SPECIAL COMMUNICATION

Inflammatory arthritis and Mycobacterium Tuberculosis infection: a diagnostic and management challenge for Knee arthroplasty in endemic areas

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Abstract

Tuberculosis continues to be one of the most challenging health problems more prevalent in developing countries. Pakistan ranks 5th in tuberculosis prevalence among the high-burden countries. Prosthetic joint infection of the knee by acid fast bacilli is a rare and distressing complication, occurring in nearly 1% of primary joint arthroplasties requiring prolonged medical treatment and multiple surgeries. A recent publication extensively reviewed English literature from 1952 to 2016, and reported only 64 prosthetic joint infection with tuberculosis, of which 27 cases involved the knee. Tuberculosis is a global health problem adding to the challenges that arthroplasty surgeons face in our resource-constrained setting. Furthermore, it presents as other inflammatory arthritis with almost same laboratory and radiological findings. The current paper was planned to highlight the preoperative and postoperative challenges that the arthroplasty surgeon may have in diagnosis and management of this rare infection. We included studies from 1996 to date which reported knee tuberculosis prosthetic joint infection that were managed by medication alone or with surgical intervention in patients who had undergone arthroplasty.

Keywords: Knee arthroplasty, TB prosthetic joint infection, Endemic, Inflammatory arthritis.

Introduction

Tuberculosis (TB) continues to be one of the most challenging health problems and is more prevalent in developing countries. Pakistan ranks fifth in TB prevalence amongst the high-burden countries.[1] In this day and age joint replacement surgeries have become popular in developing countries where TB also has high prevalence. Prosthetic joint infection (PJI) of the knee by acid fast bacilli (AFB) is a rare and distressing complication occurring in nearly 1% of primary joint arthroplasties[2,3] requiring prolonged medical treatment and multiple surgeries. Patients can present with a palpable mass (cold abscess), draining sinus/fistula, and painful erythema. Therefore high clinical suspicion is mandatory for diagnosis of PJI by mycobacterium. Adding to this challenge is inflammatory arthritis affecting the knee joint present with almost identical features on clinical examination, laboratory tests and radiographic findings. Laboratory tests include tuberculin skin test (TST), erythrocytes sedimentation rate (ESR) and cultures of synovial fluid, cytology and histology with different rates of accuracy. In endemic areas with mycobacterium TB (MTB), the low threshold of suspicious is indeed helpful for early diagnosis and management of this catastrophic infection.

Factors contributing to delayed diagnosis include its low incidence, varied clinical manifestations, co-infection with pyogenic bacteria accounting for 37% cases, and low index of suspicion.[4]

First case of peri-PJI with MTB was reported in 1977(5). A recently 2018 publication extensively reviewed English-language literature from 1952 to 2016, and reported only 64 PJI with TB, of which 27 cases involved the knee.[6]

Discussion

Pathology: Three pathogenic mechanisms have been reported: active TB arthritis present at the time of surgery but not known to clinician; TB spread by haematogenous route from foci elsewhere; and surgical trauma to old granulomas resulting in recurrence of TB arthritis.[5-8] Recent studies have highlighted human immunodeficiency virus (HIV) as an important risk factor for re-activation of TB in previously infected joints.[9,10] Estimated risk of re-activation has been reported between 0% and 31%, with total knee arthroplasty (TKA) more at risk than total hip arthroplasty (THA) (27% and 6%).[11] Staphylococcus is the most common organism for prosthetic infections followed by gram-negative and streptococcus species, while atypical infections are rare.[18,12]

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MTB has limited biofilm-formation capacity which, if formed, is very thin and has a lesser tendency to adhere to implants compared to the biofilm-forming staphylococci which have ample biofilm-forming capacity and stronger ability to multiply and adhere on surface of all types of implants.[13-15] Because of these factors, MTB is more susceptible to anti-TB agents and, if implant is stable, removal of hardware is not needed.[13,16] Nevertheless, emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB has complicated its management.[16]

Table-1: Clinical utility of different tests in diagnosing extra-pulmonary TB(27, 28).

