 113 (8.0%) subjects who underwent CT scans were received empirical TB treatment due to suspected findings of TB on CT in IGRA-positive healthcare workers (HCWs). Our observations show that asymptomatic TB can be diagnosed by imaging and empirically treated in a clinical setting, and these results suggest a role of imaging in IGRA-positive HCWs. Considering that empirical TB treatment was not performed in the group who performed only CXR without CT, it can be assumed that the diagnostic role in CT was greater than that of CXR.

Because of radiation dose and availability and cost, chest CT scans were restrictively used for specific patient group to predict the development of TB. Incidence of TB on CT in liver transplant candidates was 40.0% in the post-transplant TB group and 17.3% in the control group (p = 0.018). In addition, of the 10 patients who underwent chest CT before liver transplant and developed TB, 5 (50%) showed abnormal findings only on chest CT scans, whereas their CXR results were normal (9, 10). In a similar fashion, sensitivity of CXRs in our study was only 66.7% and 3 of 9 CT-positive cases were negative in CXR results. It means that CXRs have limitations to reveal TB finding for TB progression in a high-risk group. Another setting for TB screening using IGRA and chest CT was patients with inflammatory bowel disease (IBD) from TB high-prevalence regions. Because immunosuppressants used in IBD make the risk of TB progression, chest CT have been used to reveal TB findings, which have been reported as 22.8% (10). Our results are consistent with previous studies showing the better diagnostic performance of chest CT for the detection of TB foci than CXRs (9, 11, 12).

According to previous studies of LTBI in Korea, the prevalence of LTBI among HCWs was 13.6%–15.8% (13-15), which was similar to our results (12.9%). Regarding active TB, recent studies of TB screening in hospital workers using chest CT showed that the prevalence of active TB on CT was 0.5% to 1.2% (5), which is different from the incidence of active TB in our study (5.3%). It is because our study performed screening CT on only those who were positive for IGRA. The incidence of CT-positive TB, including active and indeterminate activity in this study (n = 9, 8.0%), was similar to the result of other study that reported 10.0% active TB on CT in screening combining IGRA and CT scans (16).

Many studies have been made on mandatory testing of TB infection and recommended treatment from HCWs at medical institutions (13, 17, 18). However, according to recent WHO guidelines, systematic TB infection testing and treatment for HCWs from countries with a high TB burden have conditional recommendations with low to very low certainty in the estimates of effect (19). In our study, only 16.1% of subjects with TB infection received LTBI treatment, and the proportion of subjects receiving LTBI treatment differed between CT-negative and CXR-negative group (30.7% vs. 16.5%). Such results reflect that LTBI treatments were optional and depends on the clinician's decision and patient`s compliance. Because the subjects endure the possible complication of TB medications including hepatotoxicity, thrombocytopenia, anaphylactic shock, it is necessary to find individuals who will benefit from TB medication.

CTs have been used as secondary examinations for the evaluation of TB activity for subjects with TB infection. It suggests that active TB finding on CT provides the evidence of anti-TB medications in TB infection subjects for clinicians to determine the activity of TB. Several studies have focused on the combined use of CT findings and microbiologic tests for TB (20, 21). It has been recognized that the combination of CT findings of consolidation and QuantiFERON-TB Gold In-Tube test results ensure clinicians to refine decision-making in subjects with a TB PCR-negative bronchial aspirate (22). In our study, all subjects with positive IGRA results were negative for TB PCR testing using bronchial aspiration specimen. However, anti-TB medications were treated in all 9 subjects (100%) with positive TB findings on CT regardless of negative microbiological results. This retrospective result shows the clinician's preference for radiologic examination to determine the anti-TB medications for HCWs with positive IGRA results.

Development of active TB without preventive treatment was observed in one subject who underwent CXR without CT scan. Although further prospective study is necessary to show the predictive value of CT in subjects with TB infection, our retrospective study demonstrates the potential role of CT in prophylactic treatment for TB activation. In addition, 3 out of 9 subjects (33.3%) with positive CT results were normal in CXR. Therefore, it is possible that the active TB disease was overlooked in the CXR-only subject group.

There were several limitations to our study. First, we retrospectively included only a small number of patients with a selection with the same ethnic background and geographic region; therefore, the results of this study should be interpreted cautiously. Second, IGRA-negative subjects were excluded from the analysis. Because CT was performed selectively in IGRA-positive subjects only, the incidence of TB was increased in this study. Third, the radiologic activity of TB was evaluated with consensus readings. We did not measure the variability between the reviewers for the classification of TB findings.

In conclusion, the use of CT for IGRA-positive subjects helped diagnose asymptomatic TB in HCWs. Further study is necessary to show the predictive value of CT screening for active TB in HCWs.

Author Contributions

Conceptualization, C.Y.R., J.K.N.; data curation, all authors; formal analysis, all authors; investigation, all authors; methodology, C.Y.R., J.K.N.; project administration, C.Y.R., J.K.N.; supervision, C.Y.R., J.K.N.; validation, all authors; visualization, C.Y.R., J.K.N.; writing—original draft, C.Y.R., J.K.N.; and writing—review & editing, all authors.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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대한영상의학회지

인터페론-감마 분비 검사를 이용한 의료 종사자의 결핵 스크리닝에서 흉부 X선 사진 및 CT 소견: 후향적 관찰 연구

최예라[1,2] · 이정규[3] · 허은영[3] · 김덕겸[3] · 진광남[1,2]*

목적 인터페론-감마 분비 검사(interferon-gamma release assay; 이하 IGRA) 결과가 양성인 의료종사자의 흉부 X선(chest X-ray; 이하 CXR) 및 CT 결과를 기반으로 결핵의 발생률을 조사하고, 결핵 진단에서 진단 영상의 추가적인 역할을 알아보고자 하였다.

대상과 방법 IGRA를 시행 받은 1976명의 의료 종사자 중에서 IGRA 양성자를 후향적으로 조사하였다. 상부 폐야의 군집 결절 또는 선형 음영을 흉부 X선 양성으로 간주하였고, CT 결핵 소견은 활성, 활동성미정, 비활동성, 정상으로 분류하였다. 활성 또는 활동성미정을 CT 양성으로 정의하였다.

결과 IGRA 검사 결과 255명(12.9%)에서 양성이었다. CXR과 CT는 각각 249명(99.2%)과 113명(45.0%)에서 시행되었다. CXR 양성 소견은 249명 중 7명(2.8%), CT 양성 소견은 113명 중 9명(8.0%)에서 각각 나왔다. 9명의 CT 양성 대상자 중 활성 또는 활동성미정 결핵 소견은 각각 6명(5.3%)과 3명(2.7%)에서 발견되었다. Acid-fast bacilli 염색, 배양 및 결핵에 대한 polymerase chain reaction을 포함한 미생물적 검사는 9명의 CT 양성 피험자 모두에서 음성이었다. CT 양성 피험자 9명은 경험적 항결핵약물 치료를 받았고, 이 9명 중 3명은 CXR 음성 소견이었다.

결론 IGRA 양성 의료 종사자에서 CT 검사는 무증상 결핵을 진단하는 데 도움을 주었다.

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