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Review

Mapping the epidemiology and trends of extra-pulmonary tuberculosis in Saudi Arabia

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ABSTRACT

An extra-pulmonary tuberculosis (EPTB) infection rate of 30% in Saudi Arabia remains above the global rate. A variable rate of infection in each province has been reported and the involvement of most organs has been cited. Nationwide collective data on the current trends of infection are scarce and the factors behind the increased rate of EPTB are perplexing. This review endeavors to shed light into the epidemiology of EPTB, various types of infections sites, geographical differences in the infection rate, known risk factors, and challenges in the diagnosis and management of EPTB in Saudi Arabia.

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Introduction

Despite the developments in treatment and diagnosis, tuberculosis (TB) remains an enormous public health problem [1]. A decreasing or stable trend of new TB cases was observed from developed or industrialized nations. However, some developing countries show an increasing trend, whereas many others exhibit a very slow decline in incidence [1]. TB is primarily a disease of the lungs (pulmonary tuberculosis [PTB]), but can affect almost any organ in the body and the occurrence at sites other than the lung is defined as extra-pulmonary tuberculosis (EPTB). Despite the fact that EPTB is a serious clinical problem because of the diagnostic challenges encountered and the propensity to cause high morbidity and mortality, it receives less interest mainly due to low infectious potential [2,3]. The deadly synergisms between TB and human immunodeficiency virus (HIV) with the emergence of drug resistance have complicated the control of TB globally.

Extra-pulmonary involvement of mycobacteria can mostly happen through the lymphatic or hematogenous dissemination to any part of the body. In addition, the bacteria can stay dormant for a very long time. Due to higher efficacy in infecting any organ, the mycobacterium has a wide variety of clinical manifestations. Additionally, EPTB poses certain challenges in its diagnosis and management, even in resource-rich countries. The diagnosis is always cumbersome owing to the wide spectrum of clinical presentations, limited specificity of manifestations, and difficulties in obtaining specimens for diagnosis [4]. When considering the diagnostic difficulties of EPTB, the real magnitude of the problem at the community level may be underestimated, even with the current management system in most countries, including Saudi Arabia. To draw attention towards the magnitude of EPTB infections, in this review we attempted to show the current understanding of the epidemiology of EPTB, diversity in its clinical presentations, and the future research prospects required in Saudi Arabia.

Global trend on epidemiology and clinical pattern of EPTB

EPTB has been reported in almost all global regions, particularly in developed countries [1,4,5]. The World Health Organization data shows 0.8 million EPTB cases among the 6.1 million of new TB cases reported in 2013 [1]. The HIV epidemic, rising numbers of immigrants from developing countries to developed countries, and a fair amount of immune disorders are assumed to be responsible for this rise in TB cases in many countries [1–3,6,7]. A 10-year surveillance data from the European Union (EU) showed an increasing trend of EPTB in the member states [8]. A 13 year data from

the United States also showed an increasing proportion of EPTB compared with the decreasing trend of PTB [9].

Trends of clinical patterns of EPTB in most global regions were highly diverse in presentation. In the USA, a nationwide report shows lymphatic TB (40.4%) as the most prominent followed by pleural TB (19.8%), bone and joints TB (11.3%), genitourinary (6.5%), tuberculous meningitis (5.4%), peritoneal (4.9%), and 11.8% of other sites [9]. However, in the EU, the trend was different as it showed a higher predominance of pleural TB (36.7%), followed by lymphatic TB (30.5%), genitourinary (6.9%), bone and joints (5.1%), central nervous system (4.4%), gastrointestinal (2.7%), and other sites (9.4%) [8]. Recent data from Brazil also showed a similar trend to the EU, with the dominance of pleural TB (42%) followed by lymphatic TB (21%), meninges (6%), bone (5%), genitourinary (3%), miliary (8%), and others (15%) [10]. Nationwide data or large scale data were scarce from the major TB endemic regions of Africa and Asia.

