Correspondence

Extra pulmonary tuberculosis in Saudi Arabia

Sir,

Mycobacterium tuberculosis (*M.tuberculosis*) induced extra-pulmonary morbidity was thoroughly reviewed in a recent issue of Saudi Medical Journal by Alrajhi and Al-Barrak.[1] Certainly the true disease morbidly in Saudi Arabia would have been explicit had there been an adequate laboratory set-up to carry out different microbiological investigations on those with clinical evidence of tuberculosis. Molecular biology investigations would be desirable during prospective plans to ascertain the true magnitude of *M.tuberculosis* induced extra-pulmonary morbidity. At a tertiary health care center in the Indian capital metropolis, New Delhi, preliminary studies using polymerase chain reaction (PCR) have pointed to extensive *M.tuberculosis* replication in placental tissue.

Investigations for *M.tuberculosis* replication in placenta were carried out at the Sant Parmanand Hospital, a 100-bed hospital, located in the northern part of the Indian capital during the period extending from February 2000 to August 2001. Placental tissues from 24 women, aged 19-37, were examined by microbiological and molecular biology assays for *M.tuberculosis*. All women had strong clinical evidence pointing to tuberculosis and had an elevated erythrocyte sedimentation rate. Nine samples were positive during culture in the Mycobacteria Growth Indicator tube (MGITTM OADC: Becton Dickinson, Cockeysville), and 10 in the Lowenstein-Jensen medium. Amplification of a 240 bp region (460-700) from the gene encoding MPB 64 protein of *M.tuberculosis* in 24 placental tissues showed a positive band on gel electrophoresis in 18 specimens.

Reports on congenital military tuberculosis as well as a placental tuberculosis infection have been very uncommon. Since the 1980s, there have been only 30 published cases reports of congenital military tuberculosis in English literature.[2] A solitary tubercular infection of placenta was reported during the mid-1990s in Calcutta, India.[3] The magnitude of placental tuberculosis in Saudi Arabia would interest epidemiologists and clinicians. Precise data would be available by concurrent use of different molecular biology techniques, such as nucleic acid probe assays (AccuProbe) or *M.tuberculosis* gene amplification. Exact identification of mycobacterium species for extra-pulmonary tuberculosis induced morbidity or mortality would be ideal even in remote locations in Saudi Arabia or elsewhere. A commercially available 16s ribosomal deoxyribonucleic acid (DNA) sequencing kit as well as the additional sequencing libraries[4] would assist the clinicians and epidemiologists to work out the precise epidemiology of extra pulmonary tuberculosis.[1]

Tuberculosis-endemic areas should also be able to use the real-time PCR, which is the most practical variation of standard PCR, which does not depend on time-consuming manipulations and processing of the reaction. The advanced nucleic acid analyzer,[5] which is based on silicon chip-based spectro fluorometeric thermal cyclers has been useful during field operations using low-power battery operation. That would indeed be an asset for future research on extra pulmonary replication of different mycobacterium species.

Nirmala Agarwal
Department of Obstetrics & Gynecology
Subhash C. Arya
Department of Microbiology
Sant Parmanand Hospital
18 Alipore Road
Delhi 110054
India

Reply from Author

Dr. Agrawal points to the under-diagnosis and under-reporting of extrapulmonary tuberculosis. Even diagnosed cases are fairly delayed in both diagnosis and treatment resulting in increased morbidity, mortality and cost of care.[6] Although molecular diagnosis techniques are promising for faster and reliable modes of diagnosis confirmation, they remain limited by their shortcomings, especially in settings of limited resources and medical facilities. This is typical in endemic areas for tuberculosis in developing countries. We believe that sound clinical judgement, heightened suspicion and an essential laboratory setup for pathology and microbiology are far more suitable for the areas where tuberculosis remains endemic, namely developing countries. A well informed clinician in an endemic area is prepared to start antituberculosis therapy for a case suspected for tuberculous meningitis based on clinical and basic cerebrospinal fluid (CSF) data; even if stain and polymerase chain reaction (PCR) or ligase chain reaction (LCx) from CSF are negative for *M.tuberculosis*.

