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Infection or metal hypersensitivity ? The diagnostic challenge of failure in metal-on-metal bearings

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The use of second generation metal-on-metal hip articulations has gained favour in the past few years. A hypersensitivity reaction to the metal-on-metal bearing, although rare, is a reported complication and is a novel mode of failure of these implants. Differentiating failure secondary to infection from failure secondary to metal hypersensitivity represents a significant diagnostic challenge. A retrospective review of all cases of hip arthroplasty using metal-on-metal bearings over a 5-year period at a tertiary referral centre identified 3 cases of failure secondary to metal hypersensitivity. Clinical presentation, serological markers, radiological imaging and histological analysis of all cases identified were evaluated. Histological analysis of periprosthetic tissue in all 3 cases identified characteristic features such as perivascular lymphocytic aggregates and chronic inflammation consistent with aseptic lymphocytic vasculitis-associated lesions (ALVAL). This study highlights that failure secondary to metal hypersensitivity must be considered in patients presenting with the reappearance of persistent pain, marked joint effusion, and the development of early osteolysis in the absence of infection.

Keywords : metal-on-metal bearings ; total hip arthroplasty ; metal hypersensitivity.

INTRODUCTION

In recent years, the use of second generation metal-on-metal hip articulations has gained favour. The theoretical advantage is the reduced volumetric wear compared to metal-on-polyethylene articulations, leading to a reduction in the incidence of osteolysis and aseptic loosening. Failure of these implants secondary to metal hypersensitivity, although rare, is a reported complication (*6,13*). These reactions were originally described in first generation metal-on-metal articulations (*4,5*) but are becoming an increasingly publicised occurrence in relation to second-generation articulations (*8,13*).

Metal-on-metal bearings, despite of having lower volumetric wear, produce much more particles than metal-on-polyethylene bearings due to the smaller particle size (0.05 μm). These particles have a high

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specific surface area, leading to the corrosion of the metal constituents with the release of metal ions into the surrounding tissues. Metal-stimulated lymphocytes release powerful cytokines promoting the release of local inflammatory mediators (*7*). This leads to osteolysis, joint effusion and pain. In metal-on-polyethylene articulations the larger wear particles (0.2-0.8 μm) activate macrophages but do not promote the immunological response seen in metal hypersensitivity. The clinical picture seen with metal hypersensitivity is not dissimilar to that of hip infection.

In patients presenting postoperatively with hip pain, joint effusion, and difficulty mobilising, one must always consider infection, but also the possibility of metal hypersensitivity. Differentiating between these two distinct clinical entities can present a significant diagnostic challenge.

In this case series we describe three cases of metal hypersensitivity mimicking clinically hip infection, and accompanied by raised inflammatory markers. This case series, the largest to date from a single unit, highlights the difficulty that exists in differentiating between infection and metal hypersensitivity and emphasises the importance of histology in making an accurate diagnosis.

CASE REPORTS

Case 1

A 60-year-old woman presented to the orthopaedic clinic with a four-month history of progressive right hip pain, two years after a right-sided metal-on-metal total hip arthroplasty. An uncemented Corail® 11 mm femoral stem (DePuy, France) and an uncemented DePuy ASR® size 58 standard acetabular component with a DePuy ASR® XL size 51 unipolar femoral implant (DePuy Orthopaedics, UK) which had a metal-on-metal articulation had been implanted. The cup abduction angle was 55° and it was anteverted 15°. The pain was localised to the right hip, groin and proximal thigh, and was exacerbated by mobilisation. There was no history of preceding trauma.

Physical examination demonstrated an antalgic gait. There was a well healed scar but with marked swelling and induration at the right hip. The range of motion was limited to approximately 0° to 70° of flexion with pain on internal and external rotation. Her neurovascular status was intact distally.

