Extrapulmonary tuberculosis: are statistical reports accurate?

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Abstract: Before discussing the epidemiology of extrapulmonary tuberculosis (EPTB) and particularly urogenital tuberculosis (UGTB), unification of the terminology is necessary. The term 'urogenital tuberculosis' is preferable to 'genitourinary tuberculosis', as renal and urinary tract tuberculosis is more common than genital tuberculosis. Some understand the term 'extrapulmonary tuberculosis' as a specific tuberculosis (TB) lesion of all organs excluding the bronchus, lungs, pleura and intrathoracic bronchopulmonary lymph nodes, but others consider pleural TB as one form of EPTB — and it is a reason for very different proportions in the spectrum of EPTB. Enigmatic tendencies have also been revealed in patients' distribution — in neighbouring regions the incidence rate may differ significantly. Although there is no clear explanation for these tendencies, careful study of the epidemiology of EPTB in different conditions will improve early diagnosis.

Keywords: extrapulmonary, incidence rate, infection, tuberculosis, urogenital

Introduction

Over the centuries many people have died from tuberculosis (TB), which now accounts for about 5000 human deaths daily [WHO, 2002]. However, there are some positive tendencies in the epidemiology. In 2009 the World Health Organization (WHO) reported about 9.4 million incident cases of TB, with approximately a third of the world's total population being infected, while only 8.6 million people fell ill with TB in 2012, including 1.1 million cases among people with human immunodeficiency virus (HIV). But according to WHO reports in 2012, 1.3 million people died, an estimated 450,000 people developed multidrug-resistant TB globally (MDR-TB) and there were an estimated 170,000 deaths from MDR-TB [WHO, 2012].

TB is a multisystem disease with myriad presentations and manifestations; it can affect any organ or tissue, excluding only the hair and nails. While the WHO has recognized TB as a global problem, this applies to TB as a whole and principally pulmonary TB (PTB). TB (both pulmonary and extrapulmonary) leads to male and female infertility [Lenk and Schroeder, 2001; Scherban and Kulchavenya, 2008], and in some studies sexual transmission of TB has been described [Scherban and Kulchavenya, 2008].

One of the reasons for the incorrect estimation of the epidemiology of extrapulmonary TB (EPTB) is a difference in terminology. Some authors consider EPTB as TB of any organ, excluding exactly bronchopulmonary lesions, and so they consider pleural TB to be a form of EPTB too. Others think that the division of the lung and their covering pleura into two separate organs is incorrect and ascribe both organs to PTB, and instead of EPTB use the terms extrathoracic TB (ETTB) or extrarespiratory TB, which merge the TB of all organs except thoracic ones. This is one reason for confusion with the proportions of EPTB/ETTB forms.

Methods

A search of Medline/PubMed with the keywords 'epidemiology, extrapulmonary, tuberculosis, urogenital' was made and the most recent articles analysed for the incidence rate, prevalence and spectrum of EPTB.

Results

The Medline/PubMed search with the keywords 'epidemiology, tuberculosis, extrapulmonary, urogenital' resulted in only six titles. The keywords 'epidemiology, extrapulmonary, tuberculosis' gave a total of 963 titles.

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Significance of extrapulmonary tuberculosis

The incidence of TB is declining in the European Union (EU)/European Economic Area (EEA) but remains a significant public health problem. Although PTB accounts for the majority of cases and is the main transmissible form of the disease, EPTB also contributes to the burden of disease and does not receive specific attention in international control strategies.

Sandgren and colleagues made a descriptive analysis to assess the burden and trends of EPTB in EU/EEA countries. During 2002 to 2011, 167,652 cases of EPTB were reported by the 30 Member States. EPTB accounted for 19.3% of all notified cases, ranging from 5.8% to 44.4% among Member States. Overall, TB notification rates decreased in 2002–2011 due to a decrease in PTB. Notification rates of EPTB remained stable at 3.4 per 100,000 in 2002 and 3.2 per 100,000 in 2011. Thus the proportion of EPTB increased from 16.4% in 2002 to 22.4% in 2011. Of all EPTB cases reported during 2002–2011, 37.9% were foreign-born or citizens of another country, 33.7% were culture-confirmed and the overall treatment success was 81.4%. Thus a significant percentage of notified TB cases are extrapulmonary, and in contrast to PTB, EPTB rates are not decreasing [Sandgren *et al.* 2013].

