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Bone graft tuberculosis outbreak in USA: Is it a concern in India?

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ABSTRACT

Globally, 25% of the population is infected with tuberculosis, which poses a leading cause of death worldwide. The transmission of tuberculosis (TB) during organ transplant is reported in the literature whereas only one report has been published on the transmission of TB, during bone allograft transplantation. In the US, in May 2021, an outbreak of TB occurred in patients undergoing spine surgery with bone allograft. This bone graft was retrieved from 80 years deceased donor with latent TB, which was not diagnosed earlier. The recipients were started with a long course of anti-tuberculous drugs. This review narrates the pathway of TB spread among transplant recipients and the strategies to be followed while performing organ or tissue transplantation.

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1. Introduction

Tuberculosis (TB) is a communicable disease, caused by *Mycobacterium tuberculosis*, and is the 13th leading cause of death worldwide.[1] A total of 25% of the world population is infected with TB, which is curable and preventable. Globally, every year almost 2 to 3 million human organ and tissue allografts are transplanted.[2] For solid organ transplant, the rate of infection transmission from donor to recipients is less than 1% whereas, for allograft tissue transplant, the rate of infection transmission is unknown.[2] World Health Assembly (WHA) directs the member states "to implement the policies for effective procurement, processing, and transplantation of human cells, tissues, and organs, including ensuring accountability for human material for transplantation and its traceability."[3] In this review, we throw limelight on the outbreak of allograft-derived TB in spine surgeries in the US in 2021.

2. TB transmission in organ transplant

Various infections are transmitted through solid organ transplantation namely HIV, Hepatitis B and C, CMV, EBV, and a few bacterial and parasitic infections.[4] In the literature, there is a well-documented high incidence of donor-derived TB after organ transplantation, which carries a high risk of mortality.[5] The transmission of *M.tb* through tissue grafts is very rare but few reports stated that TB transmission occurs via bone, heart valves, and dura mater grafts. TB may lodge in organ transplant recipients via an occult lymphohematogenous dissemination route.[5]

The occurrence of TB in solid organ transplant ranges from 20 to 74 times more frequent whereas twice as frequent in the case of hematopoietic stem cell transplant. Such recipients contract active TB from latent TB either from the donor or from the recipient. A total of 15 proven reports of TB transmission after organ transplantation exist. They presented in multiple ways; viz. pulmonary TB, genitourinary TB, graft granulomata, miliary TB, foot granuloma, and graft TB abscesses.[6] The confirmed diagnosis for TB transmission is proven by restriction fragment length polymorphism (RFLP) analysis and/or hemi-nested inverse polymerase chain reaction in both donor and recipient. In organ or tissue transplant cases, there can be four different scenarios for *M.tuberculosis* infection, namely a) endogenous reactivation of latent TB in the recipient candidate, b) reactivation of latent TB in the living or deceased donor, c) de novo infection or exposure of TB in the post-transplantation period, and d) active TB patient requiring organ or tissue transplantation.[6]

Active TB disease prevention solely depends on proper and reliable detection and management of latent TB either in the transplant recipient or the organ or tissue donor and awareness

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about the post-transplantation exposure of the disease.[7] When the risk of *M.tb* contraction is high, therapeutic decisions have to be made without the diagnostic evidence of TB.

3. Use of allografts in orthopaedics

Banked bone allografts have been used for a variety of orthopaedic and trauma scenarios like primary and revision replacement arthroplasty, spinal fusion, bone defects, pseudoarthrosis, bone tumors, and arthrodesis. With the profound risk of disease transmission among allografts, either gamma irradiation or ethylene oxide is used to sterilize the allograft which may alter the biological property of the allograft. The bone allograft preparation possesses the risk of disease transmission, decreases the biological integrity of the graft, and induces postoperative infection. These quality assurances have to be addressed to the recipients by the treating doctor.

