Disseminated TB: still being missed and misunderstood

There has been a scarcity of literature on the epidemiology of disseminated TB in recent years. Although it is considered relatively uncommon, representing only 2–3% of all TB cases, the true extent of disseminated TB worldwide is unknown.\(^1,2\) The myriad of non-specific and variable presentations frequently leads to a delay in diagnosis and a resulting high mortality rate, despite the availability of effective treatment.\(^2,3\) It is suspected that the emergence of HIV, the expansion of organ transplantation programmes, and the increasingly widespread use of immunosuppressive therapies have changed the epidemiology of disseminated TB.\(^3\) Disseminated TB occurs because of the inadequacy of host defenses in containing the infection, allowing the organism to proliferate and disseminate throughout the body. Multi-organ involvement is thought to be much more common than is recognised because once the organism is identified in any specimen, other sites may not be sampled.\(^4\)

In this issue of the Journal, Saikia et al. have published an autopsy study of disseminated TB.\(^5\) The authors recognise the importance of disseminated TB and aimed to characterise its frequency among inpatient deaths at a tertiary care centre in India. Among 4,219 post-neonatal autopsies performed over 29 years, they found a total of 243 (5.8%) cases of disseminated TB. The diagnostic challenge of disseminated TB is highlighted in this study, where, in one third of cases, a diagnosis of TB was not suspected antemortem. Similar findings were reported in a systematic review and meta-analysis by Gupta et al.,\(^6\) who found a pooled proportion of disseminated disease to be 87.9% among autopsies performed in HIV-infected adults across 12 studies, although disseminated disease was not formally defined. TB also remained undiagnosed at death in 45.8% of cases, which echoed the worrisome findings from Saikia et al.\(^5,6\) The alarming number of disseminated TB cases among inpatient deaths, particularly those who were not diagnosed antemortem, should raise awareness of the need to have a higher threshold of suspicion of the disease and recognition of its high morbidity and mortality.

Disseminated TB can present in a myriad of ways, with non-specific clinical symptoms, which makes a prompt diagnosis a difficult task. Chest X-ray patterns may not always display classic miliary disease (Figure). Multisystem TB involvement can often mimic malignancy, sarcoidosis, lymphoproliferative disorders and/or fungal diseases. Thus, having a high index of suspicion is critical, in both high TB incidence settings, as well as low TB incidence settings, where it is expected to be more challenging to diagnose due to the decline in disease prevalence.\(^7\) Unrecognised TB among hospitalised patients poses serious infection control and occupational health and safety risks. Institution of early anti-TB treatment, once specimens have been collected and before a diagnosis is confirmed, is also critical in preventing morbidity and death.\(^1\) The authors reported that only 143 (58.3%) cases were receiving anti-TB treatment. This result is in line with findings from another autopsy study by Karat et al. that found only 10 out of 16 (62.5%) individuals with advanced HIV and autopsy evidence of TB were started on TB treatment antemortem.\(^8\) Previous studies have shown that treatment delays in disseminated TB by mere days can contribute to a high mortality rate.\(^9\) These findings highlight the need to improve recognition and prompt treatment of disseminated TB globally. Unfortunately, in the short term, COVID-19 may have added to the challenge of diagnosing disseminated TB. Stringent lockdowns and overwhelmed healthcare systems have caused disruption in routine TB services, which can lead to further delays in diagnosis and ongoing transmission.\(^10,11\)

Saikia et al.’s 29-year review of a large number of autopsies in a single tertiary centre in a (presumed) low HIV and high TB incidence setting serves to underscore the utility of autopsy studies in general.\(^5\) Autopsy remains the gold standard method of ascertaining cause of death, and not only highlighted the significant burden of disseminated TB among inpatient deaths, but also the considerable proportion of undiagnosed cases. In low TB incidence countries, post-mortems are now rarely performed. However, even in such settings, it is not unheard of for disseminated TB to be diagnosed post-mortem. Long et al. found that 14% of disseminated TB cases in a Canadian province were not diagnosed until post-mortem.\(^2\) The discordance between pre-mortem and post-mortem diagnoses is perhaps less marked in resource-rich settings with greater access to more sophisticated laboratory and radiological investigations. However, in resource-constrained settings, stronger clinical awareness and appreciation of risk factors for disseminated TB are likely warranted in order to achieve TB elimination.

