Case Report

Haematogenous Periprosthetic Hip Joint Infection Caused by *Salmonella* May Be Paucisymptomatic: A Report of 2 Cases

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Abstract
Periprosthetic joint infection (PJI) with *Salmonella* is rare. We therefore describe two cases of PJI with *Salmonella* spp. Case one is a 79-year-old female that presented with fever and acute left hip pain 16 months after revision total hip arthroplasty (THA) performed due to instability. Case two is a 82-year-old male after revision THA due to periprosthetic pseudotumor 22 years after THA. Microbiological work up of intra-operatively obtained specimen showed growth of *Salmonella* spp. In both patients, implant-retaining treatment was successful. Patients with PJI with *Salmonella* may be oligosymptomatic, potentially delaying the diagnosis. Successful implant-retraining treatment is possible.

Introduction

The incidence of periprosthetic joint infection (PJI) after primary total hip arthroplasty (THA) is approximately 1% [1, 2] and higher after revision [3, 4]. Most PJI are due to intra-operative contamination and less often due to haematogenous spread [5, 6]. Most common causative microorganisms are *Staphylococci* [7, 8], while Gram-negative bacilli are involved in less than 10% of PJI [9].
PJI with *Salmonella* spp is very rare. Gupta et al. [10] stated in their case series that only 0.2% of all PJsIs at their institute were caused by *Salmonella* spp, accounting for 6 cases over a period of 44 years. Otherwise, only some isolated case reports have been published to the best of our knowledge [11, 12]. We herewith report 2 cases of haematogenous PJI of the hip caused by *Salmonella* spp treated at our hospital. Both cases had the particularity of being secondary to an asymptomatic bacteriaemia, one patient remarkably presenting no associated symptoms at all before a scheduled revision for another reason, a fact that further increased diagnostic difficulties.

**Case Report**

**Case One**

A 79-year-old female with a history of type 2 diabetes without medication and bronchial asthma treated with daily inhalation of budesonide presented with fever and acute left hip pain 16 months after revision THA performed due to instability. Five days after primary implantation of a THA through an anterior approach in another hospital, the patient had been referred for revision due to instability with dislocation of the cup and consecutive luxation of the THA (Fig. 1). Revision with replacement and reconstruction of the cup using a Burch-Schneider anti-protrusion cage with a cemented cup was performed through an anterior approach. The root cause for instability had been a bone substance defect of the anterior acetabulum caused by over-reaming. Recovery was uneventful.

At readmission, the patient reported hip pain for 5 days without any fever or chills. Serum CRP was 290 mg/L (<5 mg/L), and white blood cell count was 10.72 G/L (3.0–9.6 G/L). Joint fluid aspiration showed 195’300 leucocytes/µL with 94% polymorphonuclear (PMN) granulocytes and growth of *Salmonella* spp. A CT scan of the abdomen showed no intra-abdominal or intrapelvic abscess. Revision with debridement, replacement of modular components, and application of local antibiotics with ceftriaxone-loaded calcium sulphate pellets was performed. Intra-operative tissue biopsies showed >100 PMN/10 high-power fields and growth of *Salmonella* spp in all samples. Systemic antibiotic treatment consisted initially of ceftriaxone, changed to oral ciprofloxacin after 11 days. Total treatment duration was 12 weeks post-operatively. Detailed history revealed a short gastroenteritis following ingestion of a chicken salad approximately 1 week before symptoms of the hip developed.

Six weeks after revision of PJI, the patient was readmitted for an episode of diverticulitis. Although she did not report any pain of the left hip, a CT scan of the abdomen showed some fluid around the THA. Therefore, joint fluid aspiration was repeated and showed no growth of microorganisms. At the latest follow-up two and a half years after revision, the patient had no complaints about the hip. Conventional radiographs revealed three small osteolytic lesions in Gruen zones 2, 5, and 6, respectively, but as the patient was asymptomatic, no further investigations were performed.

