Pseudotumors in Association with Well-Functioning Metal-on-Metal Hip Prostheses

A Case-Control Study Using Three-Dimensional Computed Tomography and Magnetic Resonance Imaging

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Introduction: Many papers have been published recently on the subject of pseudotumors surrounding metal-on-metal hip resurfacing and replacement prostheses. These pseudotumors are sterile, inflammatory lesions within the periprosthetic tissues and have been variously termed masses, cysts, bursae, collections, or aseptic lymphocyte-dominated vasculitis-associated lesions (ALVAL). The prevalence of pseudotumors in patients with a well-functioning metal-on-metal hip prosthesis is not well known. The purpose of this study was to quantify the prevalence of pseudotumors adjacent to well-functioning and painful metal-on-metal hip prostheses, to characterize these lesions with use of magnetic resonance imaging, and to assess the relationship between their presence and acetabular cup position with use of three-dimensional computed tomography.

Methods: We performed a case-control study to compare the magnetic resonance imaging findings of patients with a well-functioning unilateral metal-on-metal hip prosthesis and patients with a painful prosthesis (defined by either revision arthroplasty performed because of unexplained pain or an Oxford hip score of <30 of 48 possible points). Thirty patients with a painful hip prosthesis and twenty-eight controls with a well-functioning prosthesis were recruited consecutively. All patients also underwent computed tomography to assess the position of the acetabular component.

Results: Thirty-four patients were diagnosed with a pseudotumor. However, the prevalence of pseudotumors in patients with a painful hip (seventeen of thirty, 57%) was not significantly different from the prevalence in the control group (seventeen of twenty-eight, 61%). No objective differences in pseudotumor characteristics between the groups were identified. No clear association between the presence of a pseudotumor and acetabular component position was identified. The Oxford hip score in the group with a painful hip (mean, 20.2; 95% confidence interval [CI], 12.7 to 45.8) was poorer than that in the control group (mean, 41.2; 95% CI, 18.5 to 45.8; $p \leq 0.0001$).

Conclusions: A periprosthetic cystic pseudotumor was diagnosed commonly (in thirty-four [59%] of the entire study cohort) with use of metal artifact reduction sequence (MARS) magnetic resonance imaging in this series of patients with a metal-on-metal hip prosthesis. The prevalence of pseudotumors was similar in patients with a well-functioning hip prosthesis and

continued

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A commentary by Joshua J. Jacobs, MD, is linked to the online version of this article at jbjs.org.

patients with a painful hip. Pseudotumors were also diagnosed commonly in patients with a well-positioned acetabular component. Although magnetic resonance imaging is useful for surgical planning, the presence of a cystic pseudotumor may not necessarily indicate the need for revision arthroplasty. Further correlation of clinical and imaging data is needed to determine the natural history of pseudotumors to guide clinical practice.

Level of Evidence: Therapeutic Level III. See Instructions for Authors for a complete description of levels of evidence.

Many papers have been published recently on the subject of pseudotumors surrounding metal-on-metal hip resurfacing and replacement prostheses[1-7]. These pseudotumors have been variously termed masses, cysts, bursae, collections, or aseptic lymphocyte-dominated vasculitis-associated lesions (ALVAL)[1]. The identification of these lesions has contributed to decision by the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom to publish a safety alert for all metal-on-metal hip replacements[8]. The recommendations included the use of cross-sectional imaging with use of metal artifact reduction sequence (MARS) magnetic resonance imaging (MRI), computed tomography (CT), or ultrasonography to detect pseudotumors, which are thought to represent an adverse reaction to wear debris from metal-on-metal hip prostheses[7].

MRI is an excellent imaging modality for assessing soft tissues, the bone cortex, and the underlying bone marrow, but it is impaired by large magnetic-susceptibility artifacts from metal-on-metal hip prostheses[9]. MRI sequences that reduce the artifacts resulting from metallic prostheses use a variety of techniques including increasing the imaging bandwidth and employing viewing-angle tilting[10-25]. MARS MRI is a recently developed technique that provides good metal-artifact suppression while minimizing image blurring and scanning time[12-14].