Solovic and colleagues reported the percentage of EPTB cases among TB in the EU ranged from 4% to 48%. This difference might be explained by differences in risk factors for EPTB or challenges in diagnosis [Solovic *et al.* 2013]. Mazza-Stalder and colleagues considered the share of EPTB was increasing, at 20–40%. In 1984 EPTB was a major health problem in Australia, where 24.3% of all new TB notifications were extrapulmonary in origin [Mazza-Stalder *et al.* 2012]. The commonest sites of disease were the lymph nodes, urogenital tract, pleura and bone [Dwyer *et al.* 1987]. By the 1980s, the availability of anti-TB chemotherapy had reduced the incidence and prevalence of tuberculosis, but changing patterns of population emigration and the development of large pools of immune-compromised individuals had reversed the downward trend of tuberculosis [Levashev *et al.* 2006].

In the past century in Oklahoma, USA, a greater proportion of newly diagnosed cases of EPTB occurred in nonwhites. This was especially true of TB meningitis, TB lymphadenitis and miliary TB [Snider, 1975]. At that time EPTB was frequent in Africa and had a great severity due to delayed diagnosis and multifocal forms [Aubry *et al.* 1979]. At Boston, USA, in the 1980s EPTB represented 4.5% of all new cases of active TB and tended to occur in older patients. Sites of involvement included lymph nodes, genitourinary tract, bone and articular sites, the meninges, peritoneum, adrenal glands, pericardium, and miscellaneous sites, in that order [Alvarez and McCabe, 1984].

Among the 2161 TB cases diagnosed in Spain between 1991 and 2008, 1186 were PTB and 705 EPTB. The number of EPTB cases decreased more slowly than PTB. EPTB increased from 30.6% of cases in 1991–1996 to 37.6% in 2003–2008 (lymphatic sites increased by 27%) [García-Rodríguez *et al.* 2011]. The authors concluded, that whilst there has been a reduction in the overall incidence of TB, the proportion of EPTB had increased. This could be explained by an increase in life expectancy and the predominance of women in the population, and by a decline in Bacillus Calmette-Guérin (BCG) vaccinated patients.

In a retrospective study, Lin and colleagues compared patients with EPTB and PTB in southern Taiwan [Lin *et al.* 2009]. They found that, among a total of 766 TB patients, EPTB was diagnosed in 102 (13.3%) and PTB in 664 (86.7%); 19.6% of EPTB patients also had PTB. The most frequently involved EPTB site was the bone and joints (24.5%). The incidence of EPTB *versus* PTB decreased significantly for each decade increase in patient age. Multivariate logistic regression analysis showed that being female, not being diabetic, having end-stage renal disease and not smoking were independent risk factors for EPTB [Lin *et al.* 2009].

EPTB had an increasing rate in Turkey in 2001–2007 but the reason remains largely unknown [Gunal *et al.* 2011].

Spectrum of EPTB

Navarro-Vilasaró and colleagues reported that urogenital TB (UGTB) was the third most frequent extrapulmonary tuberculous infection, following pleural and nodal involvement in Spain in 2008 [Navarro-Vilasaró *et al.* 2008]. In the opinion of Abbara and Davidson, UGTB is the second most common form of EPPB, with more than 90% of cases occurring in developing countries [Abbara and Davidson, 2011].

Although UGTB in all countries is considered a severe problem, Goth and Joshi listed this form of EPTB as 'others'. Among 198 EPTB patients they revealed pleural TB in 87 and lymph node TB in 97; generalized EPTB was diagnosed in seven patients as well as all remaining forms, including UGTB, in another seven [Goth and Joshi, 2004].