Autopsy studies also play a key role in determining
the frequency of disseminated TB as a cause of death, especially among immunocompromised patients, such as those receiving transplant immunosuppression or those with comorbidities receiving systemic corticosteroids or tumour necrosis factor (TNF) inhibitors. In countries with low TB incidence, immunosuppression-related reactivation is not uncommonly seen in migrant populations with remotely acquired latent TB infection (LTBI). Whether the emergence of HIV and widespread use of immunosuppressive therapies has influenced the epidemiology of disseminated TB in general is yet to be determined. Saikia et al.'s study reported a decline in the number of disseminated TB cases among inpatient deaths, from 125 (9.8%) in 1988–1997 to 75 (4.6%) in 1998–2007 and 43 (3.3%) in 2008–2016. This may be related to the implementation of the national TB programme in India in 1993.5 Conflicting data showing an increase in post-mortem prevalence of both TB and disseminated TB have been reported elsewhere in the literature. Severe immunosuppression may interfere with the ability to form caseating granuloma, making it harder to have a histopathological diagnosis. As yet unclear, is the role of the pathogen itself; there may be strain-related virulence factors that predispose to dissemination.

Autopsy studies are, however, not without limitations and often suffer from selection bias so may not provide accurate prevalence estimates. As reported in other autopsy studies, patient selection for autopsy might potentially enrich the proportion with TB in those studied. As a tertiary referral centre, the series described by Saikia et al. may not be representative of the actual population contribution of disseminated TB. As the authors astutely point out, patients often seek treatment at peripheral centres, and there may be a delay in diagnosis by the time patients present at the tertiary referral centre. There can also be a number of different factors such as access to healthcare, health infrastructure, socioeconomic and behavioral factors that affect whether a patient is hospitalised. Thus, the conclusions from this study cannot be generalised to other levels of care. Also, more work is needed to establish the optimum use of molecular techniques in post-mortem specimens. A post-mortem study by Garcia-Basteiro et al. reported that the use of highly sensitive molecular testing in diagnostic autopsies may contribute to identifying TB cases that would have otherwise been missed. Polymerase chain reaction is more reliable than histopathological studies for the detection of TB in liver and bone marrow biopsy specimens. Several studies have also emphasised the importance of performing autopsies systematically to avoid bias. In the study by Saikia et al. not all organs were sampled, nor were the autopsies performed in their entirety in all cases. A gross examination was performed, and depending on the lesions identified, random sampling from different organs was undertaken. The limitations of this methodology constitute a potential bias and raises the possibility of missed diagnoses. While this study has many redeeming features, a key limitation is the lack of available antemortem radiological, laboratory and microbiological data. Comparing the clinical information of those patients who were/were not diagnosed with TB antemortem may provide diagnostic clues as to key clinical features or laboratory testing which will aid in the diagnosis of disseminated TB. Moreover, a post-mortem diagnosis of disseminated TB could be more clearly defined. It is unclear whether the post-mortem diagnosis was based solely on histopathological appearances with special stains for acid-fast bacilli, and/or whether molecular testing was performed systematically in all cases (from 2012 onward). There is a compelling need for a more standardised case definition of a disseminated TB
case in clinical and autopsy studies to relate findings to other published work.

Further studies in this area, employing a systematic approach and use of highly sensitive molecular techniques, are needed to increase clarity and minimise bias. The study by Saikia et al. raises awareness of the significant burden of disseminated TB; however, there are still some questions left unanswered. A future study that includes systematic data collection and reporting with a standardised case definition would be powerful means of shedding light on the true burden of disseminated TB.

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