**Case Two**

A 82-year-old male presented with hip pain due to osteolysis and a periprosthetic pseudotumor caused by an adverse reaction to metal debris 22 years after THA with small diameter metal-on-metal bearing (Fig. 2, 3). The pain occurred load dependently and was felt at the hip as well as at the ipsilateral knee. Joint fluid aspiration showed no growth of microorganisms. Cell count could not be determined due to metallosis. Revision with debridement, replacement of the bearing, and filling of the osteolysis in the proximal femur with allograft was performed.
through an anterior approach. Histopathology of intra-operative samples showed a typical adverse reaction to wear debris, with an important macrophage infiltrate (Fig. 4). However, an important acute inflammatory reaction was also present with 68 PMN/10 high-power fields (Fig. 5).

Microbiological work up showed growth of *Salmonella* spp in one out of five biopsies. In the context of the virulence of this microorganism and the elevated PMN count, the diagnosis of a PJI was made. Systemic antibiotic treatment was initiated post-operatively with ceftriaxone. As resistance to quinolones was identified, trimethoprim/sulfamethoxazole was chosen as oral antibiotic for a total treatment duration of 12 weeks.

One year post-operatively, there was no evidence of infection, and the patient was pain free. Cobalt and chromium whole blood levels, pre-operatively at 9.7 μg/L (164 nmol/L) and 3.1 μg/L (59 nmol/L), respectively, regressed within 3 months to 4.4 μg/L (75 nmol/L) and 2.7 μg/L (51 nmol/L) respectively, but remained in this range up to 1 year post-operatively due to contralateral THA of the same bearing type.
Discussion

While PJI complicates up to 40% of *Staphylococcus aureus* bacteriaemia in patients with major joint replacements [14, 15], it is a rare complication of bacteriaemia with *Salmonella* spp and affects predominantly immunocompromised and thus elderly patients [16–19]. Despite the germ’s high pathogenicity, affected patients can be oligosymptomatic leading to delayed or missed diagnosis. Patient 1 had only short lasting and self-limiting gastrointestinal symptoms without clinical signs of sepsis. Patient 2 remarkably presented no symptoms of an infection at all before a scheduled revision for another reason. Nevertheless, patient 1 developed haematogenous PJI that became symptomatic within a delay of 1 week. Patient 2 denied having had any signs of gastrointestinal infection or sepsis at all. Nevertheless, *Salmonella* spp seeded into a pre-existing pseudotumor caused by adverse reaction to metal debris due to a metal-on-metal THA. Pre-operative aspiration had been sterile, while the cell count was uninterpretable due to metallosis.

In both patients reported on, implant-retaining treatment with debridement and exchange of the modular components were successful. This is especially fortunate in both cases, as some risk factors for failure were present [20]. In case one, exchange of the modular components was limited to the ball head, and incomplete debridement of the interface.

![Fig. 2. Conventional antero-posterior (upper row) and axial (lower row) radiographs of the affected right hip of case two.](image-url)
Fig. 3. Pre-operative axial T1-weighted MRI sequence of case two, depicting the right hip. A large periprosthetic pseudotumor (white stars) affecting the hip joint developed due to an adverse reaction to metal debris 22 years after THA with small diameter metal-on-metal bearing. Aspiration before revision had remained sterile. Determination of cell count was not possible due to metallosis. The presence of a large necrotic pseudotumor with manifest metallosis could be confirmed intra-operatively. One of the five biopsies sampled for microbiological work up revealed Salmonella spp. Histopathology revealed an acute inflammatory reaction with 68 PMN/10 HPF.

Fig. 4. Histomorphology of a biopsy of the neocapsule (×200, haematoxylin-eosin-staining) of the hip of case two. The patient presented with a periprosthetic pseudotumor affecting the hip joint due to adverse reaction to metal debris 22 years after THA with small diameter metal-on-metal bearing. This histomor- phology shows an adjacent area to the intra-articular space (asterisk) lined by an acellular eosinophilic necrotic zone (triangle) representing the periprosthetic pseudotumor. The deep hypercellular macrophagic infiltrate contains intra-cytoplasmatic brown granules of hemosiderin pigment characterizing a resorption reaction of intra-articular bleeding and shows some admixed foreign body giant cells (arrows). The losange marks the deepest hypocellular fibrotic zone of the capsule. No visible deposits of metallic wear particles are visualized in the sample.