Within the last decade, the spectrum of EPTB in Siberia has changed significantly [Kulchavenya *et al*. 2013]. TB of the central nervous system almost doubled from 4.9% to 8.7%, mostly due to comorbidity with HIV. Bone and joint TB increased by about half, from 20.3% to 34.5%, and among this group TB spondylitis with neurological disorders predominated — the most debilitating form of the disease. The proportion of UGTB decreased from 42.9% to 31.7%. In contrast, there was a decrease of peripheral lymph node TB from 16.7% in 1999 to 11.2% in 2011, with fistulous disease still frequent. At the end of the last century ocular TB accounted for 7.4% and in 2008 (in 2009 listed in 'others') for 4.4% of the patients with EPTB. Accordingly, in 1999 'other' forms of TB accounted for 7.8% and in 2009 for 15.8% (in 2011, 13.9%). The increase is partly due to inclusion of patients with ocular TB in this group, and partly due to better diagnosis of TB of the skin, abdominal organs, breast, etc. [Kulchavenya *et al*. 2013].

In Nepal, common sites for EPTB are the lymph nodes (42.6%) and peritoneum and/or intestines (14.8%) [Sreeramareddy *et al*. 2008]. In Turkey in 2001–2007 the most commonly seen two types of EPTB were genitourinary TB (27.2%) and meningeal TB (19.4%). TB of bone/joints, pleura, lymph nodes, skin, and peritoneal TB occurred at a frequency ranging from 9.7% to 10.7% [Gunal *et al*. 2011]. Other authors from the same region reported slightly different data. Among 141 EPTB patients in Istanbul over 7 years, meningeal TB accounted for 23%, and TB lymphadenitis 21%. Other types of EPTB were skeletal, miliary, peritoneal, abscess, UGTB, cutaneous and gastrointestinal involvement which ranged between 18% and 1%. Mean age was 42 and female/male ratio was almost equal [Sevgi *et al*. 2013].

In 2009 almost a fifth of TB cases in the United States were extrapulmonary; unexplained slower annual case count decreases have occurred in EPTB compared with annual case count decreases in PTB cases. From 1993 to 2006, among 253,299 cases, 73.6% were PTB and 18.7% were EPTB, including lymphatic (40.4%), pleural (19.8%), bone and/or joint (11.3%), genitourinary (6.5%), meningeal (5.4%), peritoneal (4.9%) and unclassified EPTB (11.8%) cases [Peto *et al*. 2009]. In France in 2012 the most frequent clinical presentations of EPTB were lymphadenitis, pleuritis and osteoarticular TB. Peritoneal, urogenital or meningeal TB were less frequent, and their diagnosis was often difficult due to the wide differential diagnosis and the low sensitivity of diagnostic tests including cultures and genetic amplification tests [Mazza-Stalder *et al*. 2012]. In some countries the rate of growth of bone and joint TB has reached the leading position among EPTB [Kulchavenya *et al*. 2013]. Location of TB on the spine remains the most common form of skeletal TB, representing 62.2% of all osteoarticulary locations [Didilescu and Tănăsescu, 2012; Wiler *et al*. 2010]. The skeletal form was responsible for 3% of the total number of cases, with 50% of these due to spinal tuberculosis [Wiler *et al*. 2010].

In the Moscow region, the frequency of UGTB increased three-fold between 1996 and 2002; 49.4% of patients were revealed late, with complications [Batyrov *et al*. 2004]. Tarasenko and colleagues noted that 60% of new UGTB patients had destructive cavernous forms [kidney tuberculosis (KTB) level 3–4] and 44% had disability [Tarasenko *et al*. 2011]. In Bashkortostan, surprisingly there was the lowest incidence rate of UGTB in Russia. There, female genital TB (FGTB) prevailed in 1998–2006, but from 2007, bone and joint TB was the leader among EPTB (29.5%), followed by FGTB (27.4%), then lymphonodal TB (17.9%). The share of UGTB was 9.5% only [Tuktamysheva *et al*. 2011].