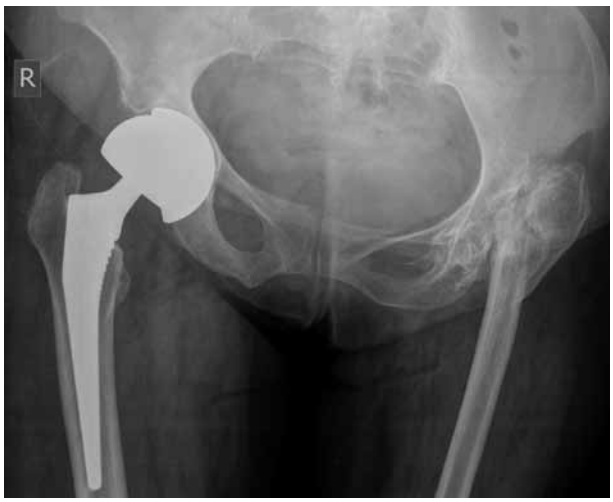

Fig. 1. — Radiographs of pelvis demonstrating evidence of osteolysis and rotation of the acetabular component (Case # 1).

Radiographs of the pelvis demonstrated evidence of osteolysis and rotation of the acetabular component, with a cup abduction angle of 85° (Fig. 1). Serological inflammatory biomarkers were elevated : erythrocyte sedimentation rate was 45 mm/hr (normal, 0 to 22 mm/hr), C-reactive protein level was 74.8 mg/L (normal, < 8.0 mg/L), and blood leukocyte count was 7.4×10^9/L (normal, 3.5 to 10.5×10^9/L).

An image-guided hip aspiration was performed, with the patient having not had antibiotic therapy. No organisms were cultured from the aspirate. The patient underwent extensive workups for inflammatory, rheumatologic and infectious aetiologies, but no cause of the signs and symptoms was identified. Because of continued symptoms, the patient was taken to the operating room for exploration of the possibilities of a culture-negative infection or a hypersensitivity reaction to debris from the metal-on-metal bearing of the right hip prosthesis.

Surgical exploration revealed hypertrophic synovial tissue within a neocapsule, with a turbid yellow fluid within the joint. The appearance was consistent with metallosis with no obvious sign of

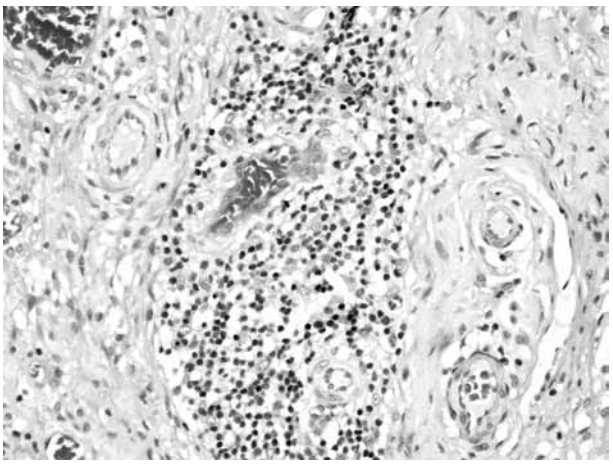

Fig. 2. — Histological appearance of tissue obtained intraoperatively, showing chronic inflammation with perivascular lymphocytic aggregates (haematoxylin and eosin, ×200) (Case # 1).

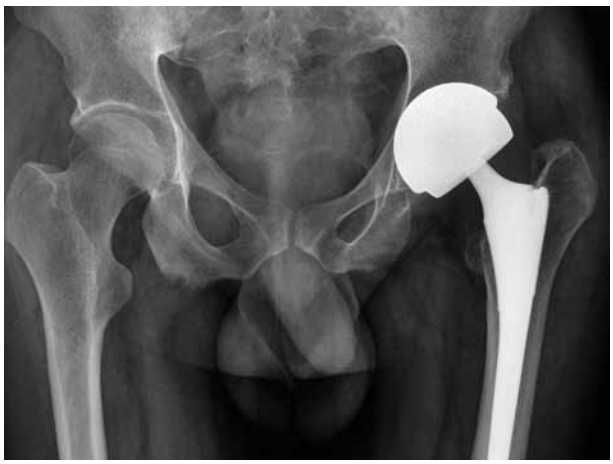

Fig. 3. — Radiographs of pelvis revealed well-seated uncemented metal-on-metal total hip prostheses without evidence of loosening, osteolysis, or implant failure (Case # 2).

infection. A thorough washout was performed and the prosthesis was left *in situ*.

