The menace of tuberculosis and the role of nuclear medicine in tackling it. Now its time to tighten the loose strings

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Abstract

Tuberculosis is a global medical problem. The radioisotopes have played an important role in the diagnosis and treatment of many problems including various cancers. In the early period after the discovery of radioactivity, isotopes or radionuclides like radium were used for the treatment of tuberculosis (TB) but they failed completely. Later, nuclear medicine has developed techniques for sensitive and rapid detection of TB. Many of the currently applied molecular biology techniques of nuclear medicine find applications in diagnostic research of TB. Still, the detection of lesions of unknown origin, the differentiation of active from inactive TB lesions and also the response to treatment, especially in cases of drug resistant TB are the main fields that need better approaches for identification by nuclear medicine techniques.

Introduction

There are many diseases, which are not amenable to cure using prevalent options, and tuberculosis (TB) is one of them. Any new discovery in the realm of science is viewed with an expectant anticipation that it may hold the answers for hitherto unsolved questions; the same is also true for radioactivity. At first the discovery of radioactivity created an undue hype and at one time it was being viewed as a panacea. After concerted experimentation, the application of radiopharmaceuticals (RF) greatly benefited medicine in fields like thyroidology and oncology and also TB at least *in vitro*. The following article gives a bird's eye view of deep bonding between TB and nuclear medicine.

About tuberculosis

Tuberculosis is a prehistoric disease. Mummified remains from northern Egypt dating from 3400 B.C. provide strong evidence for the presence of spinal TB [1, 2]. The first known description of tuberculous spondylitis was written in Sanskrit between 1500 and 700 B.C. [3, 4]. In Greek TB is called 'Phthisis', meaning: deterioration or consumption because the victims appeared to be consumed by the disease. Hippocrates in 460 B.C. depicted phthisis as the most widespread disease of those times. Tuberculosis has been previously thought to be hereditary in origin until around 1880 A.D., when the German scientist Robert Koch discovered its bacterial cause, the organism mycobacterium tuberculosis (MTB). He thus, established TB as an infectious disease. He was awarded the Nobel Prize for Medicine in 1905, for his work on MTB.

As per the World Health Organization (WHO) 2009 report [5] in the year 2007, the estimated global incidence of TB was 9.27 million new cases, with an estimated 13.7 million prevalent cases and estimated 1.3 million deaths among HIV-negative incident cases of TB (2 per 10000 population). Additionally, there were 456000 deaths among incident TB cases who were HIV-positive. The incidence is rising and is partly contributed to the spread of acquired immunodeficiency syndrome [6].

In addition to the resurgence of TB, multidrug resistant TB (MDR-TB) and extensively drug resistant TB (XDR-TB) have recently become an increasing concern in nearly 55 countries in 2007. Laboratory delays in the growth, identification and reporting of the MDR-TB cases has contributed, at least in part, to the spread of the disease [5]. The estimated 1.8 million deaths means approximately 35000 deaths per week or nearly 5000 every day, thus, 206 deaths in an hour and more than 3 deaths every minute. Tuberculosis is thus a global emergency and that is why alongside child mortality, maternal and infant mortality, HIV and malaria, TB is one of five global health issues included within the eight millennium development goals (MDG) defined by the UN in 2000 [7].

Approaches to treat tuberculosis

The pre-antibiotic era. Historical events

Though TB is an ancient scourge, it has been intractable to treatment till recently. In the pre-antibiotic era TB was attempted to be treated by many approaches, like witchcraft [8, 9], ultraviolet (UV) rays [10] and even radioactivity after the discovery of radioactivity in late 19th century. Incidentally in the year 1903 when Becquerel and Curies were awarded the Nobel Prize for Physics for their discovery of radioactivity, Niels Finsen was awarded the Nobel Prize in Medicine for his discovery that light in the UV spectrum could be used to treat skin TB (lupus vulgaris) [10]. This type of treatment popularly known as Actinotherapy, continued to be used for this condition till the 1950s when eventually was replaced by antibiotics. Since the discovery of radioactivity [11-13], radionuclides have been used based mainly on their skin effect [13-16]. Radium was used first to treat lupus (cutaneous TB) and then superficial skin cancers by Henri Danlos and Paul Bloch in Paris in 1901 [17] in 1901, Strebel also reported favourable early results in the treatment of lupus with radium [18]. In his Nobel address, on 1903 Henri Becquerel mentioned that radium was being applied experimentally to treat skin lesions caused by