EPTB comprises 20–25% of the total burden of the disease, in which UGTB is 4% according to a report by Singh and colleagues [Singh *et al*. 2011]. It has been well described that the urogenital system is a common site of EPTB in adults, but the true incidence of UGTB is less clear, and reports have varied from 4% to 73% [Singh *et al*. 2011].

UGTB
Before anti-TB drugs were created, the prevalence of UGTB was huge. Every fifth urological in-patient had UGTB and more than a third of all pyonephrosis was due to TB. In that era, it

was mostly young people who got sick with TB, equally male and female [Marion, 1931]. Now UGTB is the most common form among EPTB in countries with epidemic TB, but in countries with low incidence rates, UGTB is revealed to be rarer [Kulchavenya *et al.* 2012]. In developed countries, between 2 and 10% of patients with PTB also have UGTB; in developing countries this proportion increases up to 15–20% [Figueiredo and Lucon, 2008]. In developed countries, the genitourinary manifestation is responsible for over 40% of extrapulmonary cases [Bacci *et al.* 2012]. In Europe UGTB is diagnosed more often in migrants than in the indigenous population [Lenk, 2011]. About 20% of patients cured of PTB had EPTB later, mostly UGTB [Lenk and Schroeder, 2001]. Renal involvement in TB can be part of a disseminated infection or a localized genitourinary disease. Renal involvement by TB infection is underdiagnosed in most health care centres [Daher Ede *et al.* 2013].

In 2006 a programme on the fight against TB was begun in the Stavropol region of Russia. A special algorithm for the early diagnosis of UGTB was implemented in general practice clinics; seminars on clinical features and laboratory diagnosis were organized. As result, the share of UGTB among EPTB increased from 31% in 2005 to 46% in 2009. At a glance this looks as a worsening of the situation — but the spectrum of newly revealed UGTB patients changed significantly. Predominantly KTB level 1–2 was diagnosed, whereas earlier more than half of patients had KTB level 3–4 [Urtenov and Tarasenko, 2011].

To estimate the prevalence and spectrum of KTB in children and teenagers in an epidemic region, the histories of 131 patients with UGTB in Siberia and 819 UGTB patients in Kyrgyzstan were reviewed [Mukanbaev and Kulchavenya, 2013]. Among them, cases of children and teenagers were selected and analysed. In Siberia only two children and one teenager with UGTB were revealed (2.3% among all the cohort of UGTB); all had first level KTB inflammation — TB of the parenchyma. All children were asymptomatic and were diagnosed because they had contact with TB infection. A 17-year old girl had a long history of recurrent urinary tract infection (UTI), and as antibacterial therapy was insufficiently effective, UGTB was suspected and her urine was cultured. All children and teenagers had positive cultures in urine; *M. tuberculosis* (Mtb)

was sensitive to all anti-TB drugs. All had isolated KTB [Mukanbaev and Kulchavenya, 2013].

In Kyrgyzstan 17 children and 21 teenagers were diagnosed with UGTB (4.6% of all UGTB patients). All had a long history, underwent surgical interventions, six had fistulae, and two teenagers had microcystis (bladder TB grade 4). First level KTB was diagnosed in two children only, second level KTB in four patients, third level KTB in eight, and fourth level KTB in three. One boy had also genital TB. Thus, 64.5% patients were revealed in the late complicated stage. Only one patient had isolated KTB; in others lymph nodal, skeletal or PTB were diagnosed. Mtb in urine was found in 11 children, plus growth in sputum in three. Among the 21 teenagers, complicated UGTB was diagnosed in 11 patients (52.4%). Mtb was found in nine adolescents and diagnosis in the rest was confirmed by histology. Generalized TB was found in 17 patients. Surgery was performed in 11 children (64.7%) and 16 teenagers (76.2%) [Mukanbaev and Kulchavenya, 2013]. Thus, late diagnosis of UGTB predominated in Kyrgyzstan; in Siberia all children and teenagers were revealed in time and cured by chemotherapy, without surgery. Medical services should be improved in regions with severe epidemic TB.