Fig. 5. Higher magnification histomorphology of the same capsule specimen as Fig. 4 (×400, haematoxylin-eosin staining) of the patient in case two. The fibrous capsule shows loss of lining cell layer (asterisk marking the intra-articular space) and displays proliferated fibroblasts and macrophages displaying slim, respectively, plump oval nuclei. Importantly, multiple neutrophils (arrows) infiltrate the capsule tissue representing acute inflammation consistent with a florid joint infection with 68 PMN/10 HPF [13].

between the anti-protrusion ring and the bone could not be avoided. In case two, diagnosis was established only post-operatively, and no biofilm-active antibiotic treatment was available due to the germ’s resistance to quinolones. Antimicrobial treatment in case one
was enhanced by local application of ceftriaxone-loaded CaSO₄ pellets [21, 22]. The essential parameters determining success of component-retaining procedures encompass duration of symptoms, stability of the implants, and exchange of the modular components [20, 23]. However, success of therapy may be improved greatly with additional topical application of antibiotic-loaded degradable calcium-based carrier materials, particularly in case of longer duration of symptoms [21].

In presenting these cases, we hope to raise awareness to PJI caused by Salmonella spp. The patients may be oligo- or even asymptomatic, making the diagnosis particularly challenging. Adequate sampling of biopsies for microbiological work up as well as for histopathology should be performed at every revision, even if another reason for failure was clearly identified pre-operatively. Gram-negative bacilli are rarely causative of PJI and Salmonella spp even rarer [9–12]. Gram-negative bacteria may, however, be resistant to most antibiotic regimes empirically employed in PJI [24]. Rapid identification of this is the essence. In both cases, implant-retaining treatment was successful despite the presence of some factors generally accepted as being associated with an unfavourable outcome [20]. Results of implant retaining-treatment may be improved with use of topical antibiotic-loaded degradable calcium-based materials [21].

**Statements of Ethics**

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from both patients for publication of this case report and any accompanying images. This retrospective review of patient data did not require ethical approval in accordance with local guidelines.

**Conflict of Interest Statement**

The authors declare that they have no conflicts of interest.

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**Author Contributions**

Lara Pozzi: writing the original draft of and editing the manuscript. Corina Dommann-Scherrer: assessment of histopathomorphology and reviewing and editing of the manuscript. Christoph Meier and Peter Wahl: reviewing and editing of the manuscript.

**Data Availability Statement**

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.
References

1. Gundtoft PH, Overgaard S, Schonheyder HC, Moller JK, Kjaeraaard-Andersen P, Pedersen AB. The “true” incidence of surgically treated deep prosthetic joint infection after 32,896 primary total hip arthroplasties: a prospective cohort study. *Acta Orthop.* 2015;86(3):326–34.

2. Huotari K, Peltola M, Jamsen E. The incidence of late prosthetic joint infections: a registry-based study of 112,708 primary hip and knee replacements. *Acta Orthop.* 2015;86(3):321–5.

3. Badarudeen S, Shu AC, Ong KL, Baykal D, Lau E, Malkani AL. Complications after revision total hip arthroplasty in the medicare population. *J Arthroplasty.* 2017;32(6):1954–8.

4. Lora-Tamayo J, Senneville E, Ribera A, Bernard L, Dupon M, Zeller V, et al. The not-so-good prognosis of streptococcal periprosthetic joint infection managed by implant retention: the results of a large multicenter study. *Clin Infect Dis.* 2017;64(12):1742–52.

5. Honkanen M, Jamsen E, Karppepin M, Huttunen R, Eskelinen A, Syrjanen J. Periprosthetic joint infections as a consequence of bacteremia. *Open Forum Infect Dis.* 2019;6(6):ofz218.

6. Pulido L, Ghanem E, Joshi A, Purtill J, Parvizi J. Periprosthetic joint infection: the incidence, timing, and predisposing factors. *Clin Orthop Relat Res.* 2008;466(7):1710–5.