Pathological examination of pseudocapsular tissue revealed fibrovascular connective tissue with extensive surface fibrin deposition associated with fissuring and a focally dense lymphohistiocytic reaction. Beneath the fibrin, a focally dense perivascular, predominantly lymphocytic, inflammatory cell infiltrate with scattered polymorphonuclear and plasma cells was noted (Fig. 2). Cultures of four different tissue specimens and two fluid samples were analyzed separately. Only one tissue specimen showed growth, and this was considered a contaminant and not suggestive of infection.

Six weeks post-op the patient had a revision total hip arthroplasty performed with the acetabular component changed to an uncemented Pinnacle® 60mm acetabular component (DePuy Orthopaedics, UK), the uncemented Corail® femoral stem (DePuy Orthopaedics, UK) was left *in situ*. A 32 mm femoral head was utilised with a metal-on-polyethylene bearing.

Three months postoperatively, the patient reported complete resolution of the right hip pain and she had no further analgesic requirements. The swelling and tenderness surrounding the hip had also resolved. At one-year follow-up the patient remains symptom free.

Case 2

A 69-year-old man presented to the emergency department with a three-week history of progressive right hip pain and difficulty weight-bearing, four years after a left sided metal-on-metal total hip arthroplasty for osteoarthritis. An uncemented Synergy femoral stem (Smith & Nephew, UK) and an uncemented Birmingham modular head and acetabular component (Smith & Nephew, UK) with a metal-on-metal articulation had been implanted. The cup abduction angle was 45° and it was anteverted 20°.The pain was localised to the right hip and was exacerbated on weight-bearing mobilisation. There was no history of preceding trauma.

Physical examination revealed low grade pyrexia and an inability to weight bear. The prior scar was well healed ; however, there was marked swelling and tenderness surrounding the left hip joint. The range of motion of the left hip was limited in all directions by pain. Neurovascular status was intact distally.

Radiographs of the pelvis revealed well-seated uncemented metal-on-metal total hip prostheses without evidence of loosening, osteolysis, or implant failure (Fig. 3). Isotope bone scan showed no sign of increased uptake in the hip area. Serum inflammatory markers were elevated. The

erythrocyte sedimentation rate was 26 mm/hr (normal, 0 to 22 mm/hr), the C-reactive protein level was 47 mg/L (normal, < 8.0 mg/L), and the blood leukocyte count was 12×10^9/L (normal, 3.5 to 10.5×10^9/L).

An image-guided hip aspiration was done and no organisms grew on culture of the aspirate. The patient did not have any antibiotics administered over the previous 3 months. He was extensively investigated for inflammatory and infectious aetiologies, but no cause was identified.

Because of continued symptoms, a surgical exploration was performed revealing a hypertrophic synovial tissue neocapsule with a turbid white fluid within the joint. There was definite appearance of metallosis with no obvious sign of infection. A thorough washout was performed and the prosthesis was left *in situ*. Pathological examination of periprosthetic membrane demonstrated changes once again consistent with ALVAL. Cultures of three different tissue specimens and two swabs of the prosthesis were analyzed separately. Special precautions were taken to minimize tissue contamination and samples were transferred to the laboratory for processing as quickly as possible. There was no growth after incubation for 10 days in various culture media.

Six weeks post-op the patient had a revision total hip arthroplasty performed with the acetabular component changed to an uncemented 60 mm Pinnacle® acetabular component (DePuy Orthopaedics, UK). The Cormet® femoral component was removed and an uncemented size 15 Synergy® femoral stem (Smith & Nephew, UK) was inserted. A size 32 mm head with a metal-on-polyethylene bearing was utilised.

Three months postoperatively, the patient reported complete resolution of the left hip pain and was mobilising independently. At one-year follow-up the patient remains symptom free.

Case 3

A 37-year-old man presented to the emergency department with a two-day history of left hip pain and swelling, two years after a right sided metal-on-metal total hip arthroplasty, originally performed for Perthes disease. A cemented Cormet femoral component and uncemented Cormet acetabular component (Corin, UK) with a metal-on-metal articulation had been implanted. The cup abduction angle was 45° and it was anteverted 15°. The pain had a sudden onset two days previously and the patient was unable to mobilise. The pain was present in the right groin and proximal thigh. There was no history of trauma.