Vietnam is one of 22 countries with the highest prevalence of TB — 100 cases per 100,000 inhabitants [Chau Giang, 2004]. Between 1989 and 1994, 167 new UGTB patients were revealed; 43.7% were aged 30 to 50 years. UGTB only was diagnosed in 77.2%, the combination of PTB and UGTB was found in 19.2%, and UGTB and other forms of EPTB in 3.5% of patients. KTB was diagnosed in 13.2%, TB of the ureter was diagnosed in 25.7%, and bladder TB in 26.3%; 27% had MGTB [Nguyen Phuc Cam *et al.* 2009].

A total of 131 historic cases of UGTB revealed in 2009–2011 in Siberia were analysed by Zhukova and colleagues [Zhukova *et al.* 2013]. The most common form was KTB (74.8%). Isolated KTB was found more often in women (56.8%). Middle-aged and elderly patients were more often revealed in the cavernous stage of KTB; young patients had small forms. Among all UGTB patients, an asymptomatic course was found in 12.2%, and among KTB patients in 15.9%. Every third patient complained of flank

Table 1. Comparison of the spectrum of extrapulmonary tuberculosis (%).

Reference	Location	Pleural TB	Neural TB	UGTB	Bone and joints TB	Lymph node TB	Abdominal TB	Others
Peto *et al.* [2009]	USA	19.8	5.4	6.5	11.3	40.4	4.9	11.8
Kulchavenya *et al.* [2013]	Russia, Siberia, 1999	n/a	4.9	42.9	20.3	16.7	n/a	7.8
Kulchavenya *et al.* [2013]	Russia, Siberia, 2011	n/a	8.7	31.7	34.5	11.2	n/a	13.9
Tuktamysheva *et al.* [2011]	Russia, Bashkortostan	n/a	n/a	36.9	29.5	17.9	n/a	n/a
Gunal *et al.* [2011]	Turkey, Malatya	n/a	19.4	27.2	n/a	n/a	n/a	n/a
Sevgi *et al.* [2013]	Turkey, Istanbul	n/a	23.0	n/a	n/a	21.0	n/a	n/a
Singh *et al.* [2011]	Germany Nepal	n/a	14.3	8.6	20.0	37.1	5.7	n/a
Sreeramareddy *et al.* [2008]		n/a	n/a	n/a	n/a	42.6	14.8	n/a

n/a, not applicable; TB, tuberculosis; UGTB, urogenital tuberculosis.

pain and dysuria (35.2% and 39.8%, respectively), 17% presented with toxicity symptoms, 9.1% renal colic, and 7.9% gross haematuria. Mtb in urine was found in 31.8% in all levels of isolated KTB. UGTB has no specific symptoms; even sterile pyuria occurs only in 25%. The authors concluded that all urogenital tract infections should be suspected to be UGTB in patients living in a region with a high incidence rate, who had contact with tuberculosis infection, and who had a recurrent course of the disease, resistant to standard therapy [Zhukova *et al.* 2013].

Table 1 shows a summary of the spectrum EPTB in different regions. The huge and not credible differences in the figures emphasise the problem of estimation in statistical reports. We cannot compare figures of the incidence and spectrum until all authors agree a unique terminology in EPTB.

Different prevalence of UGTB

Fritjofsson and Kollberg analysed the incidence of UGTB in Sweden, and found 1–4 new cases of UGTB per 100,000 inhabitants per year. The incidence of UGTB showed geographical variation within the country [Fritjofsson and Kollberg, 1973]. The same situation was found in Hungary, where the number of new cases in one province was as high as 10 per 100,000 inhabitants per year, while in another part of the country only 2–3 cases were reported. Unexplainably different prevalences of UGTB in neighbouring regions have also been found in Siberia [Kulchavenya and Krasnov, 2012] — a predominance in the number of EPTB cases in one region relative to another within 20–50 km — and there is currently no clear reason for this phenomenon.