	Tuberculin Skin Test (TST)	Smear for AFB	Xpert(39)	Histology
Sensitivity, (95% CI)	94% (87-98)	25% (12-42)	70% (50-85)	100% (85.7-100)
Specificity, (95% CI)	88% (74-96)	100% (75-100)	100% (75-100)	100% (95.5-100)
PPV, (95% CI)	95% (88-98)	100% (66-100)	100% (86-100)	100% (85.7-100)
NPV, (95% CI)	86% (72-94)	32.5% (19-49)	72.8% (31-97)	100% (95.5-100)

Clinical presentation: PJI of knee with MTB has a varied clinical presentation. Constitutional symptoms, including fever, weight loss and night sweats, are not seen in all cases and a previous history of pulmonary Koch's is often absent.[17,18] Patients can present with a palpable mass (cold abscess), draining sinus/fistula, and painful erythema. Therefore high clinical suspicion is mandatory for diagnosis of PJI by mycobacterium. Onset of symptoms within 2 month after arthroplasty is considered "early presentation" whereas onset of symptoms after 2 months is labelled as "delayed presentation".[7,19]

Role of lab investigation: The ESR level may be elevated, but has a low specificity. ESR levels remain elevated for about 90 days or more than a year after arthroplasty, making it a less valuable test at least during this timeframe.[14,20] TST is sensitive, but has a reduced positive predictive value (PPV) in populations with a low infection rate. It may report false negative results in patients who are immune-compromised, malnourished or HIV-positive.[3] It is also not able to differentiate between active and latent TB. Clinical utility of different tests in diagnosing extra-pulmonary TB also need to be considered (Table 1).

Role of radiological investigation: Plain radiographs either of knee or chest are not specific. Radiological findings may show subchondral cysts, subchondral erosions or implant loosening, but these findings may also be present with pyogenic infection, aseptic loosening and will be absent in early presentation where the implant is stable.[21,22]

Magnetic resonance imaging (MRI) has low sensitivity due to artefacts caused by the implant. MRI findings reveal large intra-articular effusions, peri-articular osteoporosis, and gross thickening of the remaining synovial membrane which are not clinically relevant in isolation after arthroplasty.[8]

Nuclear medicine is the most valuable diagnostic procedure to detect the prosthesis involvement and loosening,[23] but literature review has reported their use to be limited. Bone scans findings with technecium-99m or indium-111 are non-specific because findings mimic pyogenic infection, metastatic disease and non-specific inflammation.[5]

Grams staining / histological diagnosis: Aspiration of synovial fluid is another modality, but yield is low, with reported sensitivity of 80%. Literature reports synovial biopsy as gold standard in diagnosing PJI of knees.[24-26] It has sensitivity of about 90%, but should always be added with cultures to get information about antibiotic resistance.[27,28]

Culture specimens taken from draining sinuses are usually contaminated.[3,6] Staining and visualisation of mycobacterium with Ziehl-nelson is time-saving and cost-effective, but yield of positive test is less than culture.[17]

Polymerase chain reaction (PCR), though one of the recent diagnostic modalities, has significant specificity, but is less sensitive at 60%. There are limited studies mentioning its use in the diagnosis of PJI.[29-32]

Treatment: Since PJI of knee with mycobacterium is rare, with varied presentation and delayed diagnoses; there are no specific guidelines for its management. Several different treatment plans have been advised for PJI of knee by AFB. Management varies from case to case. Literature reports treatment options that range from chemotherapy alone to arthrodesis or revision in addition to chemotherapy.

Conservative management: Early onset PJI of knee has been managed by retention of the implant with prolonged chemotherapy. There is great controversy regarding treatment duration of chemotherapy and combination of drugs in the literature. Cases of PJI with

Table-2: The cases of tuberculosis-prosthetic joint infection (TB-PJI) managed with medications alone.