7. Schäfer P, Fink B, Sandow D, Margull A, Berger I, Frommelt L. Prolonged bacterial culture to identify late peri-prosthetic joint infection: a promising strategy. *Clin Infect Dis.* 2008;47(11):1403–9.

8. Font-Vizcarra L, García S, Martínez-Pastor JC, Sierra JM, Soriano A. Blood culture flasks for culturing synovial fluid in prosthetic joint infections. *Clin Orthop Relat Res.* 2010;468(8):2238–43.

9. Hölleyman RJ, Baker PN, Charlett A, Gould K, Deehan DJ. Analysis of causative microorganism in 248 primary hip arthroplasties revised for infection: a study using the NJR dataset. *Hip International.* 2016;26(1):82–9.

10. Gupta A, Berbari EF, Osmon DR, Virk A. Prosthetic joint infection due to Salmonella species: a case series. *Bio Med Central Infectious Diseases.* 2014;14:633–6.

11. de la Torre B, Tena D, Arias M, Romanillos I. Recurrent prosthetic joint infection due to Salmonella enterica: case report and literature review. *Eur J Orthop Surg Traumatol.* 2012;22(Suppl 1):89–97.

12. Toth K, Janoszig G, Kovacs G, Sisak K, Rudner E. Successful treatment of late Salmonella infections in total hip replacement: report of two cases. *BMC Infect Dis.* 2010;10:160.

13. Morawietz L, Tiddens O, Mueller M, Tohtz S, Gansukh T, Schroeder JH, et al. Twenty-three neutrophil granulocytes in 10 high-power fields is the best histopathological threshold to differentiate between aseptic and septic endoprostheses loosening. *Histopathology.* 2009;54(7):847–53.

14. Sendi P, Bandier F, Graber P, Zimmerli W. Periprosthetic joint infection following *Staphylococcus aureus* bacteremia. *J Infect.* 2011;63(1):17–22.

15. Tande AJ, Palraj BR, Osmon DR, Berbari EF, Baddour LM, Lohse CM, et al. Clinical presentation, risk factors, and outcomes of hematogenous prosthetic joint infection in patients with *Staphylococcus aureus* bacteremia. *Am J Med.* 2016;129(2):221.e11–20.

16. Ekinci M, Bayram S, Akgül T, Ersin M, Yazıcıoğlu O. Periprosthetic joint infection caused by Salmonella: case reports of two azathioprine and prednisolone induced-immunocompromised patients. *Hip Pelvis.* 2017;29(2):139–44.

17. Kobayashi H, Hall GS, Tuohy MJ, Knott C, Procop GW, Bauer TW. Bilateral periprosthetic joint infection caused by *Salmonella enterica* serotype Enteritidis, and identification of *Salmonella* sp using molecular techniques. *Int J Infect Dis.* 2009;13(6):e463–6.

18. Rajgopal A, Panda I, Gupta A. Unusual *Salmonella typhi* periprosthetic joint infection involving bilateral knees: management options and literature review. *BMJ Case Rep.* 2017:2017;

19. Cohen JB, Bartlett JA, Corey GR. Extra-intestinal manifestations of salmonella infections. *Medicine.* 1987;66(5):349–88.

20. Wouthuysen-Bakker M, Sehiltotte M, Lomas J, Taylor A, Palomares EB, Murillo O, et al. Clinical outcome and risk factors for failure in late acute prosthetic joint infections treated with debridement and implant retention. *J Infect.* 2019;78(1):40–7.

21. Gramlich Y, Johnson T, Kemmerer M, Walter G, Hoffmann R, Klug A. Salvage procedure for chronic periprosthetic knee infection: the application of DAIR results in better remission rates and infection-free survivorship when used with topical degradable calcium-based antibiotics. *Knee Surg Sports Traumatol Arthrosc.* 2020;28(9):2823–34.

22. Wothuysen-Bakker M, Sehiltotte M, Lomas J, Taylor A, Palomares EB, Murillo O, et al. Clinical outcome and risk factors for failure in late acute prosthetic joint infections treated with debridement and implant retention. *J Bone Joint Surg Am.* 2016;88(6):1231–7.