Age–gender features of UGTB patients

Some authors have found that UGTB affects more men than women [Daher Ede *et al.* 2013; Benchekroun *et al.* 1998; El Khader *et al.* 1997; Tanthanuch *et al.* 2010]; others exactly the contrary [Mazza-Stalder *et al.* 2012; Aubry *et al.* 1979; García-Rodríguez *et al.* 2011; Singh *et al.* 2011]. It would seem that UGTB, as with any other kidney disease, should be seen more often in female patients because menses, gravidity and inflammation of female genitals may hinder the passage of urine. Urinary stasis creates the possibility of fixation of Mtb to the urothelium, and, thus, of developing renal TB.

For a long time women were predominant among urological TB patients in Siberia, but in 2009 the gender difference disappeared, and in 2010 the proportion of men to women was 1.0:0.8 [Kulchavenya and Krasnov, 2010]. In Japan the male to female score has been reported to be 2:1 among UGTB patients as a whole, but among KTB patients the gender difference was absent [Noguchi *et al.* 1986]. In Vietnam the sex proportion was 1:1.8 in favour of women [Nguyen Phuc Cam *et al.* 2009]. Analysis of age–gender proportions showed that girls were ill more often than boys — as well as old women [Noguchi *et al.* 1986].

On the whole, the proportion of men to women among EPTB patients depends on the form of the disease. Concerning UGTB, superiority of female patients is found when UGTB includes both urological and gynecological TB, although in some regions there has also been female superiority among urological TB.

Age–gender correlation in KTB has been estimated by Zhukova and colleagues [Zhukova *et al.* 2013]. KTB levels 2–3 were diagnosed in

women 1.7–2.1 times more often than in men; at KTB level 1 and KTB level 4 there was insignificant predomination of male patients. The age–clinical distribution of nephrotuberculosis showed a lower level of KTB in younger patients. The predominance of middle-aged and elderly patients among cavernous and policavernous KTB mirrors the pathogenesis of this disease — a slow progressive course under the mask of another disease [Zhukova *et al*. 2013].

Cases of renal tuberculosis constituted 0.89% of urological inpatients in China over a duration of 11 years from 2000 to 2010. The incidence rates were higher in 40–60 years old patients (45.61%); 48% of the patients were farmers or unemployed [Huang *et al*. 2013]. Among the 64 patients, 38 (59.4%) were male with a mean age of 60.3 ± 16.1 years old. The overall mortality rate was 26.2%. Poor prognostic factors included age over 65 years [hazard ratio (HR) 4.03], cardiovascular disease (HR 5.96), receiving steroids (HR 10.16) and not being treated (HR 4.81) [Hsu *et al*. 2011]. Urinary tract TB was more common in males, with a male/female ratio of 1.3:1. In contrast, Hsieh and colleagues more often diagnosed UGTB in female patients [Hsieh *et al*. 2006].

Female genital tuberculosis

One more problem in the real estimation of statistical reports on EPTB is female genital tuberculosis (FGTB). In fact FGTB is a part of UGTB, although some authors separate out FGTB as a special form.

In eastern Sudan, of the 2778 women presenting with various gynaecologic symptoms, 44 suspected cases of FGTB were identified. Granulomatous tissue reactions were observed in 25 of the suspected FGTB cases, yielding an incidence of 0.9%. The majority (80%) of these patients presented with chronic pelvic and lower abdominal pain; however, 68.0% presented with pelvic mass, cyst and/or abscess; 48.0% had dyspareunia; 40.0% were infertile; 28% had menstrual dysfunction; 20.0% had dysmenorrhea; and 4.0% experienced postmenopausal bleeding. Body mass index, residence and educational level were significantly different between women diagnosed with FGTB and those where FGTB was excluded ($p = 0.02$, 0.03 and 0.01, respectively). However, no significant differences were found in age and Bacillus Calmette-Guérin vaccination status [Ali and Abdallah, 2012].