Author/year (ref.)	Age/sex	Time elapsed from arthroplasty to joint infection	Time elapsed from joint infection to diagnosis	Concomitant infections	Medical therapy (duration in months)*	Follow-up from end of therapy (months)	Complications
Marschall et al. 2008[40]	48/M	6 months	3 months	None	I, P, E, $M^{6} \rightarrow$ I, P, E, R^{6}	Not reported	Death due to disseminated TB
Neogi et al. 2009[18]	73/F	14 years	2 months	None	I, P, E, $R^{4} \rightarrow$ I, P, $R^{3} \rightarrow$ I, R^{11}	36	Not reported
Kadakia AP et al. 2007[16]	85/F	1 month	3 months	Staphylococcus	I, P, E, R^{6}	Not reported	Not reported
Veloci1et al(2018)[6]	34/F	8 months	4 years	None	I, R^{18}, P, E^{2}	24	None
Egües Dubuc C et al. 2014[41]	77/F	Not reported	1 year	None	I, P, R (on therapy)	48	None

I: Isoniazid P: Pyrazinamide R: Rifampicin E: Ethambutol M: Moxifloxacin

MTB managed with medications alone are worth taking a look at (Table 2).

Surgical management: Surgical treatment options include debridement alone, single-stage or two-stage implant exchange or removal of prosthesis and arthrodesis. Chemotherapy alone or with surgical debridement has been used in early onset PJI. In late onset PJI, implant usually gets loose, and removal of implant is often required.[33]Wolfgang shared his experience of late onset PJI in knee, managed with removal of implant, extensive debridement and two-stage revisions with adjuvant chemotherapy and good results at 1-year follow-up.[32] A successful case of staged procedure in TB arthritis is also known. Figure 1 and 2 summarize a case of 55 years old lady presented with right knee pain, stiffness and difficulty walking not responding to conservative measures. Right knee was swollen, warm and tender with moderate effusion. Active range of motion 0-110 degrees. No varus/valgus or AP instability was seen on clinical examination. Blood tests were normal except for ESR and CRP, 75mm/hr and 2.14mg/dL, respectively. These features suggested erosive arthritis, which could be inflammatory. However TB should be considered high up in the differentials particularly in endemic areas with MTB. Patient underwent debridement and open biopsy at first stage, which confirmed the diagnosis of TB.

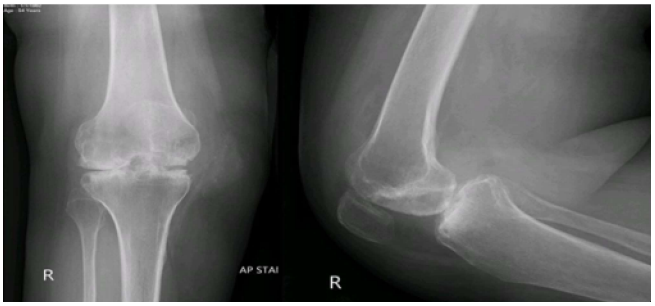

Figure-1: Preoperative knee x-ray showing juxta-articular osteopenia, peripheral osseous erosions and narrowing of joint space.

Multidisciplinary approach including the surgeon, infectious disease team and microbiologist was followed. Following ATT for 10 months, patient had a successful TKA with an excellent outcome.

This strengthens the concept that not every erosive arthritis is a systemic inflammatory rheumatoid type, particularly so in our endemic areas of TB. Patient had no varus/valgus or AnteroPosterior (AP) instability on clinical examination. Blood tests were normal except for raised ESR and CRP. Pre-operative knee X-ray showed juxta-articular osteopenia, peripheral osseous erosions and narrowing of joint space. These features suggested erosive arthritis, which could be inflammatory. However, TB should be considered high up in the differentials, particularly in endemic areas with MTB. Patient underwent debridement and open biopsy at first stage, which confirmed the diagnosis of TB.

In endemic areas, one, therefore, has to make sure that TB is considered in the differential diagnosis of inflammatory arthritis as the radiological features alone

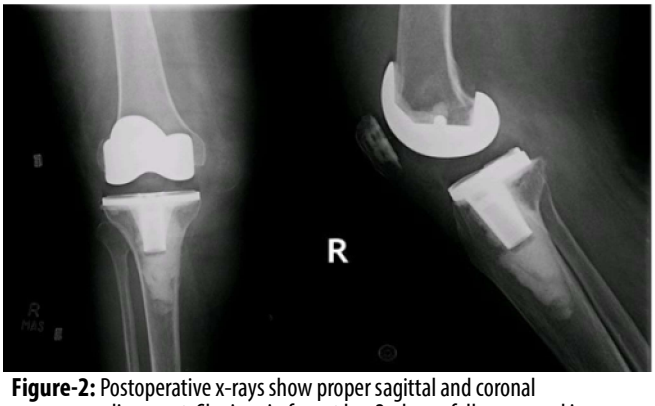

Figure-2: Postoperative x-rays show proper sagittal and coronal alignment. She is pain free at her 2nd year follow-up and is walking without any support.