Epidemiology of EPTB in Saudi Arabia

Annual case rates of EPTB have been recorded in Saudi Arabia since 1989. A considerable drop in the rate of incidence was reported in the initial period. However a gradual increase was evident since 1994 [11]. In 1991, the proportion of EPTB in the country was 11.7% of the total reported TB cases, followed by a sharp increase to 28.2% in 1997 [12,13]. However, a recent national TB notification registry data showed a consistent level of EPTB cases in the country – around 30% of total reported TB cases annually [14,15]. Fig. 1 explains the incidence rate of EPTB reported during 2005–2012. Interestingly, recent trends show a slight decrease in the rate of EPTB in connection with the decreasing trend of total notified TB cases in the country. The incidence rate ranges from 3.5–5 cases/10⁵ population in recent years when compared with the total TB incidence of 17–21 cases/10⁵ population in the same period [14,15]. Nonetheless, a variation of EPTB proportions was reported from several institutions, ranging from 15% to 63%. However, these data are based on a single institution and thus a nationwide picture could not be possibly drawn. A recent nationwide study conducted only with culture positive cases reported 20% EPTB among the 1904 patients examined [16–20].

Until now there were only two nationwide studies that looked deep into the clinical features and epidemiology of EPTB in the country [21,22]. Memish et al. [21] reported on the incidence and risk factors of EPTB on nationwide data collected during 2010–2011 from the national disease notification system. The data covered all the provinces of the country through the current TB notification system. The data showed

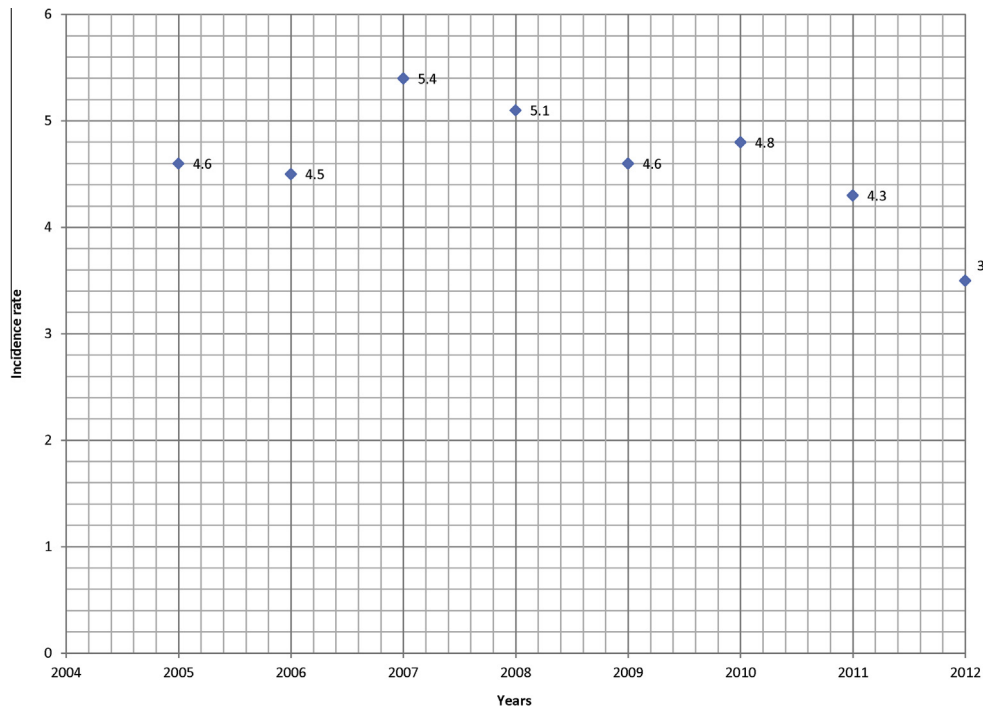


Fig. 1 – The figure shows the incidence rate of extra-pulmonary tuberculosis in Saudi Arabia during 2005–2012, data abstracted from the annual statistics reports of the Ministry of Health of Saudi Arabia.