A recent study used ultrasonography to screen asymptomatic patients with a metal-on-metal hip prosthesis for pseudotumors and estimated the prevalence to be 6.5%[26]. The sensitivity of ultrasonography for the detection of pseudotumors is not known, but it is likely that small, deep pseudotumors may be more reliably diagnosed with use of MARS MRI. We are not aware of any studies that used MRI to quantify the prevalence of pseudotumors in patients with a well-functioning metal-on-metal hip prosthesis or to compare the prevalence with that in patients with a painful hip prosthesis. The purpose of this study was to perform a case-control study to compare the prevalence and characteristics of pseudotumors in patients with painful and well-functioning metal-on-metal hip prostheses. In addition, the relationship between the presence of pseudotumors and acetabular cup position was characterized with use of three-dimensional computed tomography.

Materials and Methods

Power Analysis

A medical statistician performed a two-proportion power analysis to determine the sample size necessary to provide 90% power when a p value of 0.05 was considered significant. Assuming a pseudotumor prevalence of 60% in patients with a painful metal-on-metal hip replacement[27] and 4% in patients with a well-functioning replacement[26], the minimum sample size of each group was calculated to be thirteen.

Patients

All patients had a unilateral metal-on-metal hip prosthesis and were imaged prospectively. The case group was defined as patients with either unexplained hip pain sufficient to result in revision or an Oxford hip score of <30 of a possible 48 points. Unexplained hip pain was defined as pain with an etiology that remained unclear after assessment of the hip by means of the clinical history, physical examination, laboratory blood tests for markers of infection, and serial radiographs. The control group was defined as patients who did not volunteer pain as a symptom during the assessment and were satisfied with the results of the arthroplasty.

Forty potential control patients were selected from among the patients receiving routine follow-up at our arthroplasty clinic. After excluding patients who did not meet the inclusion criteria, were lost to follow-up, or

TABLE I Method of Classification of Lesions with Use of MARS MRI*

Pseudotumor Type	Wall	Contents	Shape
1	Thin-walled	Fluid-like: hypointense on T1, hyperintense on T2	Flat, with walls mainly in apposition
2a	Thick-walled or irregular	Fluid-like: hypointense on T1, hyperintense on T2	Not flat, with >50% of the walls not in apposition
2b	Thick-walled or irregular	Atypical fluid: hyperintense on T1, variable on T2	Any shape
3	Solid throughout	Mixed signal	Any shape

*MARS MRI = metal artifact reduction sequence magnetic resonance imaging.

TABLE II Comparison of the Patient Groups

Variable	Well-Functioning Group (N = 28)	Painful Group (N = 30)	P Value
Type of implant *(no.)*			
ADEPT	1	2	
ASR	0	5	
Biomet	0	1	
BHR	12	9	
Cormet	15	7	
Durom	0	6	
Oxford hip score*	46 (41.5 to 48)	20 (10-30)	<0.001
Cup inclination angle*† *(deg)*	45 (38-51)	44 (36-52)	0.869
Cup version angle*† *(deg)*	20 (12-26)	15 (8-21)	0.238

*The values are given as the median, with the interquartile range in parentheses. †Measured with use of three-dimensional computed tomography.

TABLE III Logistic Regression Analysis

Predictor	Painful Group	Well-Functioning Group	Adjusted Odds Ratio	95% Confidence Interval	P Value
Presence of pseudotumor	17 patients (57%)	17 patients (61%)	1.392	0.420 to 4.608	0.589
Age at primary arthroplasty	50 yr (42-59 yr)*	57 (51-64)*	1.054 per year	0.992 to 1.121	0.091
Time since primary arthroplasty	31 mo (22-41 mo)*	47 (29-62)*	1.032 per month	1.000 to 1.065	0.051

*The values are given as the median, with the interquartile range in parentheses.

were unwilling to take part in the study, twenty-eight suitable patients were included in the control group. Potential patients in the case group were recruited from either our follow-up clinic or tertiary referrals to our center. The first thirty patients in this group to undergo CT and MRI formed the case group. We were blinded to the results of the clinical investigations prior to patient recruitment. No scans were repeated.