Table-3: The cases of tuberculosis-prosthetic joint infection (TB-PJI) managed surgically.

Author/year (ref.)	Age/sex	Time elapsed from arthroplasty to joint infection	Time elapsed from joint infection to diagnosis	Concomitant infections	Medical therapy (duration in months)*	Surgical procedure	Surgery Time elapsed from start of medical therapy to surgery (months)	Follow-up from end of therapy (months)	Complications
Veloci1 et al 2008[6]	62/M	Postoperatively	3 years	None	I, R (18), P^{2}	Debridement and implant retained	Not reported	1 month	None
Su et al 1996[42]	16 knees , in 2 groups (A & B)	A: 8 knees before TKA B: 8 knees diagnosed within 12 months post TKA	Variable	None	A: 20m before TKA and 12m postTKA B: 12m post TKA only	Only Anti Tuberculosis Therapy(ATT) for 1 case Debridement + ATT for 3 cases Excisional arthroplasty for 1 case of recurrent infection in group A	Within 12m	36	5 cases of reactivation (1 in group A and 4 in group B)
Tokumoto et al. 1995[31]	71/F	2 months	Not reported	S. aureus	I, E^{18}	Debridement, explant and later arthrodesis	9	96	None
Tokumoto et al. 1995[31]	70/F	38 years	3 months	None	I,R^{12}	Debridement and explant	Surgery first	24	Not reported
Lusk et al. 1995[43]	75/F	16 years	Not reported	Not reported	I,R,P (0.7) $\rightarrow$I, P, E (5.3)	Debridement and removal of arthroplasty	Surgery first	6	Death(other reasons)
Spinner et al. 1996[44]	70/F	5 years	2 months	Coagulasenegative Staphylococcus	R, E^{12}	Debridement	Surgery first	30	None
Al-Shaikh & Goodman 2003[45]	73/F	8 months	5 months	S. aureus	I, r, P, E (2.1) $\rightarrow$ I, R, P^{12}	Debridement and later arthrodesis	5 months	12	None
Marmor et al. 2004[14]	66/M	2 months	4 months	None	I, R ,P^{16}	Debridement and staged exchange	(procedures 14 months apart)	60	None
Marmor et al.2004[14]	65/F	3 months NR	6 months	None	I, E, P^{8}	Debridement and staged exchange	Removal first, reimplantation 14 months	84	None
Wang et al. 2007[46]	72/M	1 year	3 months	None	I, R, P, E (0.7)	Debridement	Surgery first	1	Death due to MODS
Khater et al. 2007[8]	75/F	3 months	1 month	S. aureus	I, R, P, E (unclear duration) $\rightarrow$ I, E^{18}	Debridement and explant	NR	18	None
de Haan et al. 2008[20]	75/F	3 months	1 month	None	I, R, P, E^{9}	Debridement	9	36	None
Lee et al. 2009[47]	79/F	2 months	2 months	Not reported	R, E^{12}	Debridement	Surgery first	13	None
Uppal S et al. 2010[36]	27/F	1 month	3 years	Not reported	I, R, P, E^{18}	Debridement	9	Not Reported	None
Kadakia AP et al. 2007[16]	85/F	1 month	3 months	Staphylococcus	I, R, P, E^{6}	None	Variable	Not reported	Not reported
Harwin SF et al. [11]; 2013[48]	60/F	7 months	2 years	None	I, R^{21},P, E^{12}	Staged exchange	13	24	None
Klein GR et al. 2012[38]	36/F	11 months	1 year	None	I, R, E, P, M, A^{19}	Staged exchange 36 months	Removal first, reimplantation	7	None
Carrega G et al. 2012[37]	72/F	7 years	Not reported	None	I,R^{12}, E^{12}	Staged exchange	Surgery first	12	None
Carrega G et al. [19]; 2012[37]	80/F	Not reported	Not reported	None	I, R ^{14}, E^{12}	Staged exchange	Surgery first	7	Not reported