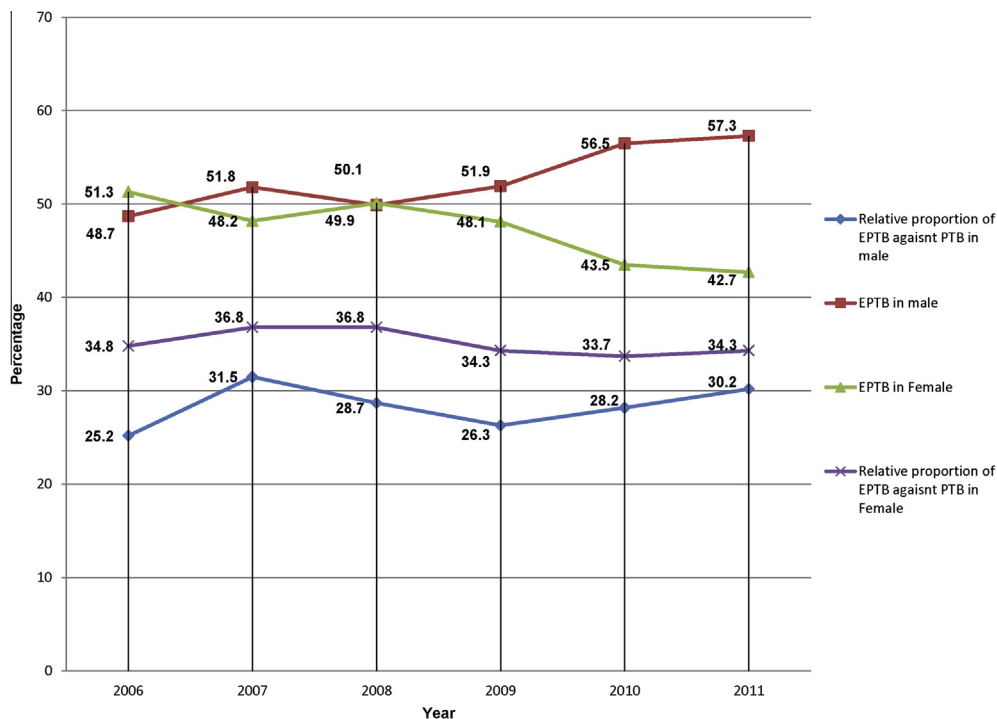


Fig. 2 – This figure shows the relative proportions of extra-pulmonary tuberculosis in male and female patients in Saudi Arabia along with the relative proportions against pulmonary TB. The data have been abstracted from the Ministry of Health Annual statistics reports for the period 2006–2011. EPTB = extra-pulmonary tuberculosis; PTB = pulmonary tuberculosis.

a minimal increase in EPTB cases from 30% in 2010 to 32% in 2011. In particular, Saudi nationals are more prone to EPTB than non-Saudis, and females are mostly getting EPTB than PTB. Interestingly, house wives and household workers

sharing the same environment were found with higher proportions of EPTB [21]. Recently, another nationwide data on 381 culture positive EPTB cases collected during 2009–2010 showed almost similar findings of the previous study [21],