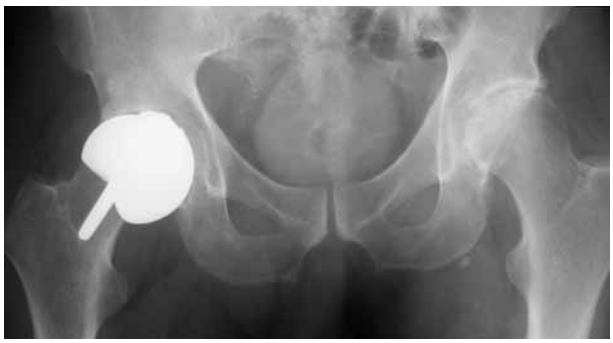

Fig. 4. — Radiographs of pelvis showing evidence of osteolysis involving the acetabular component which was significantly rotated and had spun out of position (Case # 3).

Physical examination revealed that the patient was unable to weight bear. There was a well healed scar but marked swelling of the right hip, with no evidence of erythema. The range of motion of the right hip was limited to approximately 0 to 45° of flexion with minimal internal and external rotation. Neurovascular status was intact distally.

Radiographs of the pelvis showed evidence of osteolysis involving the acetabular component of the hip resurfacing arthroplasty, which was markedly rotated and had spun out (Fig. 4).

Serum inflammatory markers were elevated. The erythrocyte sedimentation rate was 43 mm/hr (normal, 0 to 22 mm/hr), the C-reactive protein level was 64 mg/L (normal, < 8.0 mg/L) and the blood leukocyte count was 5.3×10^9/L (normal, 3.5 to 10.5×10^9/L).

Septic loosening of the acetabular component had been suspected as a result of the clinical presentation and raised inflammatory markers. Surgical exploration revealed a thickened pseudocapsule

with a necrotic lining. A white turbid fluid was found within the joint. As infection was suspected all components of the joint were removed as part of a Girdlestone resection arthroplasty. Thorough washout was performed. Antibiotics were commenced after tissue and fluid samples were taken for histology, culture and sensitivity. The patient was continued on intravenous antibiotic therapy.

Pathological examination of periprosthetic membrane demonstrated changes once again consistent with ALVAL. No organisms grew on culture of two intraoperative tissue samples and three intraoperative swab specimens. Antibiotics were discontinued at this stage.

Four weeks post-op the patient had a revision total hip arthroplasty performed utilising an uncemented 64 mm Pinnacle® acetabular component (DePuy Orthopaedics, UK) and an uncemented size 7 Summit® femoral stem (DePuy Orthopaedics, UK). A 32 mm femoral head with a metal-on-polyethylene bearing was used. Three months postoperatively, the patient reported a complete resolution of the right hip pain and was mobilising independently. At one-year follow-up the patient remains symptom free.

DISCUSSION

We present three cases of hip arthroplasty failure secondary to metal hypersensitivity, mimicking hip infection. There has been some discussion regarding metal hypersensitivity reactions mimicking the infected hip (*1,3,9*). However, an extensive review of the literature reveals only two cases in which elevated inflammatory markers have been raised in the setting of a metal hypersensitivity, only one of which was histologically proven (*9*). All of our cases, despite some differences in their clinical presentations, appeared to mimic hip infection. Case 1 presented with a longer duration of symptoms with features suggestive of infection, such as pain, an effusion and raised inflammatory markers. Cases 2 and 3 presented more abruptly with features suggestive of septic loosening with raised inflammatory markers. All cases required histological analysis to differentiate between infection and metal hypersensitivity.

Our cases highlight the diagnostic challenge and therapeutic implications posed by metal hypersensitivity. If infection can be out ruled, then the patient can have a one-stage revision and avoid the highly inadequate Girdlestone operation. This reduces length of hospital stay and prolonged antibiotic treatment is not required. If, however, periprosthetic infection is missed, reimplantation of the prosthesis without appropriate debridement and antibiotics would likely result in persistent infection. Some authors recommend that in cases of metal hypersensitivity, the metal liner should be exchanged for an alternative bearing surface as the treatment of choice (*9,13*).

The sensitivities and specificities of various tests to diagnose infection vary greatly (Table I) (*3,11,12 14*). Interestingly, intra-operative surgical opinion has been documented to have a specificity of 87% and a sensitivity of 70%. CRP and ESR are noted to have a high diagnostic accuracy (*12*). The combination of white cell sulphur colloid scan and Technetium Tc^{99m} bone scan has also been shown to have a high accuracy in diagnosing infection and its use in diagnosing metal hypersensitivity related joint failure has also been reported (*3*).