I: Isoniazid P: Pyrazinamide R: Rifampicin E: Ethambutol M: Moxifloxacin A: Amikacin

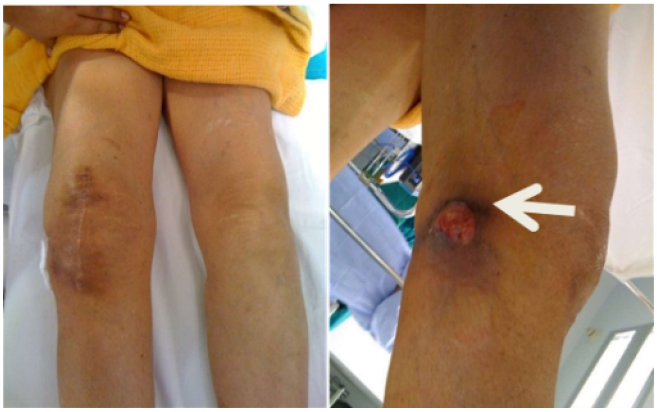

Figure-3: Right knee swelling and healed healthy scar with discharging sinus and non-healing wound over the lateral aspect of popliteal fossa (arrow).

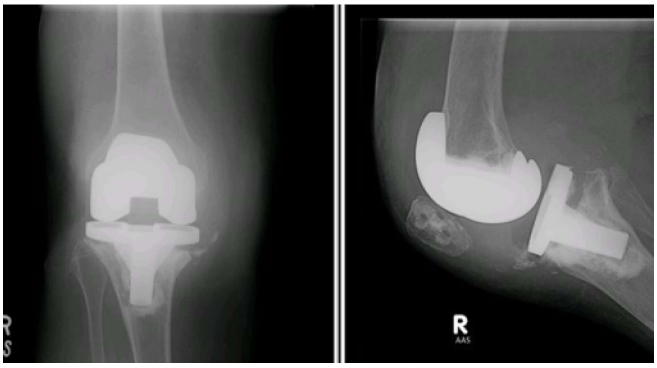

Figure-4: X-rays showing the osteolysis around the unstable implant with significant bone loss and erosions with knee effusion.

are not enough to differentiate between these conditions. Indeed, these two different pathologies of arthritis present with same laboratory and radiological findings include elevated ESR and CRP, as well as erosive arthritis without formation of osteophytes and with mono-articular involvement.

Cases of TB-PJI managed surgically by debridement and retention of implant, debridement and explant, staged procedure (debridement followed by TKA) or arthrodesis have been known (Table 3).[34]

Surgical treatment depends on the status of implant fixation. Implant may be retained if it is stable and only debridement followed by chemotherapy may be required. This strategy has been reported successfully in multiple cases and studies.[19,29,35,36]

In case of implant loosening or co-infection with pyogenic organism, removal of loose implant and staged revision have been reported.[37,38] In recurrent infection cases in severely sick patients, arthrodesis, if bone stock is available, or above-knee amputation, in cases with significant bone loss and destruction, can be potential options to improve patients' quality of life. Figure 3 and 4 showing a 68 year old lady with multiple comorbids. Right TKA done for reported advanced OA outside our institution. Presented with pain and swelling of right knee within 11 months postoperatively. Patient underwent debridement and implant removal. Peroperative cultures grew MTB. Planned for revision TKA once free from disease or arthrodesis. Patient was kept on ATT but was not compliant and had multiple hospital admissions due to heart failure, asthma, electrolyte imbalance and drowsiness. This unfortunate sick lady had recurrent TB infection with significant bone loss and ultimately underwent above knee amputation.

Conclusion

Obtaining synovial specimens and specifically requesting TB culture and histology are the most pertinent investigations. Early diagnosis and treatment may prevent prosthetic loosening and avoid revision surgery with significant benefit to the patient and optimising outcomes and resources. Adding to this challenge is inflammatory arthritis affecting the knee joint present with almost identical features on clinical examination, laboratory tests and radiographical findings. TB should always be amongst differential diagnosis in cases of erosive inflammatory arthritis in endemic areas. Needless to say that this issue should be dealt with in multi-disciplinary setting including experienced surgeon, infection disease control consultant, histopathologist and public health workers to improve the outcome of these patients in a developing country.

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