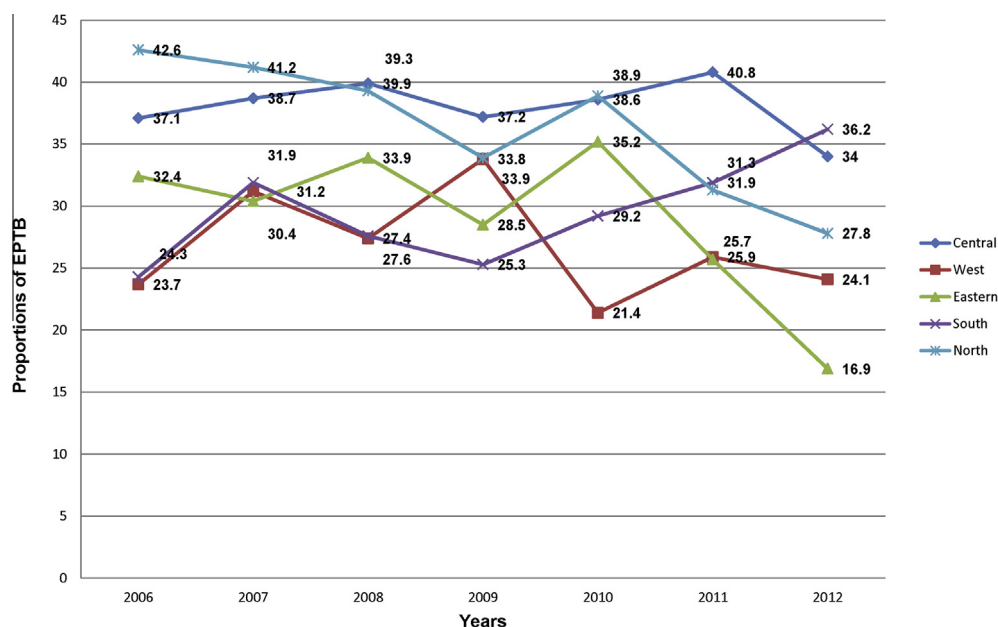


Fig. 3 – The figure shows the relative proportions of extra-pulmonary tuberculosis in five major geographical regions of the Kingdom. These values are against the pulmonary tuberculosis percentage abstracted from the annual statistics books of the Ministry of Health of Saudi Arabia for the period of 2006–2012.

as female gender and Saudi nationality as predisposing factors.

Gender associated incidence of PTB and EPTB in Saudi Arabia

Data published by the Ministry of Health of Saudi Arabia on the national incidence of tuberculosis during 2006–2011 showed a higher relative incidence of EPTB among female patients. Another recent study also reported the predominance of EPTB among females compared with males, particularly among household workers and their close contacts [21]. Fig. 2 depicts the proportions of EPTB among male and female patients during the period of 2006–2011 and the relative proportions of EPTB against PTB. Saudi Arabia also shows the same trend as the rest of the world, that female gender is a predisposing risk factor for the development of EPTB as opposed to PTB [2–5,9,23].

Geographical difference of EPTB prevalence in Saudi Arabia

The geographical differences in relative proportions of EPTB with PTB were clearly visible in major provinces of Saudi Arabia. Annual TB incidence notification published by the Ministry of Health has been adapted to make an analysis for a period of 7 years (2006–2012). The results are abstracted in Fig. 3. The major finding showed that central provinces of the country consistently reported a relative proportion of 34–41% EPTB in the past 7 years. In 2006, Northern provinces reported the highest proportion of EPTB as 42.6%. Later, the trend showed a decline in EPTB incidence in the North similar to the Eastern provinces. Surprisingly, most populated

provinces of the West and South showed comparatively lower proportions of EPTB (Fig. 3). Another recent study also showed a similar trend of EPTB proportions in different provinces of the country [21].

Clinical patterns of EPTB in Saudi Arabia

Clinical patterns of EPTB in the country in most of the recent studies showed huge diversity in manifestations. Most common sites of infection reported in the country were lymph nodes, bones, abdomen, nervous system, and pleura followed by all other rare sites including miliary TB. Fig. 4 depicts the results of a literature review which analyzed the extra-pulmonary sites of infection abstracted from various published studies during 1990–2013 in Saudi Arabia.

A couple of studies recently showed, for the first time, the data on clinical features of EPTB in the country with a domination of lymphatic TB. Data by Memish et al. [21] showed the second most common site of infection is bone, followed by central nervous system and gastrointestinal system, while Al-Hajjaj et al. [22] reported gastrointestinal, central nervous system, followed by bone, respectively, as the most infected sites (Fig. 5). However, this difference can be mainly due to the sample collection strategy, as Al-Hajjaj et al. [22] reported only on confirmed culture positive cases while other data was from the national TB reporting registry. Furthermore, the variations may point out the difficulties faced in diagnosing and proper sampling for culturing of the isolates.

Lymphatic TB

Intrathoracic and extra thoracic lymph nodes are the most affected site of infection by *Mycobacterium tuberculosis* among

EPTB cases in the country. Cervical adenopathy is the most common, but inguinal, axillary, mesenteric, submandibular, and mediastinal involvement have been described in different studies [24–26]. Lymphadenitis is common in all regions of the country and prevails with an average of 40% of the reported EPTB cases [20,27,28]. In Saudi Arabia, lymphatic TB is a disease of young adults, as the majority of patients were younger than 35 years. Furthermore, a higher preponderance of female gender was also noticed in many studies reported with lymphatic TB in the country [28]. This finding is in contrast with a trend in the Western world, where lymphatic TB is more common among the elderly. Preponderance of females with lymphatic TB may have a direct impact from the population structure of immigrants, particularly household workers from the TB endemic regions. They are sequestered in the close environment of houses with constant exposure to family members. Varghese et al., recently proposed the chances of effective transmission of TB among households through the relatively close activity between house maids and family members [29,30]. Interestingly, after the introduction of the new vaccine strain (Danish SSI 1331) for routine administration, a slight elevation in the rate of lymphatic TB among children younger than 1 year was serially reported [31,32].

