Short Communication

Assessment of Nosocomial Transmission of Tuberculosis in a Psychiatric Hospital Using a Whole Blood Interferon-Gamma Assay

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SUMMARY: We conducted a contact investigation in a psychiatric hospital to evaluate the nosocomial transmission of tuberculosis (TB). Contacts included hospital healthcare workers (HCWs) and inpatients who had been exposed to an index case of pulmonary TB. Contacts were evaluated for Mycobacterium tuberculosis infection with standard screening methods as well as the QuantiFERON®-TB Gold (QFT-G) test. A tuberculin skin test (TST) was administered to 3 individuals who were under 30 years old, and all tests were negative. Chest X-ray examination was performed for all 46 contacts (9 HCWs and 37 patients). Five had abnormal chest X-ray results that were not compatible with TB, and 41 had normal chest X-rays. As regards the QFT-G test, 23 of the 46 (50%) contacts, 1 HCW (an 81-year-old male) and 22 patients, were positive. The results suggest that there was significant nosocomial transmission of TB infection among inpatients in this psychiatric hospital. Moreover, these findings indicate that the use of chest X-ray and TST, i.e., conventional methods of detection will leave TB infection undetected in many individuals. Thus, introduction of screening for TB infection using the QFT-G test in long-term care facilities such as psychiatric hospitals may enable the detection and treatment of individuals with latent TB in whom the infection would otherwise be missed by other conventional screening methods.

Although the incidence of tuberculosis (TB) in Japan gradually decreased for 4 successive years after 1999, TB outbreaks have recently increased in schools, business offices, and hospitals (1). In particular, based on the officially reported number of nosocomial TB infections from 2000 to 2006 (2), the frequency of such outbreaks in psychiatric hospitals is estimated to be approximately 3.5 times that of general hospitals. Several reasons for this difference have been suggested, including the inability of psychiatric inpatients to properly report symptoms, crowded living conditions with poor ventilation, and the general lack of alertness to TB among medical professionals in Japan (3). To control the spread of TB infection, most developed countries screen contacts of TB patients, and infected individuals are referred for chemoprophylaxis. The standardized methods for investigating contacts include the tuberculin skin test (TST) and chest X-ray examination. In Japan, contacts under 30 years of age are examined with both TST and chest X-ray examination, and contacts older than 30 years are offered only chest X-ray examination. However, both of these methods have significant limitations. The specificity of the TST has been severely reduced in Japan due to the widespread use of the BCG vaccination (4). Because frequent revaccination with BCG has commonly affected schoolchildren, especially those in school until the mid-1970s, many individuals aged 30 years or older have strong TST reactions that are indistinguishable from positive responses due to infection with Mycobacterium tuberculosis. As a result, the current Japanese guidelines for contact investigations have recommended TST only for those under 30 years of age. For those over 30 years old, no active measures are taken to examine individuals for latent tuberculosis infection (LTBI) and screening involves chest X-rays with the aim of early detection of the development of active disease.

The relatively recent identification of proteins specific for Mycobacterium tuberculosis by genomic and immunological methods has facilitated the development of more specific diagnostic systems for TB infection (5). The M. tuberculosis proteins ESAT-6 and CFP-10 are absent from all BCG substrains and most non-tuberculous mycobacteria, and have been shown to induce strong interferon (IFN)-γ production by effector T cells derived from M. tuberculosis infected mice (6-8). Using these antigens as stimulants, a new diagnostic test, QuantiFERON®-TB Gold (QFT-G, called QuantiFERON®TB-2G in Japan), has been developed and was demonstrated to have high sensitivity for detecting individuals with active TB and high specificity in low-risk, BCG-vaccinated subjects (9). Furthermore, we and others have shown that the QFT-G test also detects LTBI (10-15). As numerous published studies on QFT-G have shown that QFT-G reflects M. tuberculosis infection more accurately than TST (16), QFT-G is now used for contact investigations instead of, or in addition to, TST in several developed countries, including Japan. In this study, we evaluated the usefulness of the QFT-G test in comparison with that of the traditional methods used for contact investigations in a Japanese psychiatric hospital.

The index case was a 44-year-old Japanese male inpatient at a psychiatric hospital. He presented with a high temperature on 30 August 2003, and was treated with general antibiotics. However, he had repeated bouts of fever over the next few months, and developed a cough in November. On 22 December 2003, his sputum smear was found to be positive (2+) for acid-fast bacilli. Active pulmonary TB was also detected by chest X-ray. M. tuberculosis infection was subsequently confirmed by positive culture and a nucleic acid amplifica-
tion test. On 26 December 2003, the patient was admitted to a general hospital and was treated for pulmonary TB. During the few months leading up to late December 2003, when the index case was presumably infectious, the patient had been in free contact with other patients on the psychiatric hospital wards, and was often seen to spit saliva and phlegm. Chest X-ray examination was carried out to screen his three roommates on 27 December 2003, and no abnormalities were observed.

On 16 January 2004, an initial contact investigation, including medical examination, interview, chest X-ray, and sputum examination for symptomatic subjects was performed for 44 inpatients and 19 healthcare workers (HCWs) who lived or worked on the same floor as the individual with the index case. Three subjects had abnormal chest radiographs, and one was diagnosed with active TB based on the chest X-ray findings. For the other two subjects, bronchoalveolar lavage was carried out on 24 March 2004, and a culture of the bronchial fluid from one of the two subjects tested positive for M. tuberculosis, with a restriction fragment length polymorphism (RFLP) pattern identical to that of the index case, and thus chemotherapy was initiated. On 19 January 2004, TST was performed for 10 of those contacts who were less than 30 years old, and the TST results were interpreted as described previously (17). Seven of these contacts showed strong positive TST reactions, and they were prescribed chemoprophylaxis with isoniazid (INH).