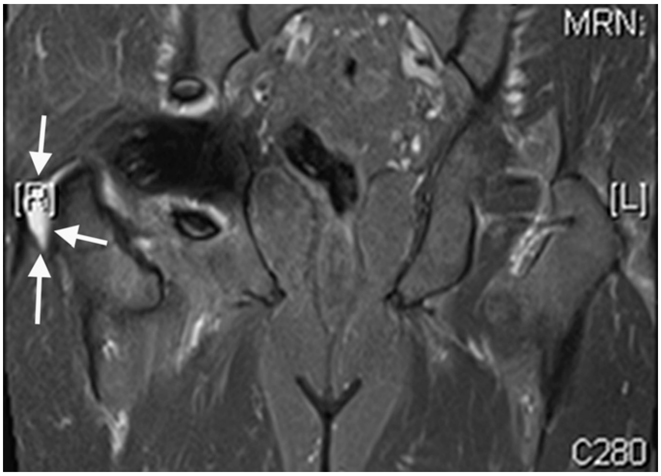

Fig. 1-A

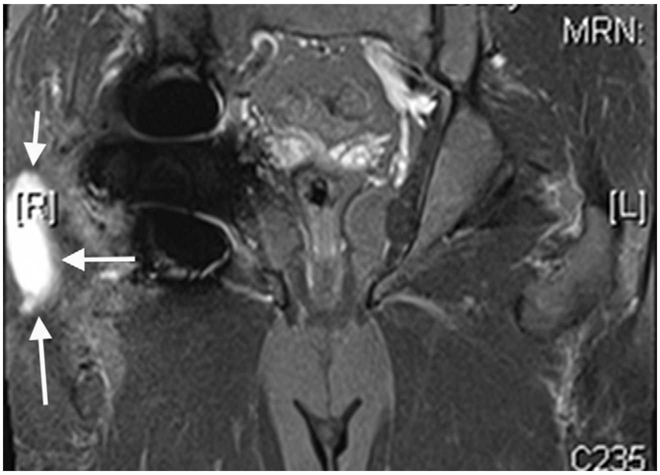

Fig. 1-B

Magnetic resonance images of a type-1 pseudotumor (arrows; see Table I for details) adjacent to a metal-on-metal hip prosthesis that was well functioning (**Fig. 1-A**) and to one that was painful (**Fig. 1-B**).