Central nervous system

Brain tuberculoma, meningitis, intracranial tuberculoma, and spine TB are the most common infections reported in the country affecting the central nervous system [33–37]. However, other rare forms of TB to sites like the craniocervical

junction and lumbar root, along with serious concern on vertebral and paravertebral sites also were reported [16,20,38,39]. A recent study on a nationwide data collection reported an overall proportion of 7.1% central nervous system TB among the total EPTB cases reported [21]. In addition, another nationwide study on culture positive cases showed the predominance of 11.8% of central nervous system TB during 2009–2010 [22]. Central nervous system TB is more confined to the adults in the country. Interestingly, tuberculosis meningitis and other form of central nervous systems TB are reported less among children [39,40].

Gastrointestinal TB

Abdominal or gastrointestinal TB is one of the common manifestations of EPTB in Saudi Arabia [16,33,41]. The national average of reported cases of gastrointestinal TB during 2010–2011 was 5.4%. Al-Hajoj et al. [22] reported a proportion of 17.3% of culture confirmed gastrointestinal TB cases from a nationwide sample collection. Involvement of various sites of the abdomen, predominantly the peritoneum, liver, and small intestine were reported in the country [33,42]. Colon, spleen, pancreas, ileocecum, esophagus, duodenum, umbilical area, and abdominal wall were also reported with TB in several studies [41–45]. TB peritonitis (results mostly from the reactivation of latent foci in the peritoneum) is the most common clinical manifestation reported among patients with HIV infection or cirrhosis and in those undergoing continuous ambulatory peritoneal dialysis from different provinces of the kingdom [33,42,46].

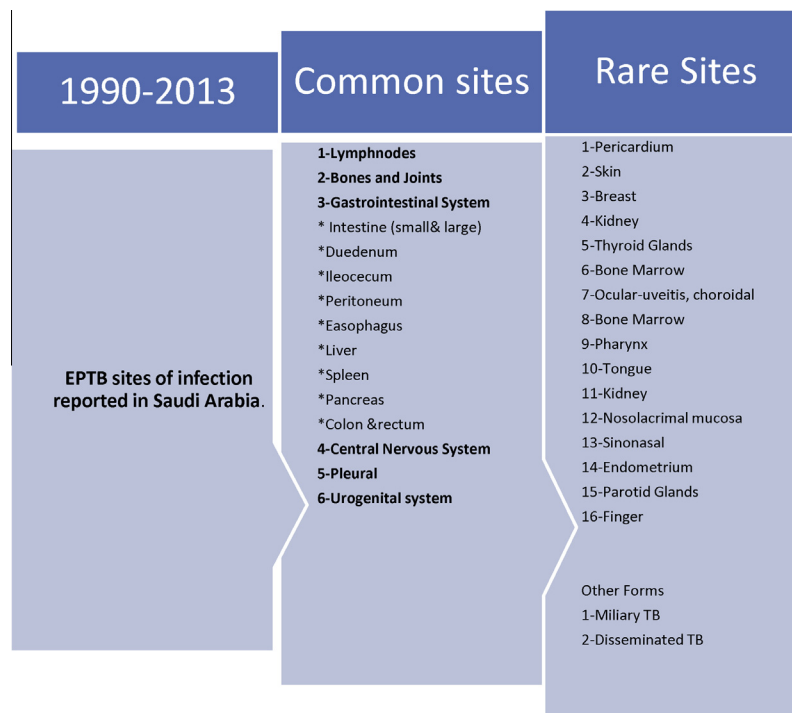


Fig. 4 – This illustration is created from data abstracted from an online literature review (PubMed, Google Scholar) conducted using the terms “extra-pulmonary tuberculosis in Saudi Arabia”, “tuberculosis in Saudi Arabia”, “tuberculosis case reports in Saudi Arabia”, and “Mycobacterium tuberculosis in Saudi Arabia”.

