CASE REPORT

Tuberculous periprosthetic infection precipitated by infliximab therapy

Rajesh Malhotra, Deepak Gautam, Naman Wahal

Department of Orthopaedics,
All India Institute of Medical
Sciences, New Delhi, Delhi,
India

Correspondence to
Dr Naman Wahal,
namanwahal@gmail.com

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SUMMARY

Biological therapy with TNF- α inhibitors have been increasingly used in the treatment of inflammatory arthritis. Systemic tuberculosis infections are often known to occur following treatment with these biological agents. However, no case of periprosthetic tuberculous infection of the hip following this therapy has been reported. We report a case of a 45-year-old man who developed periprosthetic tuberculous infection soon after infliximab injection. We also discuss the need of pretreatment awareness, high index of suspicion, early diagnosis and management of such case.

BACKGROUND

Immunosuppressive agents, though a greatest achievement in modern day medicine, can precipitate tuberculous infection in certain cases.

CASE PRESENTATION

A 45 year-old man presented with severe pain in his left thigh for 2 weeks with inability to bear weight on his left lower limb. He was a known case of ankylosing spondylitis for 25 years and had undergone bilateral total hip arthroplasty at the age of 22 years. Seven years back, he underwent sequential revision total hip arthroplasty (right followed by left at an interval of 6 weeks) in our institute. He gave a history of short intravenous course of infliximab (monoclonal antibody against tumour necrosis factor- α) 2 months back from a rheumatology institute for an episode of acute polyarthralgia. He had also symptoms of evening rise of temperature for the past 1 month; however, there was no associated anorexia or weight loss. On examination, there was a tender swelling on the anterior aspect of the thigh with a discharging sinus (figure 2A).

INVESTIGATIONS

Erythrocyte sedimentation rates (ESR) and C reactive peptide (CRP) levels were elevated (149 mm/hour and 21 mg/L, respectively). X-rays revealed osteolysis of proximal femur and acetabulum without any evidence of loosening or subsidence of the revision implant (figure 1A, B). Multiple cultures of the discharged fluid were sterile. Contrast-enhanced CT scan was performed (MRI was not an option given the presence of metallic implants in the body) which revealed multifocal cortical breach in the left proximal femur with collection in the overlying vastus intermedius muscle and the intermuscular plane of vastus intermedius and rectus femoris muscle with a discharging sinus over anterolateral aspect of thigh (figure 2B, C).

Figure 1 (A) Immediate postoperative X-ray of both hips with pelvis and upper thigh showing implants in situ. (B) 7 years follow-up X-ray showing osteolysis around the proximal femur.

Figure 2 (A) Clinical picture of the left thigh showing discharging sinus on the anterior aspect of the left thigh. (B) Coronal section of the CT scan of the left thigh showing periprosthetic collection. (C) Axial section of the CT scan of the left thigh showing a periprosthetic collection with a draining sinus.

There was no obvious effusion in the left hip joint space.

Culture of the tissue from the sinus tract was reported sterile including those for fungi and *Mycobacterium tuberculosis*. Histopathology of the sinus tract tissue revealed non-specific chronic inflammation with occasional epithelioid granulomas. Subsequently, the thigh abscess was also aspirated under ultrasound guidance which gave sterile cultures and negative reports for acid-fast bacilli staining. PCR reported to be positive for *Mycobacterium tuberculosis*.

Multidrug oral antitubercular therapy (ATT) was initiated with standard four drug regimen (isoniazid, rifampicin, pyrazinamide and ethambutol) as per our institute's protocol. Within 6 weeks of the treatment, patient reported symptomatic relief with reduction in the amount of discharge and his ability to walk with partial weight bearing. The size of collection decreased from 30 to 10 cc as evidenced on ultrasonogram. CRP values started declining; however, ESR still remained high for first 3 months. The patient was continued on ATT for 18 months after the withdrawal of pyrazinamide and ethambutol from the regimen 4 months

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after it was started. His liver function tests ESR and CRP were serially monitored.

DIFFERENTIAL DIAGNOSIS

Tuberculous periprosthetic infection, pyogenic periprosthetic infection and aseptic loosening of the prosthesis.

TREATMENT

Treated with multidrug ATT for 18 months which was stopped after confirmation of resolution of infection by serological and radiological investigations.

OUTCOME AND FOLLOW-UP

Outcome

He started walking full weight bearing thereafter and was completely pain free. The sinus healed completely after 8 months.

Follow-up

At the latest follow-up that is, 1 year following the completion of ATT, he is walking without support with a healed sinus. ESR and CRP values are 5 mm/hour and 0.4 mg/L, respectively. Contrast-enhanced CT scan was performed which showed complete resolution of the intermuscular collection and a healed sinus tract (figure 3A–C). X-ray revealed improved bone density of the proximal femur and comparable density with the contralateral side (figure 4).

Figure 3 (A) Coronal section of the CT scan of left thigh showing resolution of the abscess. (B) Axial section of the CT scan of left thigh with no draining sinus. (C) Clinical picture of the left thigh showing a healed sinus.

Figure 4 Eighteen months follow-up (after starting ATT) X-ray of hips along with pelvis and proximal thigh showing similar radiodensity in the proximal femur of both sides. There is no evidence of loosening or subsidence as compared with the previous X-rays. ATT, antitubercular treatment.

DISCUSSION

India has about one-fourth of the total global burden of tuberculosis. Of about 8.6 million new cases of tuberculosis reported in 2012, India reported about 2.3 million cases.¹ Of the total new cases, about 15% constitute extrapulmonary tuberculosis (EPTB).² Diagnosis of tuberculosis in endemic areas is made on clinical and radiological presentation.³ However, very few cases of *Mycobacterium tuberculosis* infection following hip joint replacement have been reported so far. We present a review of periprosthetic infection by *M. tuberculosis* after total hip replacement and their management (table 1).