Culture of intraoperative specimens, including tissue samples and swabs, has traditionally been regarded as the gold standard in diagnosing hip infection. Despite this, some authors highlight the presence of a high rate of false positives and false negatives when using this test. Bauer *et al* argue against relying on intra-operative cultures, citing inappropriate incubation times, inappropriate choice of media, previous antimicrobial therapy and cross contamination as contributing to reducing the diagnostic accuracy of this test (*3*). In our 3 cases, specimens were inoculated for 10 days in various culture media, including blood and chocolate agar, Brain-heart bouillon, Wilkins Chalgren agar and McConkey agar. Studies have demonstrated that some microorganisms require a minimum incubation time of 8 days, since these microorganisms grow slowly (*15*).

Histopathology is widely reported as the most accurate predictor of infection. The predominance of neutrophils in periprosthetic tissue is the key diagnostic feature. Pandey *et al* suggested that the

Table I. — The sensitivities and specificities of various tests to diagnose infection post total hip arthroplasty (*2,3,4,5,11,12*)

Test	Specificity	Sensitivity
WBC	96%	20%
ESR	86%	82%
CRP	92%	96%
Combined white cell sulphur colloid scan	100%	70%
Technetium Tc99m bone scan	64%	100%
FDG-PET	89%	90%
Hip Aspiration	60%	88%
Intra-op Histology Permanent section	97%	100%
Intra-op Histology Frozen section	96%	90%
Intra-op C&S tissue	97%	94%
Intra-op C&S swabs	99%	76%
Intra-op Surgeon's Opinion	87%	70%

presence of one or more neutrophils per high power field (× 400) on average after examination of 10 fields in arthroplasty tissues correlated strongly with the microbiological diagnosis of joint infection (*11*). This stringent criterion resulted in high specificity (97%) and sensitivity (100%) when compared to other studies.

Histological analysis is integral to differentiating between infection and metal hypersensitivity. The typical histological findings of lymphocytic proliferation in the periprosthetic tissues seem to suggest a delayed-type hypersensitivity reaction. The term aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL) coined by Willert *et al* has been used to describe these features (*13*). The histological appearance typically seen in metal-on-metal joint failures is a diffuse collection of perivascular lymphocytes, plasma cells, localized bleeding, necrosis, fibrin exudation, and presence of macrophages with drop-like inclusions. This is different from the typical macrophage dominated appearance of metal-on-polyethylene periprosthetic membranes and from that seen in infection.

A precise test for assessing metal hypersensitivity has yet to be developed. Patch testing has been used for many years but many experts doubt the applicability of skin testing to the study of immune responses to implants (*6*). The short duration of dermal contact in patch testing is different to the long term closed environment of the orthopaedic implant. There are also concerns that patch testing could possibly induce hypersensitivity in a previously insensitive patient. *In vitro* tests like lymphocyte transformation testing, leukocyte migration inhibition testing, cytokine enzyme linked immunosorbent assay (ELISA) methods appear more promising but are expensive and labour intensive. However, these tests are unavailable in many hospitals and have not been proven in a clinical setting.

As previously mentioned, exchange of the metal liner for an alternative bearing surface has been recommended as the mainstay of treatment (*9,13*). Making the right diagnosis before or during the revision operation is important in directing treatment. It has been recommended that in cases of suspected metal hypersensitivity, an arthroscopic biopsy followed by histological analysis should be performed (*3*). Although this gives a good view of the intracapsular space it does not give access to the periprosthetic membrane, located at the interface between bone and prosthesis, which is the recommended site of biopsy for diagnosing infection or hypersensitivity (*10*). This is an invasive procedure, not without its own risks. We feel that an intra-operative frozen section of periprosthetic membrane offers the potential for a future diagnostic test of choice.

The recent trend towards metal-on-metal articulations, especially in younger patients is likely to

result in an increased prevalence of hypersensitivity reactions. This case series highlights the difficulty that exists in differentiating between infection and metal hypersensitivity and emphasises the importance of histology in making an accurate diagnosis.

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