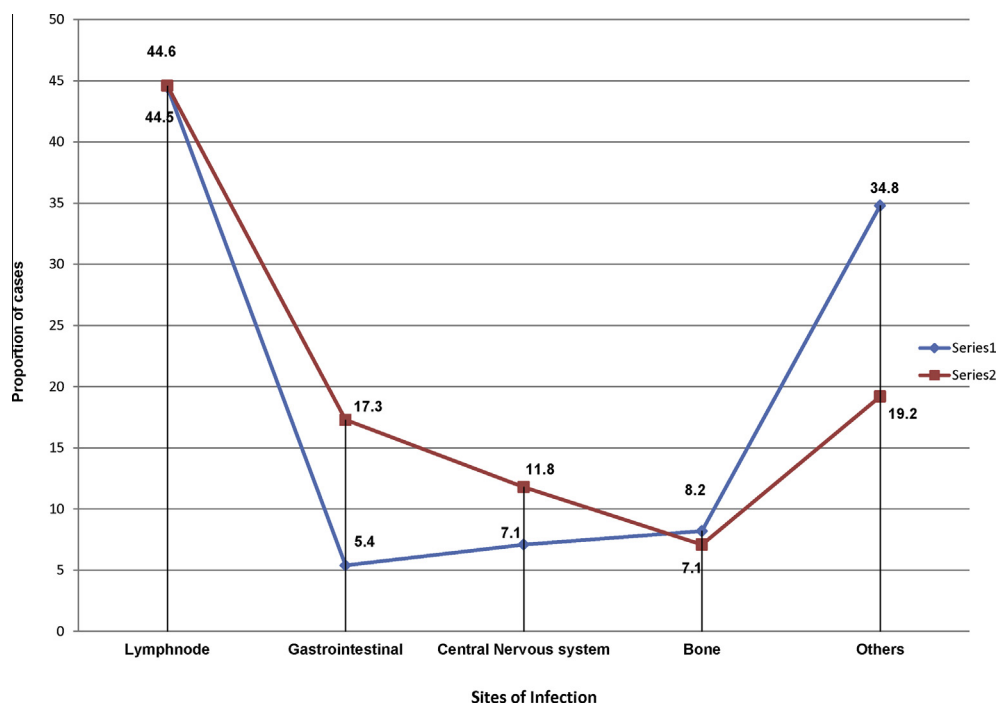


Fig. 5 – Series-1: Memish et al. [21]; Series-2: Al-Hajoj et al. [22].

Bone and joints

Bone TB predominates as the second most common site of EPTB in the country during 2010–2011 with an overall proportion of 8.2% [21]. Arthritis and spondylitis caused by *M. tuberculosis* is generally established as a clinical manifestation [47–49]. However, TB of the sternum, ribs, knee joint, zygomatic bone, talus, and cuboid have also been reported as rare incidences recently [50–52].

Pleural TB

In developed countries, pleural TB is the second most common form of EPTB after lymphatic TB [4,9,53]. Countries like Brazil and Poland showed pleural TB as the first predominated form of EPTB ahead of lymphatic TB [10,23]. However, in Saudi Arabia, a recent study analyzed with culture positive EPTB cases placed pleural TB in the fourth position. Pleural effusion is a well known clinical manifestation of TB. The largest series of pleural TB was reported from the Eastern province of the country during 1994. The study showed 35.2% of the 253 patients reported with pleural effusion had TB. Of the total 89 cases, 82% were men, 34.3% Saudi nationals, and 92% of them were positive to Mantoux testing [54]. A recent study recorded pleural TB among HIV positive patients [33].

Other rare sites

Any sites other than lymphatic, gastrointestinal, central nervous system, osteoarticular, and pleural were classified as other rare sites. A recent study (Memish et al.) showed 31% of the total notified EPTB cases during 2010–2011 belonged to other rare sites, which is relatively very high compared

with other global regions [2,4,9,21,23,53]. In a literature review (1990–2013), it has been noticed that involvement of rare sites in EPTB is common in Saudi Arabia. Genital TB was a common EPTB manifestation in the 1980s and 1990s in the country. Several previous studies reported the existence of a large level of female genital TB infections particularly among the local population [16,20,45,55]. In addition, TB of the testis (particularly epididymo-orchitis), prostate glands, urinary tract, and a rare involvement of penis also were reported [42,56–59]. Pericardial TB is another rare manifestation of EPTB reported in Saudi Arabia. Raafa and Mosieri [60] reported in a study conducted during 1981–1989 that 83% of the patients who underwent pericardectomy in an institutional heart center were observed with TB constrictive pericardial disease. However, reports were limited on pericardial TB recently except a few which reported among patients who underwent peritoneal dialysis or were reactive to HIV antigens [33,42,61].