Over a period of 30 months (July 1986 to December 1988), 57 cases of FGTB were diagnosed at Tygerberg Hospital in South Africa [Margolis *et al*. 1992]. Of these cases, 40 were diagnosed as a result of routine screening in 650 patients who presented with infertility and the other 17 were diagnosed in patients admitted to the gynaecological wards. The prevalence in patients presenting with infertility was 6.15%. The commonest gynaecological presenting symptom was infertility (73.7%). Dysmenorrhoea in 29.8% and deep dyspareunia in 12.3% were the only other frequently occurring gynaecological symptoms. Menstruation was normal in 50 patients (87.7%) [Margolis *et al*. 1992].

In another study, FGTB patients presented with infertility (70%), pelvic/abdominal pain (55%) and menstrual disturbances (25%). Tuberculosis involved the endometrium in 55.88% of the 68 cases, the tubes in 23.53%, the ovaries in 14.71% and the cervix in 5.88% [Mondal and Dutta, 2009]. In a 15-year retrospective study of 110 cases in eastern India, a total of 92 patients with FGTB were included. Patients presented with infertility (70%), pelvic/abdominal pain (55%) and menstrual disturbances (25%). FGTB involved the vulva (2), vagina (1), cervix (1), endometrium (66), fallopian tubes (24) and in 12 patients the ovaries [Mondal, 2013].

A total of 85 women with FGTB who underwent diagnostic laparoscopy for infertility or chronic pelvic pain were enrolled in the retrospective study in India. Most women were of poor socioeconomic status (68.1%). Past history of TB was seen in 34.1% of the women with PTB in 22.35% and EPTB in 11.7%. Most women presented with infertility (90.6%: primary 72.9% and secondary 17.6%) while the rest had chronic pelvic pain (9.4%). Diagnosis of genital TB was made by histopathological evidence of TB granuloma in 18.8%, positive polymerase chain reaction (PCR) in 64.7% and laparoscopic findings of genital TB in 47.1%. The various findings on laparoscopy were tubercles on the peritoneum (12.9%) or ovary (1.2%), tubovarian masses (7.1%), caseous nodules (5.8%), and encysted ascitis in 7.1% women. Various grades of pelvic adhesions were seen in 65.8% of the women [Sharma *et al*. 2008].

A retrospective clinicopathological study of 1548 cases of FGTB between 1940 and 2011 has been

conducted in Turkey. The mean age of the cases was 29.49 years. Involvement of the endometrium was noted in 1073 cases, the fallopian tubes in 164 cases and the cervix in 157 cases; 154 had multiple organ involvement. Clinically, 115 cases (7.4%) were diagnosed as having primary infertility and 12 cases (0.8%) as having secondary infertility. There was a coexistent carcinoma in 1.5% of the cases. Peritoneal tuberculosis in 21 cases and tuberculous lymphadenitis in seven cases were also seen [Türkmen *et al.* 2012].

Nonclassified and rare forms of EPTB

The group 'others' may include very rare and, so very difficult to diagnose cases. Stojanović and colleagues recently described a case of primary nasal TB. A 30-year-old man presented with shortness of breath through the nose and periodic headaches. Clinical examination showed signs of chronic rhinitis, with slight granular changes of nasal septal mucosa. Laboratory analyses were within the reference ranges. Nasal and throat swabs for bacteria and fungi were normal. Skin allergy testing to standard inhaled allergens was positive. Computer rhinomanometry showed increased nasal resistance at medium difficulty level, on the right. Radiography of paranasal sinuses indicated chronic polysinusitis on the right. Anti-allergy therapy was prescribed. The patient came for checkup after a month with subjective deterioration. Nasal endoscopy revealed the presence of dark red infiltrates with 3 mm diameter on nasal septal mucosa, dominantly on the right, with small greyish nodules. TB was established on the basis of the results of nasal mucosa biopsy [Stojanović *et al.* 2013].