lupus and by cancer [19]. Many different types of experiments with radium or other radionuclides were undertaken without any means of radiation protection. These experiments included studying the effects of uranium on TB, on diphtheria, cholera and typhoid by Pacinotti in Italy in 1899 [20]. Strassmann (1904) found that the time required to kill by radiation emitted from 10mg radium bromide, B. prodigious, streptococcus, staphylococcus and B. TB was 24, 24, 48, and 108 hours, respectively [21]. Encouraged by these results, many investigators like Soddy and Macintyre (1903 and 1904) tried to treat TB with radium [22, 23]. Soddy (1903) suggested inhalation of thorium emanation for treating TB [22]. First results of such a treatment have been published by Sharp in 1904 [24]. Williams stated in his 1904 paper results of treating 50 patients with skin lesions including lupus vulgaris with 10-100mg pure radium bromide [25]. Radium tubes were inserted into tuberculous sinuses [26]. Several patients with TB keratitis were treated by others with beta irradiation emitted radium [27, 28]. Till the discovery of antibiotics, treatment of TB was more an art rather than science. The favorable effect of radium on TB can't be attributed to the bactericidal effect of the radioactive rays and radioactivity can cause an irreversible damage to healthy tissues including cancer [29, 30].

The antibiotic era

In 1943, the discovery of streptomycin changed the treatment of TB. Streptomycin was the first antibiotic remedy for TB and Selman Waksman received the Nobel Prize in 1952 for his discovery [10]. Attention was now diverted towards new problems in diagnosing and controlling TB, such as MDR TB. Now again the utility of radionuclides was explored. This led to the use of radioactivity for in vitro diagnosis of TB. In 1969, Deland and Wagner developed a technique for automated detection of the metabolism of bacteria by the $^{14}CO_2$ liberation during the decarboxylation of ^{14}C labeled substrates in growth medium [31]. This technique was also used by others [32, 33]. Another related diagnostic method, radiometric BACTEC 460 TB method was used [34-38] and replaced by mycobacteria growth indicator tube system (Becton-Dickinson), which used fluorescence technique instead of radioactivity [39].

Molecular radiobiology techniques

Many molecular biology techniques have been used for the identification of mycobacteria in laboratory, in some institutions, these are- AccuProbe; amplification of the 16S–23S ribosomal DNA spacer region; PCR-based sequencing techniques; DNA microarrays; molecular epidemiology techniques like, restriction fragment length polymorphism (RFLP) typing; to list a few [40, 41] and the majority of them were developed using radionuclides. The role of radioisotopes in the development of molecular biology is so important that molecular biology has been called as the molecular radiobiology [42]. The molecular biology techniques have also helped in the mapping of the Mycobacterium tuberculosis genome [43], which can help in developing new approaches to tackle this menace.

Besides the identification of mycobacterium in sputum smears and culture, the diagnosis of pulmonary TB (PTB) is based on abnormal chest radiography findings. However, these tools can sometimes be of little value in the diagnosis of active PTB, particularly sputum. There must be nearly 100 MTB per milliliter of sputum for detection by the culture method [44] and not all active cases of TB may produce the sufficient number of organisms in the sputum. Furthermore, radiography cannot differentiate between active and healed lesions in suspected recurrence or assessment of response to treatment. Such a specific definitive diagnosis can only be possible by culturing bronchial washings or histological examination of specimens obtained by fiberoptic bronchoscopy, but bronchoscopy is invasive.

