Mycobacteria in the Literature: Report 02-2016

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High-resolution imaging for the diagnosis of active tuberculosis

Most clinicians think of tuberculosis (TB) as either latent/inactive or active in individual patients. The understanding that latent infection can become active disease, particularly as an individual ages or becomes immunosuppressed, is at the core of tuberculosis screening programs. However, TB is increasingly being understood, not as black or white, inactive or active, but rather as a spectrum of activity between the two extremes of completely inactive latent TB and florid disease. Current markers for latent infection are not able to predict which individual is likely to progress to symptomatic and infectious illness. The ability to identify individuals at high risk for progression to active disease would allow the limited resources of TB control programs to be targeted where they will make the most difference.

Esmail and colleagues [1] evaluated 35 asymptomatic HIV infected individuals diagnosed with latent TB using 2-deoxy-2-[18F]fluoro-d-glucose ([18F]FDG) positron emission tomography combined with computed tomography (PET–CT). None of the participants had a history of TB or symptoms of active TB; all had CD4 counts ≥350 cells/mm³. Chest radiograph (CXR) and sputum cultures were negative. Isoniazid preventative therapy was started in all after the initial PET-CT scan. Twenty-five participants (71.4%) were found to have abnormal PET-CT findings ranging from nodules to infiltrates. In 10 participants (29%), the findings were suggestive of active/subclinical disease. Four of these 10 patients developed symptoms of active disease between 7 and 90 days after the PET-CT and were treated with standard 4 drug therapy with clinical improvement; in [2], sputum cultures became positive for TB. None of the patients without PET-CT findings of “subclinical” disease developed symptoms suggestive of active disease. Six of the 10 participants diagnosed with subclinical tuberculosis underwent a follow-up PET-CT at 6 months and all showed improvement in their pulmonary findings. Only 1 of 21 patients with an abnormal PET-CT finding that was not felt to represent subclinical TB had improvement at 6 months.

This study provides additional support for the paradigm of TB infection as a spectrum of disease. It suggests that a subset of patients diagnosed with latent TB by a standard clinical evaluation actually have subclinical active disease. This understanding of TB infection as a spectrum, should spur clinicians to ensure that all patients who appear to have latent TB are investigated appropriately for active disease. The authors suggest that PET-CT could be a helpful diagnostic tool in studies of subclinical TB treatment. PET-CT is not an evaluation that is reasonable for most patients diagnosed with latent TB but this study is a reminder of the need for a clinically practical and inexpensive marker for the risk of TB disease progression and is a step towards this goal.

Reference

[1] Esmail H, Lai R, Leosky M, Wilkinson K, Graham C, Coussens A, et al. Characterization of progressive HIV-associated tuberculosis Using 2-deoxy-2-[18F]fluoro-d-glucose positron emission and computed tomography. Nat Med October 2016;22:1090–1093.

Humoral immune responses to TB

Mycobacterium tuberculosis (MTB) infects approximately one in four people globally and is a leading cause of death from infectious diseases. The toll of TB on the global economy is estimated to be 12 billion dollars per annum. A vaccine would save countless lives, end significant suffering in the developing world, and allow the vast resources spent on TB control to be spent on other pressing priorities. MTB, an intracellular pathogen, has long been considered to be an infection which is dependent primarily or purely on the cellular immune system for control. This has led to little

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evaluation of the humoral response to tuberculosis, despite the fact that antibodies are protective against many other intracellular infections and a monoclonal antibody has been protective against TB in a mouse model. The only MTB vaccine available, Bacillus Calmette–Guérin (BCG), provides limited protection. Understanding what antibodies are important in controlling tuberculosis could lead to new diagnostics or new avenues for vaccine development.

The aim of the study by Lu and colleagues [3] was to evaluate the humoral immune system response in individuals with latent and active tuberculosis. The authors evaluated 22 HIV negative individuals with latent TB and 20 individuals with a diagnosis of active tuberculosis confirmed by positive sputum smear or culture for MTB. Latent TB was defined as a positive interferon release assay (IGRA) without a history of tuberculosis or tuberculosis treatment, and no clinical symptoms of tuberculosis. Healthy IGRA negative individuals were also evaluated. Study participants with latent TB had blood drawn in the absence of treatment and individuals with active tuberculosis had blood drawn immediately prior to treatment and at day 7 of treatment. The authors conducted 70 antibody immunological tests. They found distinct differences in humoral response profiles between the individuals with active and latent TB. They found that antibody glycosylation patterns could distinguish between latent and active disease; only a single individual with active TB crossing over into the latent TB cluster. Antibodies made by individuals with latent disease were functionally superior to antibodies made by individuals with active disease, with differences noted in the promotion of phagolysosomal fusion, inflammasome activation and most importantly macrophage killing of internalized mycobacteria.