The second contact investigation was conducted using interviews, chest X-rays, and sputum examination; this second series was carried out 6 months after the first. At the time of this second investigation, one hospital staff member and six inpatients were identified by chest X-ray as having developed TB, and the individuals were administered chemotherapy. The bacteriological examinations of all of these cases were negative.

The floor plan of the hospital ward in which the index case was accommodated as an inpatient is shown in Figure 1. Eight bedrooms (A-D), each housing from 1 to 5 inpatients, were located on both sides of the ward. A room used both as a dining room and a day room (DR), a hospital staff office (SR), a restroom (WC), and elevators (EV) were also located along the center of the ward. During the initial contact investigations, TB patients were identified among those with bedrooms on both sides of the building. There appeared to be a clustering of TB cases amongst those inpatients with a bedroom near that of the index case, but as shown in Figure 1, three infections were identified in subjects with bedrooms on the other side of the building.

This spatial distribution strongly indicated that the transmission of TB infection caused by the index case had been extensive, suggesting the need for more aggressive measures to address LTBI in order to contain any further development of disease and transmission of infection. On 8 July 2004, an additional examination was performed using the QFT-G test, which was carried out as previously described (9). Nine HCWs and 37 inpatients were examined using the QFT-G test. The subject demographics and test results are summarized in Table 1. The subjects were also evaluated by TST and/or chest X-ray according to the routine procedures. TST was only conducted for the three subjects less than 30 years of age, and all of these tests three were negative (erythema diameters: 10, 18, and 25 mm). The QFT-G test results were also negative (0.01, 0.01, and 0 IU/ml). If TST had been offered to those aged 30 years or older, it would be expected that many would have shown strong reactions, independent of their infection status, and may have been indicated for LTBI treatment. This expectation is based on the observation that in a periodic check-up of a general hospital, 86% of HCWs aged 30 years or older showed TST erythema results of greater than 30 mm (Nakajima, Y., unpublished data). Chest X-ray examination revealed that 5 of the 46 subjects had abnormal chest X-ray findings not compatible with TB, and 41 subjects had no abnormalities.

Twenty-three of the 46 (50%) contacts were QFT-G positive. Only one of the 9 (11%) HCWs (a doctor aged 81 years) was QFT-G positive, whereas 22 of the 37 (59%) inpatients had a QFT-G result compatible with M. tuberculosis infection. The mean age of QFT-G-positives individuals did not significantly differ from that of the QFT-G-negatives, indicating that the high QFT-G-positive rate was not associated with age (Table 1). The one QFT-G-positive HCW, and 20 of the 22 QFT-G-positive inpatients, had normal chest X-ray radiographs. Thus, using only the traditional screening methods of TST for those under 30 years of age and chest X-ray for all, none of the 23 QFT-G-positive contacts would have been suspected of M. tuberculosis infection (Table 1).

To prevent the nosocomial transmission of TB, early identification of patients with TB is essential, as highlighted in the US Centers for Disease Control and Prevention recommendations (18). This practice may be especially relevant in long-term care facilities, such as psychiatric hospitals, where patients are often housed in close proximity for long periods of time. Several TB outbreaks in psychiatric hospitals have been reported to date (19-23), and delays in the diagnosis of TB have been identified as a key reason for the occurrence of TB outbreak. This scenario was also apparent in the present...
study, in which there was a delay of approximately 4 months until a diagnosis of TB was made after the initial onset of the symptoms in the index case. Acute awareness of the potential for TB infection on the part of the medical staff is of utmost importance for early detection of this disease in the clinical setting; such awareness could be enhanced by systematic continuing education as part of an institute’s prevention policy.

The development of the QFT-G test, which is unaffected by BCG vaccination and has very high specificity, now allows for identification of infected contacts, i.e., cases that would otherwise be missed using conventional methods alone. The availability of this new test encourages us to screen for LTBI as well as active TB and enables the prophylactic treatment of those infected before they develop active disease. By using the QFT-G test in the present contact investigation, a large number of infected individuals were identified who would otherwise have been overlooked if conventional contact investigation methods alone had been used.

Similar situations to the one described here could potentially be observed in a number of different settings, including prisons, homeless shelters, and other facilities in which the reported TB incidence rates are higher than those of the general population (24,25). The introduction of systematic screening for TB infection using QFT-G testing in such long-term care facilities may enable the detection and treatment of those individuals with LTBI who could be overlooked by other screening methods. Such a QFT-G-based program would be expected to yield a significant reduction in the incidence of TB outbreaks in these high-risk facilities.

It was not an aim of this study to evaluate whether the QFT-G test was correctly identifying truly infected persons, although previous studies demonstrating the very high specificity of this test gave us no reason to doubt the validity of our results (16). One secondary case of active TB sharing the same genotype of M. tuberculosis as that of the index case occurred in this hospital within a narrow time period, which strongly suggested the nosocomial transmission of TB infection. Moreover, compared with the approximately 12% TB infection prevalence rate expected in a non-exposed Japanese population within a similar age range (26), the observed QFT-G positivity of 60% was alarmingly high, which suggested that the high positivity observed in this study could be reliably ascribed to the recent extensive exposure. However, we cannot conclude that all of the QFT-G-positive subjects had been infected by the index case, since the QFT-G test does not distinguish between old and recent infections, it remains desirable to offer initial or baseline evaluation of low-molecular-mass proteins from Mycobacterium tuberculosis identifies members of the ESAT-6 family as immunodominant T-cell antigens. Infect. Immun., 68, 537-544 (in Japanese).