The radionuclide based nuclear medicine techniques are simple, non-invasive and rapid. They can support in vivo the diagnosis and localization of lesions and provide an image indicating the extent of disease. However, nuclear medicine techniques like gallium-67-citrate (^{67}GaC) [45], technetium pentavalent succinic acid (^{99m}Tc(V)-DMSA) [46], ^{99m}Tc-metaiodo benzyl guanidine (^{99m}Tc-MIBI), [47] etc. have not been applied to a great extent in TB and all have some limitations.

A study of 144 patients with PTB found that 95% of the 110 active patients had abnormal ^{67}GaC scans and all of the remaining 34 inactive or bacteriological negative patients had normal scans [45]. This study indicated that ^{67}GaC scans may be useful in determining the degree of activity of TB process as a complement to chest radiographs. Others, compared ^{67}GaC and thallium-201 chloride (^{201}TlCl) in detection of the activity of PTB and found sensitivity, specificity and accuracy of 83.1%, 60.7% and 74.1%, respectively for ^{67}GaC scan; the same ratios for ^{201}TlCl were 88%, 82.1% and 85.6%, respectively. It was concluded that ^{201}T1Cl scintigraphy is more useful than ^{67}GaC scintigraphy. Nevertheless, both ^{67}GaC and ^{201}TlCl have relatively poor physical characteristics, and are not readily available. Gallium-67 requires a delay of 24-48hr between injection and scanning. Others recommended against using of ^{67}GaC for TB [49]. Indium-111-octreotide, which has limitations similar to ^{67}Ga, was also used in the evaluation of PTB and showed marked uptake in PTB lesions [50]. Radiolabeled monoclonal antibodies seem specific for PTB, but their high cost, the development of human anti-mouse antibody response and the lack of experience in many institutions has limited their routine application [51].

Others, by ^{99m}Tc-MIBI pulmonary scintigraphy differentiated active from inactive PTB (Fig. 1) and they showed that lactic dehydrogenase levels in bronchoalveolar lavage fluid were increased in active PTB [52].

There is possibly a similar uptake mechanism for ^{99m}Tc-MIBI and ^{99m}Tc-tetrofosmin in PTB lesions. Technetium-99m-tetrorfosmin uptake was also increased in PTB [53]. The favorable imaging characteristics of ^{99m}Tc (140keV peak energy, 6hr half-life) and its shelf availability make ^{99m}Tc-MIBI and ^{99m}Tc-tetrofosmin superior to other RF like ^{67}GaC etc for the investigation of PTB. However, ^{99m}Tc-MIBI and ^{99m}Tc-tetrofosmin imaging of PTB is limited by their relatively high cost and

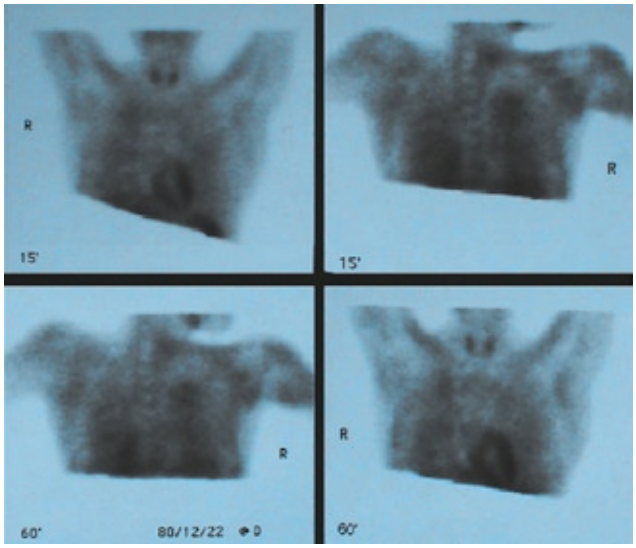

Figure 1. Non uniformly diffuse bilateral abnormal accumulation of ^{99m}Tc-MIBI in a patient with active PTB on the 15 and 60min lung scan in the anterior and posterior views, especially in the lower long lobes bilaterally (by permission of the Hell J Nucl Med).

they are also non-specific for TB because of their uptake in other lung infections and malignant processes. Technetium-99m-ciprofloxacin (infecton), showed sensitivity of 90% in detecting microbiology positive TB [54]. Other RF were tried like ^{99m}Tc-glucoheptonate and radiolabeled BCG-specific antibody have to diagnose PTB with limited results.