Most orthopaedic surgeons are unaware of the quality of bone allograft processing and from which tissue banks or manufacturers the allografts are being procured. US-FDA direct tissue banks to screen for antibodies against HIV-1 and -2, Hep B surface antigen, HCV, HTLV-1, and syphilis. The transmission of TB in bone allografts have reported in the early 1950s.[8] TB detection is challenging in routine culture as they require specific culture media and methods. Due to paucibacillary TB affection in bone, *M.tb* may not be visible on routine staining. To detect TB in bone allograft samples, tests for latent TB and histopathology of the tissue are needed. Though the usage of bone allografts is uncommon in India, it is mandatory to rule out latent TB infection.

4. An outbreak of bone graft TB

In 1953, James reported the TB transmission in the banked bone [ribs retrieved from thoracoplasty] with 4 cases [case 1 − 1st and 2nd stage fusion for spine scoliosis; case 2 − one-stage fusion for scoliosis; case 3 − 1st stage fusion for scoliosis; and case 4 − one-stage fusion for eight vertebrae].[8] A few reports have mentioned the occurrence of TB in bone allografts which was notified to the WHO.[9,10] In 2021, the US reported an unprecedented outbreak of TB in spine surgery cases where bone allograft was used.[11] Such allograft was retrieved from a single deceased donor which contain live TB bacterial cells. On May 2021, Delware hospital in the US notified the health authorities regarding the unusual occurrence of TB in patients undergoing spine surgeries where bone allografts were used from a single product lot.[11] Such patients developed spinal and disseminated TB. On June 2021, the manufacturer recalled all the unused products (n = 18) which caused concern about TB progression in such cases.

The bone allograft was procured from an 80-year-old US resident who traveled to countries with a TB incidence of >20 cases per 1 lakh population. This donor was a non-smoker and non-alcoholic without any history of active or latent TB. Due to the associated medial conditions (renal failure, coronary artery disease biventricular cardiac failure, and sleep apnea), the donor was admitted for progressive dyspnea, orthopnea, and subsequently bradycardia and underwent extended cardiopulmonary resuscitation. USG abdomen revealed hepatosplenomegaly and ascites. No testing was performed for the TB. On day 3 after initial cardiac arrest, the patient died due to cardiogenic shock. The donor risk assessment interview is compatible with TB. Nevertheless, the medical records state that the cough and dyspnea were due to cardiac failure. The donor's attender gave a history of 35 kg weight loss over the last 2 years. The attendee was unaware of the TB risk of the donor. The donor has a negative tuberculin test before renal dialysis. Mandatory microbiological testing records were negative.

The retrieved long bones of the upper and lower extremities from the donor were processed and manufactured into 154 units of the bone allograft. The concerned allograft was subjected to sterilization by the manufacturer. Despite sterilization, M.tb persisted in the bone allograft. The manufacturer performed bioburden testing on the allograft for screening bacteria and fungi and not for the tuberculous bacteria. These 154 units were distributed to 37 hospitals in 20 US states between March and April 2021. A total of 136 units were transplanted into 113 patients in 18 US states. Once the health authorities reported the TB outbreak, the manufacturer issued a notice of recall of unused allograft (11.6%) from the distributed hospitals. Out of 113 transplanted recipients, 6.19% of the recipients (n = 7) died before TB outbreak detection and 0.8% of the recipient (n = 1) died on the day of the announcement of the TB outbreak due to bone allograft. The remaining 105 allograft recipients (92.9%) were started with anti-tuberculous drugs whereas 87 recipients (82.8%) demonstrated microbiological and radiological evidence of TB. M.tb isolates from 53 allograft recipients (46.9%) and 8 unused products (44.44%) shared a unique genome sequence which was detected by single nucleotide polymorphism analysis and/or heminested inverse polymerase chain reaction. In November 2021, the culture-confirmed TB isolate and recalled lot isolate are more than 99.99% genetically identical. As of August 2022, the investigation regarding the bone allograft TB outbreak is ongoing.[11,12]