A similar case was surveyed by Sanehi and colleagues. They revealed tuberculosis of the frontal and maxillary sinuses in a 68 years-old male, who presented with a swelling above the left medial canthus, but with no other eye or nasal complaints. Clinical and radiological findings on the initial evaluation suggested that the patient had left frontal mucocoele with bilateral maxillary haziness. Diagnosis was established on biopsy and subsequent Ziehl–Nielsen (ZN) staining of nasal swabs and tuberculin skin test. Later chest X-ray examination was suggestive of pulmonary tuberculosis, which was the primary cause [Sanehi *et al.* 2008].

Dahiya and colleagues reported a case of duodenal tuberculosis, in which the patient presented with upper gastrointestinal symptoms. There was evidence of obstruction in the third part of the duodenum (D3) on oesophagogastroendoscopy, barium meal follow through and computer tomography scan of the abdomen. On exploration there was thickening of D3 and D4, causing luminal obstruction. Resection of the stricturous segment with end-to-side duodenojejunostomy was performed. A biopsy of the diseased segment revealed TB [Dahiya *et al.* 2013].

A total of five patients with gastroduodenal tuberculosis was revealed in a study in India. The most common presentation was vomiting followed by failure to thrive and weight loss; two patients had abdominal pain. Biopsy of mesenteric lymph node was possible in two cases [Upadhyaya *et al.* 2013].

An exotic site of EPTB with chronic ulceration of the tongue and laryngitis has been described — but actually it was a first clinical sign of asymptomatic pulmonary tuberculosis [Sah *et al.* 1999].

A rare case of tuberculosis of the renal artery causing renovascular arterial hypertension was described by Bouziane and colleagues. They reported a 17-year-old patient presenting with renovascular arterial hypertension, revealed thanks to the discovery of an occlusion of the right renal artery in a Duplex scan. During the intervention, the observation of pararenal and mesenteric tuberculous polyadenopathy suggested the same kind of lesion at the level of the occluded renal artery. Once anti-TB treatment had been carried out, the right renal artery was revascularized with a right iliorenal bypass using a reversed internal saphenous vein. The postoperative course was uneventful, with an 18-month follow up. Arterial pressure was normal without antihypertensive treatment and the bypass was patent [Bouziane *et al.* 2009].

Bouchikhi and colleagues found a rare case of urogenital tuberculosis in a man revealed by urethral narrowing and multiple urethroscrotal fistulas. The patient, a Moroccan man, was 40 years old. He presented with dysuria, purulent discharge and a meatic penoscrotal fistula. A retrograde and voiding urethrocystography revealed an extended narrowing of the whole anterior urethra associated with multiple fistulous portions toward the scrotum and perineum. His condition was thought to be a nonspecific sclero-inflammatory urethral stricture with complicating fistulas, and the patient underwent

a urethroplasty. The wound healing was delayed and associated with the persistence of fistulas extending into the corpus cavernosum with purulent discharge. It was the reason for suspecting TB; multiple biopsies were then performed on the periurethral tissue and fistula tracts, and the histological examination confirmed the diagnosis [Bouchikhi *et al.* 2013].

Discussion

EPTB, despite the relatively lower number of patients, plays significant role in both phthisiatry and urology. This is mostly because of greater frequency of fatal complications, more severe decrease in quality of life and closer association with HIV infection than PTB. Analysis of the literature has shown a significant underdiagnosis of EPTB patients.

The risk of becoming sick with TB is significantly higher in patients with renal failure and in comorbidity with HIV infection. Anomalies of the urogenital tract, chronic renal disease and renal transplantation also increase this risk. Late diagnosis of EPTB leads to irreversible kidney failure, even in a nonimmunocompromised patient [Gusmão *et al.* 1998; Kulchavenya and Muzyko, 2007; Rabbani *et al.* 2011; Zümrütdal *et al.* 2011].

The lack of agreement regarding terminology also hampers estimation of the real epidemiological situation in EPTB and UGTB. We have no real picture of EPTB due to defects in diagnosis, poor awareness of this disease, difficulties in identification of the infectious agent, absence of pathognomonic features, etc. However, any attempt to estimate the prevalence of EPTB is useful.

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