Others have reported a case of disseminated BCGitis in a child, which was born out of consanguineous marriage and was suspected to have some kind of immunodeficiency state resulting in extensive skeletal involvement by Mycobacterium bovis after administration of BCG vaccine. Bone scan with ^{99m}Tc-methyl diphosphonate (^{99m}Tc-MDP) revealed multiple tracer avid sites in both axial and appendicular skeleton [57] (Fig. 2). The bone scan is a sensitive but non-specific test to detect bone pathology on the basis of active bone metabolism. Others have also used ^{99m}Tc-MDP to identify bone scintigraphic features in cases of TB of the spine [58].

Fluorine-18 fluorodesoxyglucose (^{18}F-FDG) is also taken up by both inflammatory and malignant lesions and is used in the positron emission tomography (PET) scan. Thus, ^{18}F-FDG-PET scans reveal PTB lesions [59, 60] but there may be many false positive cases due to malignancy [60].

Sometimes, while investigating a patient for some other disease, PTB is unexpectedly diagnosed as mentioned below: By using ^{99m}Tc-depreotide, which has a high affinity to somatostatin receptors, 2 cases of TB, incidentally showed a positive lung scan while another 8 cases suffering from pneumonia or from TB had a true negative scan [55]. This difference could be due to the presence or absence of somatostatin receptors in these lesions. We could find no other study using ^{99m}Tc-depreotide for detection of TB.

Others while studying the diagnostic efficacy of ^{99m}Tc(V)-DMSA versus ^{67}GaC imaging in patients with highly suspected acute bone and joint infections, also incidentally detected

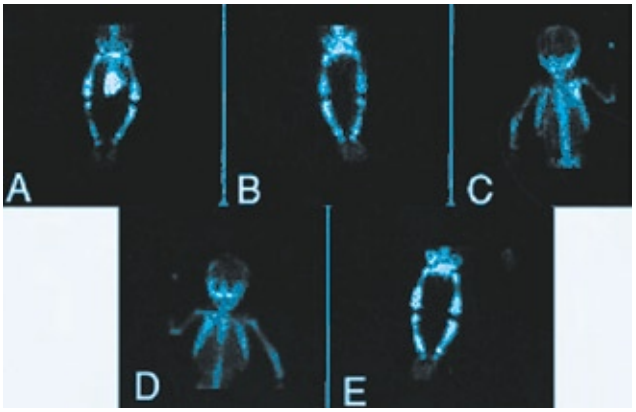

Figure 2. Whole body bone scan in a child with disseminated BCGitis revealed multiple active bone lesions in the skull, ribs, pelvic bones, femurs, tibiae and the upper limbs from humerus to the fingers (by permission of the Hell J Nucl Med).

a single case of TB by both modalities [56]. Our search in Pubmed for any other study using ^{99m}Tc-DMSA for the detection of TB was negative.

More work is necessary to better evaluate the significance of nuclear medicine techniques to diagnose lesions of TB, especially of ^{99m}Tc-DMSA, ^{99m}Tc-MIBI and ^{99m}Tc-tetrofosmin. It is pertinent to add that there is always a scope for the development of newer RF after of course hard research work. Remember that Marie and Pierre Curie only after 3 years of hard work isolated 100mg of radium for their studies.

In conclusion, TB an ancient menace is still not reined. Tuberculosis has been declared as global emergency by WHO and is a part of millennium development goals. Organisations like IAEA are also trying to fight TB. Diagnostic nuclear medicine is offering much, especially by using ^{99m}Tc(V)DMSA, ^{99m}Tc-MIBI, ^{99m}Tc-tetrofosmin and ^{18}F-FDG. Much more hard work is welcome.

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