Molecular diagnostic methods for extrapulmonary tuberculosis have had variable reliability results from various parts of the world and for various types of specimens. In a Mexican study, it was highly specific

and sensitive for extrapulmonary specimens.[7] An earlier study from France had a sensitivity of 63% for extrapulmonary specimens compared to culture.[8] In another study, sensitivity of PCR in all types of specimens (pulmonary and extrapulmonary) was 59% compared to 41% for stain and 65% for culture. Polymerase chain reaction was positive in only 78% of culture positive specimens.[9] Also, the use of molecular diagnostics in extrapulmonary specimens was associated with false positive results especially in immunocompromised patients.[10] Better results were obtained when molecular diagnosis was combined with culture techniques even when respiratory specimens were evaluated along with extrapulmonary specimens.[11]

For the time being, we believe routine use of molecular diagnostic methods for clinical decision making or epidemiology in tuberculosis should be limited to respiratory specimens using validated and approved methods or kits in well prepared laboratories by trained personnel. Microbiology and culture are still essential in this era of increased drug resistance. Above all else is the sound and thorough clinical assessment and judgement based on which clinical specimens and diagnostic tests are required.

Abdulrahman A. Alrajhi
Section of Infectious Diseases
Department of Medicine
King Faisal Specialist Hospital and Research Center
Ali M. Al-Barrak
Department of Medicine
Armed Forces Hospital
Riyadh
Kingdom of Saudi Arabia

References

1. Alrajhi AA, Al-Barrak AM. Extrapulmonary tuberculosis: epidemiology and patterns in Saudi Arabia. *Saudi Med J* 2002; 23: 503-508.
2. Pham DL, Le Van N, Truong NCH. Congenital military tuberculosis. Apropos of a case. *Rev Pneumol Clin* 1998; 54: 207-209.
3. Sarkar A, Thakur S, Majumadar S. A case of tuberculosis infection of the placenta. *J Indian Med Assoc* 1996; 94: 355-356.
4. Cloud JL, Neal H, Rosenberry R, Tussere CY, Jama M, Hillyard DR et al. Identification of Mycobacterium spp. by using a commercial 16s ribosomal DNA sequencing kit and additional sequencing libraries. *J Clin Microbiol* 2002; 40: 400-406.
5. Belgrader P, Bennett W, Hadley D, Richard J. Stratton P, Mariella R Jr et al. PCR detection of bacteria in seven minutes. *Science* 1999; 284: 449-450.
6. Chow KM, Chow VCY, Hung LCT, Wong SM, Szeto CC. Tuberculous peritonitis-associated mortality is high among patients waiting for the results of mycobacterial cultures of ascitic fluid samples. *Clin Infect Dis* 2002; 35: 409-413.
7. Portillo-Gomez L, Morris SL, Panduro A. Rapid and efficient detection of extra-pulmonary *Mycobacterium tuberculosis* by PCR analysis. *Int J Tuberc Lung Dis* 2000; 4: 361-370.
8. Bemer-Melchior P, Germaud P, Drugeon HB. Diagnosis of extrapulmonary tuberculosis by a commercial polymerase chain reaction kit. *Pathol Biol* 1998; 46: 597-603.
9. Almeda J, Garcia A, Gonzalez J, Quinto L, Ventura PJ, Vidal R et al. Clinical evaluation of an in-house IS6110 polymerase chain reaction for diagnosis of tuberculosis. *Eur J Clin Microbiol Infect Dis* 2000; 19: 859-867.
10. Vago L, Zerbi P, Caldarelli-Stefano R, Cannone M, D'Amico M, Bonetto S et al. Polymerase chain reaction for Mycobacterium tuberculosis complex DNA. Use on negative archival Ziehl-Neelsen cytologic samples. *Acta Cytologica* 2000; 44: 1023-1028.
11. Oh EJ, Park YJ, Chang CL, Kim BK, Kim SM. Improved detection and differentiation of mycobacteria with combination of *Mycobacterium* Growth Indicator Tube and Roche COBAS AMPLICOR System in conjunction with Duplex PCR. *J Microbiol Methods* 2001; 46: 29-36.