All the patients reported so far in the literature were immunocompetent except one reported by Spinner *et al.*¹¹ Our patient was in an immunosuppressed state following infliximab therapy owing to its TNF- α inhibitory effects. TNF- α plays a vital role in immune response against mycobacterial infections and helps in the containment of existing infective foci.¹² As a result, reactivation of latent tuberculosis or even disseminated tuberculosis is not uncommon with infliximab therapy. In a study published by Keane in 2001, it was found that of 70 patients who developed tuberculosis after infliximab therapy, majority (56%) of them developed EPTB and 24% developed disseminated disease.¹³ Several clinical trials carried out subsequently have also confirmed these results.^{14 15} Although there have been reports on tuberculous periprosthetic infection of knee,¹⁶ no case has been reported until where tuberculous periprosthetic infection of the hip occurred as a consequence of infliximab therapy.

Most authors advocate surgical debridement for the treatment of periprosthetic infection with *M. tuberculosis*. However, we have successfully treated two cases of recrudescence of tuberculous infection in THA carried out for tuberculosis with conservative treatment. Both patients were managed with antitubercular drugs for 1 year, which led to the complete healing.¹⁶ The antitubercular treatment was given only for 12 months in these cases as they had already completed a course of antitubercular treatment before total hip arthroplasty. We believe that tuberculosis in early stages does not cause implant failure by loosening and hence surgery can be avoided.⁴ Moreover, it has been seen that the ramifications in tubercular sinuses is often greater than what is apparent. So a complete excision of sinus is not possible in these cases, and only <1% of patients require debridement.¹⁰ This fact compounded by the possible morbidity in a young patient with a revision implant in situ undergoing a surgery for infection led the authors to adopt a conservative mode of treatment.

There has been much variation in the type and duration of antitubercular drug therapy used in previous such cases. However, most authors have used a combination of drugs that included isoniazid and rifampicin and for more than 6 months duration. Most authors report that the diagnosis should be confirmed before starting the multidrug therapy owing to its long duration. However, in endemic areas such as India the clinical and radiological suspicion combined with sterile cultures for standard organisms should be enough to start ATT.³ Our patient was screened using our national guidelines before starting infliximab therapy. As per the guideline, detailed history combined with thorough clinical examination and supplemented with sequential chest radiographs were performed before starting infliximab therapy.¹⁷ Skin testing with purified protein derivative has limited role in endemic countries and countries where BCG vaccination is given at birth. Belonging to an endemic country, we continued ATT for 18 months as per our institute's protocol.

Table 1 Review of periprosthetic tuberculous infection and their management

Author	Joint	Prosthesis removed	Procedure/surgery	Evidence of infection	Age/sex	Time of presentation postprocedure	Treatment Isoniazid (H) Rifampicin (R) Pyrazinamide (Z) Ethambutol (E)
Carrega <i>et al</i> ⁴	Hip	Yes	Two stage revision	First stage: culture (–) Second stage: culture (+) Chest X-ray: normal	79/F	Early	Short course ATT (5HRE)
Carrega <i>et al</i> ⁴	Hip	Yes	One stage replacement	Intraoperative culture (+) Chest X-ray: normal	92/F	3 years	9HRS with levofloxacin
Shanbhag <i>et al</i> ⁵	Hip	No	Debridement	Blood culture (–) Pus culture (–) Intraoperative culture (+) ESR/CRP raised	59/F	15 months	12REZ
De Nardo <i>et al</i> ⁶	Hip	Yes	Revision	Revision surgery: intraoperative culture (–) Biopsy: non-specific Quantiferon Gold (+) TB-PCR (+) ESR/CRP raised	67/F	1.5 years	2HRZE+16HR
Kreder and Davey ⁷	Hip	Yes	Revision arthroplasty	Revision Surgery: intraop culture (–) HPE: non-specific Hip aspiration: AFB (+) CXR normal	66/F	4 years	9HRZE
McCullough ⁸	Hip	No	Debridement	Surgical specimen culture (–) HPE: non-specific Sinus culture (+) X-ray: calcified mesenteric nodes in right iliac fossa Chest X-ray: normal Sputum examination (–) ESR raised	70/F	7.5 years	ATT
Cansü <i>et al</i> ⁹	Hip	No	Multiple debridements	Culture positive using line probe assay and conventional methods No focus found anywhere else in viscera	46/F	4 months	3HRZE, 13 HRE
Kumar <i>et al</i> ¹⁰	Hip	No	Conservative treatment	PCR (+)	2 patients	12 months	ATT
Current case	Hip	No	Conservative treatment	Clinical Culture (–) AFB (–) PCR (+) History of Infliximab therapy	45/M	18 months	4 HRZE, 14 HR

ATT, antitubercular treatment; E, ethambutol; ESR, erythrocyte sedimentation rates; CRP, C reactive peptide; H, isoniazid; R, rifampicin; S, streptomycin; Z, pyrazinamide.

Learning points

- There should be a high index of suspicion for *M. tuberculosis* periprosthetic infection in patients who have been exposed to infliximab therapy.
- Immunosuppressive agents such as infliximab should be cautiously started with proper counselling to in-patients with ankylosing spondylitis who already have a high risk of tuberculosis due to primary disease.
- In endemic countries such as India, ATT can be started based on clinical and radiological judgement without waiting for the culture results.
- Periprosthetic tuberculous infection can be treated conservatively with chemotherapy and early initiation of antitubercular therapy can save the patient from multiple surgeries and associated morbidities.

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Contributors RM reviewed the draft and helped in correction and inputs. NW prepared the draft of the manuscript. DG helped in clinical and radiological evaluation of the patient.

Competing interests None declared.

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