Ocular TB (uveitis, choroidal granuloma), cutaneous TBs, and bone marrow TB were reported previously in the country by several institutions [16,20,57,62–64]. Interestingly, a case of congenital TB was reported as cutaneous disease in the Central province [65]. Other sparingly reported sites of EPTB infections are thyroid glands and kidney [20,61,66,67]. In addition, some other rare sites of TB infection have also been reported, such as the parotid gland, tongue, finger, toe, and nasolacrimal mucosa [68–70]. Miliary and disseminated TB were reported in most of the major provinces of Saudi Arabia [24,33,71].

Established risk factors for EPTB in Saudi Arabia

Very few studies analyzed in detail the risk factors of EPTB in Saudi Arabia. Recently, Memish et al. [21] on an independent analysis reported the major risk factors for EPTB. The report

statistically speculates female gender, young age, non-Saudi origin, and semi-skilled jobs as independent significant risk factors. Several previous clinical studies reported different conditions as predisposing factors among EPTB patients. The most reported underlying conditions were peritoneal dialysis and hemodialysis, which were reported with almost all type of EPTB cases [42,61,72]. The other risk factors which were reported in different studies are HIV, breast cancer, diabetes, chronic liver and renal disease, leukemia, neoplasia/immunosuppression, thrombocytopenic purpura, transplantations, and immunosuppressive therapy and chronic use of steroids [20,33,46,67,72,73]. However, these factors were never analyzed independently to prove their real significance. The role of primary immunodeficiencies (PIDs) to make the host susceptible to TB was clearly observed in different studies [74–76]. Saudi Arabia is reported with the highest incidence (up to 67%) of consanguinity and related immune disorders in the world, which may have serious implications that need to be explored [77,78]. In addition, Saudi Arabia reports with an increased rate of several PIDs such as chronic granulomatous disease (5.2 cases/10⁵ live births), severe combined immunodeficiency syndrome (19 cases/10⁵ live births) which is considered as the highest in the world [79,80]. The consequences of PIDs on various infectious diseases including TB development have been reported previously from different regions including Saudi Arabia [81,82]. Thus, we insist on the fact that the large existence of PIDs in the country may have a direct influence on the large scale consistent reporting of EPTB predominance among the Saudi Arabian population. Thus, exploring the real risk factors of EPTB among Saudi and non-Saudi populations may be beneficial in an improved clinical management of EPTB in the country.

Challenges in EPTB diagnosis

Virtually any organ can be infected by EPTB, thus it has a variety of clinical manifestations that cause delays and difficulties in getting a timely diagnosis. Like any other developing country, Saudi Arabia also faces certain difficulties in the clinical management of EPTB. Advanced clinical infrastructure is under development in many parts of the country. Furthermore, currently major cities only provide the ultimate supports for the diagnosis of crucial and rare cases of EPTB which occasionally limit the access of patients from remote areas. The same as in most of the global region, the differential diagnosis of EPTB is challenging for physicians who are not well trained or experienced in TB management. In addition, the implementation of modern diagnostic technologies to all the possible centers is still under progress. Generally, the established challenges involve the difficulty in obtaining an adequate sample. Aliquoting the sample for various procedures compromises the uniform distribution of microorganisms, pauci-bacillary nature of the clinical samples, presence of inhibitors that undermine the performance of molecular techniques, and the lack of a universal sample processing technique for extra-pulmonary samples [83].

Conclusion

Saudi Arabia faces a considerable challenge from EPTB. The consistent incidence of EPTB in the country is higher than most global regions. Clinically, almost all organs were reported with TB in the country. However, the confounding factors of EPTB including the immunosuppressive conditions related to genetical disorders were never independently analyzed. Therefore, a nationwide study emphasizing the various risk factors of EPTB is warranted.

Conflicts of interest

No conflicts of interest to declare.

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