This study highlights the fact that not all antibodies are alike and it is not only how much antibody one has against a pathogen but the quality of that antibody. This study may provide the groundwork for new TB vaccine studies as well as for the development of biomarkers that help distinguish active TB from latent TB.

Reference
[2] Lu L, Chung A, Rosebrock T, et al. A functional role for antibodies in tuberculosis. (2016) Cell 167, 433–443.

Defining optimal microbiological monitoring during the treatment of MDR-TB

In 2015 there were an estimated 480,000 new cases of multidrug resistant tuberculosis (MDR TB). Monthly mycobacterial sputum culture and smear are recommended early in MDR TB treatment; monthly smears with occasional sputum culture are recommended following culture conversion. Controversy exists regarding the need and benefit of monthly cultures during the last 12 months of MDR TB treatment.

Mitnick and colleagues analyzed existing data to estimate the effect of monitoring interval (monthly versus bimonthly or quarterly) and method (smear versus culture) on timing of treatment failure detection during the final 12 months of treatment for MDR TB. They also evaluated if patient characteristics modified the timing of failure detection. Analyzed data were obtained from 3 previous meta-analysis MDR TB treatment studies as well as additional sources identified by WHO guideline committee members. Twelve studies met the investigators criteria for inclusion and included a total of 5730 patient-treatment records. These studies took place in 11 countries. In 5410 treatment records at least one on treatment culture was recorded and these 5410 patients were included in the study. Bacteriologic failure was classified as 2 or more positive cultures or smears in the last 12 months of treatment or at least one positive culture or smear in the last 3 months of treatment. Failure month was the month of the first positive culture or smear. Treatment outcomes varied greatly between studies with cures ranging from 16% to 74%. Failure was detected in 17% of cases. All included sites used monthly culture for identifying failure.

The investigators simulated three monitoring scenarios against which they compared the timing of "observed failure" detected by monthly culture in the final 12 months: one using only monthly smear; the second using results from samples collected every other month (to simulate bi-monthly monitoring) and the third using results from samples collected every third month (to simulate quarterly monitoring). They estimated the timing of observed failure in each scenario.

The detection of failure during the last 12 months of treatment depended on the frequency of culture. Monthly culture detected failure at a median of 3 months, bimonthly culture at a median of 5 months and quarterly culture at a median of 6 months. Monthly smear without culture significantly delayed failure detection to 10 months; this delay was independent of HIV status. Culture was found to be particularly and predictably important in those who were smear negative at baseline.

The authors note that, as a simulation, their study has significant limitations including the possibility that clinicians may have used information not available to the investigators to decide on a change in treatment to avoid failure. All sites had the capability of doing monthly culture and the results may not be generalizable to sites with fewer resources.

Although the results of this simulation study are not surprising, they are important as countries and public health departments struggle with appropriately allocating resources. Earlier detection of treatment failure is likely to lead to improved outcomes with earlier adjustment of the treatment program, less potential for transmission and with less chance for the development of additional resistance. More frequent monitoring is an additional expense for programs with limited resources. However, a delay in detecting MDR TB treatment failure is also likely expensive with the potential for the development of extremely drug resistant tuberculosis (XDR TB) requiring treatment with more expensive drugs, and the spread of resistant TB. The authors note that their findings highlight the importance of further developing laboratory capacity for proper management of MDR-TB. Only 21 high burden countries have met the recommendation of having one laboratory per 5 million people capable of performing mycobacterial cultures. This study also suggests that, even after culture conversion, monitoring mycobacterial sputum cultures monthly during treatment for MDR TB is ideal.

Reference
[3] Mitnick C, White R, Lu C, Rodriguez C, Bayona J, Becerra M, et al. Multidrug-resistant tuberculosis treatment failure detection depends on monitoring interval and microbiological method. Eur Respir J 2016; 48: 1160–1170. DOI: 10.1183/13993003.00462-2016