Due to the immunocompromised status of the allograft recipients, there are various factors responsible for the rapid development of spinal and disseminated TB namely a) high index of mycobacterial load, b) direct inoculation of mycobacterium into the skeletal system, c) postoperative hyperaemia facilitate dissemination of TB to the systemic organs, and d) allograft contents such as live cells and BMP facilitate *M.tb* growth. TB-positive allograft recipients are in close monitoring for the disease progression and probably in the need of a long course of anti-tuberculous drugs. The genotype of *M.tb* isolates between the allograft recipients and the unused product units confirmed that the TB outbreak is due to the bone allograft product.[11]

5. TB infection in healthcare personnel via infected bone allograft in US

Annual TB screening among health care personnels (HCPs) are not investigated routinely. The investigation by Li et al.[13] was carried over in 46 healthcare facilities and identified over approximately 5000 cases of potential TB exposures and 73 latent TB infections (LTBI) among HCPs due to the contaminated bone allograft product. Out of 73 cases of LTBI among HCPs, 20.5% cases acquired LTBI from an unusual extrapulomnonary exposures and 79.4% cases acquired LTBI through multiple exposures. Li et al. reinforced the clinicians to adhere to CDC's recommendations of Airborne and Contact Precautions for cases with draining TB wounds in hospitals. When the mixture of known and ununsual exposures of TB in the community, the collaboration among public health investigators, epidemiologists, and healthcare facilities are essential for the timely identification of the contact exposures and the implementation of appropriate infection control measures.[13]

6. Problem statement and monitoring strategies of TB

In India, TB is one of the most common infectious diseases, which causes major morbidity and mortality among the susceptible population. The rise in bone allograft use in Orthopaedic surgery increases for revision arthroplasty, bone tumor resection, etc. The current outbreak is in the US and its relevance in India is not known at present. Routinely, the testing for mycobacteria in bone allografts

is not done in India. It may be worrisome in India, however, it may not be a threat secondary to the highly vaccinated population against TB. Allograft transplantation is not very common practice and commercial allograft procurement is also uncommon in India.

Though all individuals are vaccinated against TB, the majority of the population have latent TB infection so donor screening for TB is important to avoid TB in the transplant recipient. The current outbreak has raised several questions those need to be addressed. The concern is whether testing for tuberculosis will be cost-effective? or will it cause an additional burden of tubercular cases? or burden on the health care system. How the patients would be monitored and followed up in the event of false negative cases? Monitoring and follow-up are issues that must be addressed in cases of misleading negative results. When an allograft donor has a clinical suspicion of tuberculosis, using anti-tuberculous drugs can result in drug resistance. Establishing precise recommendations for the screening of allografts is necessary, particularly for nations where tuberculosis is endemic. Further; we need to follow up with patients in which allograft has been transplanted to see if they have wound complications due to tuberculosis or any other signs and symptoms related to tuberculosis.

At this time; we suggest the following strategies to reduce the risk of transmission of TB infection via bone graft transplantation:

a) Due to the diverse cell type affection of *M.tb*, all organ or tissue donors have to be screened for previous, active, or latent TB infection.
b) Organ or tissue donors, with risk factors or symptoms and signs compatible with TB infection, must be subjected to mycobacterial (phenotypic and genotypic) testing.
c) Anticipation of tissue-derived infection while using tissue-based products containing live cells.
d) The establishment of tissue traceability and adverse event reporting is to be considered.

7. Conclusion

The outbreak of bone allograft TB poses a major public health concern with significant morbidity and mortality. To ensure organ or tissue safety, it is mandatory to do mycobacterial, other bacterial, and fungal testing. Tissue traceability and adverse events reporting play a significant role in reducing the future TB outbreak while transplanting organs or tissue to the recipients. To stop a new outbreak, it is essential to establish precise protocols for the screening of allografts for the spread of tuberculosis.

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Author statement

MJ & VKJ: Conceptualization, Methodology, Software Data curation, Writing - Original draft preparation. **RV:**Supervision, Reviewing, and Editing.

Declaration of competing interest

Nil.

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Update

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Erratum regarding missing peer review statement in previously published articles

Owing to a Publisher error, peer review statement was not included in the published versions of the following articles, that appeared in previous issues of Journal of Clinical Orthopaedics and Trauma.

The appropriate peer review statements, for each article are provided below.

1. "Correlation between height and semitendinosus tendon length, prediction of minimum semitendinosus tendon length based on height-an easy and accurate method" (Journal of Clinical Orthopaedics and Trauma., 31 (2022) 101918) https://doi.org/10.1016/j.jcot.2022.101918

Peer review statement: The author list of this article includes an editorial board members, namely Ankit Goyal and Hitesh Lal. We would like to note that they were not involved in the peer review process or any of the decision-making steps of the manuscript.

2. "Cystic bone Lesions: Diagnostic pitfalls and therapeutic considerations" (Journal of Clinical Orthopaedics and Trauma., 67 (2025) 103046) https://doi.org/10.1016/j.jcot.2025.103046

Peer review statement: The author list of this article includes an editorial board member, namely Ashish Gulia. We would like to note that they were not involved in the peer review process or any of the decision-making steps of the manuscript.

3. "Artificial intelligence-based orthopaedic perpetual design" (Journal of Clinical Orthopaedics and Trauma., 49 (2024) 102356) https://doi.org/10.1016/j.jcot.2024.102356

Peer review statement: The author list of this article includes an editorial board members, namely Abid Haleem, Abhishek Vaish and Raju Vaishya. We would like to note that they were not involved in the peer review process or any of the decision-making steps of the manuscript.

4. "Gut Microbiome - Should we treat the gut and not the bones?" (Journal of Clinical Orthopaedics and Trauma., 39 (2023) 102149) https://doi.org/10.1016/j.jcot.2023.102149

Peer review statement: The author list of this article includes an editorial board member, namely Vijay Kumar Jain. We would like to note that they were not involved in the peer review process or any of the decision-making steps of the manuscript.

5. "Decoding the hidden realm: Molecular pioneering unravelling osteoarticular tuberculosis diagnosis" (Journal of Clinical Orthopaedics and Trauma., 56 (2024) 102538) https://doi.org/10.1016/j.jcot.2024.102538

Peer review statement: The author list of this article includes an editorial board members, namely Vijay Kumar Jain and Kartikeyan Iyengar. We would like to note that they were not involved in the peer review process or any of the decision-making steps of the manuscript.

6. "Trends of publications on primary sarcomas of bone: A bibliometric analysis" (Journal of Clinical Orthopaedics and Trauma., 63 (2025) 102917) https://doi.org/10.1016/j.jcot.2025.102917

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7. "Bacteriophage therapy in infection after fracture fixation (IAFF) in orthopaedic surgery" (Journal of Clinical Orthopaedics and Trauma., 35 (2022) 102067) https://doi.org/10.1016/j.jcot.2022.102067

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8. "Combating antimicrobial resistance in osteoarticular infections: Current strategies and future directions" (Journal of Clinical Orthopaedics and Trauma., 58 (2024) 102791) https://doi.org/10.1016/j.jcot.2024.102791

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9. "*Mycobacterium Tuberculosis* infection of the wrist joint: A current concepts review" (Journal of Clinical Orthopaedics and Trauma., 44 (2023) 102257) https://doi.org/10.1016/j.jcot.2023.102257

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10. "Bone graft tuberculosis outbreak in USA: Is it a concern in India?" (Journal of Clinical Orthopaedics and Trauma., 39 (2023) 102145) https://doi.org/10.1016/j.jcot.2023.102145

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11. "Letter to editor: Sathyendra et al. Comparative study of local injections of autologous platelet rich plasma versus corticosteroid in management of chronic plantar fasciitis" (Journal of Clinical Orthopaedics and Trauma., 62 (2025) 102903) https://doi.org/10.1016/j.jcot.2024.102903

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