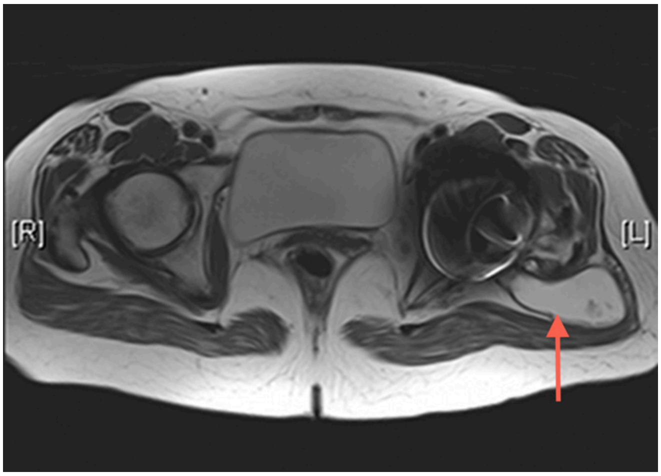

Fig. 2-A

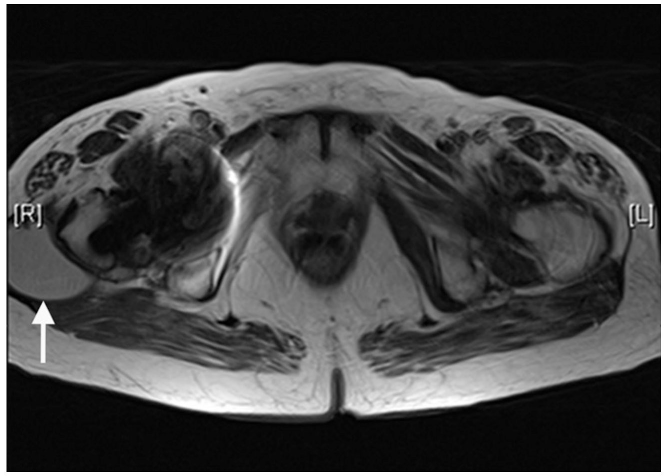

Fig. 2-B

Magnetic resonance images of a type-2a pseudotumor (arrow; see Table I for details) adjacent to a metal-on-metal hip prosthesis that was well functioning (**Fig. 2-A**) and to one that was painful (**Fig. 2-B**).

Data Collection

Hip function was assessed in each patient with use of the Oxford hip score, which is a validated, patient-completed questionnaire[28]. After providing informed consent, each patient underwent MARS MRI of the hip with use of a 1.5-T scanner (MAGNETOM 1.5T; Siemens Medical, Erlangen, Germany). MRI scans were interpreted by consensus agreement by two experienced musculoskeletal radiologists who were blinded to the clinical details. The presence or absence of periprosthetic soft tissue reactions or masses was recorded; if a lesion was present, it was categorized as discussed below.

MRI Characterization of Lesions

Table I summarizes the method of characterization of pseudotumors found on MRI scans. We characterized the wall, shape, and contents. A pseudotumor with a wall thickness of ≤2 mm was classified as "thin-walled." A crude estimate of the volume of the lesion was made by approximation to a cuboid, using the maximal anterior-posterior, superior-inferior, and medial-lateral diameters. The contents were classified according to the signal intensity on T1-weighted and T2-weighted images, as in most MRI classification systems. The pseudotumor classification differentiates simple (type 1) from complex (type 2) fluid collections and those with a solid component (type 3).

CT Scanning of the Hip

CT images were reconstructed in three dimensions, and anatomical acetabular inclination and version were defined with reference to the anterior pelvic plane[29]. These angles were converted to the radiographic equivalents with use of accepted formulas[30].

Histology

Hip neocapsule specimens were collected from patients in the case group who were undergoing revision hip arthroplasty. The articular surface was marked with a suture, and the nonarticular surface was marked circumferentially with a thin line of permanent ink to permit orientation of the specimen under light microscopy. Representative samples were selected and processed in paraffin wax. Four-micrometer-thick sections were cut and stained with hematoxylin

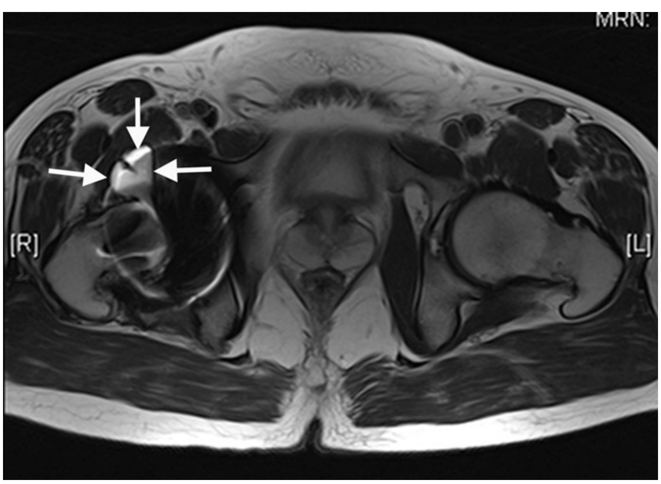

Fig. 3-A

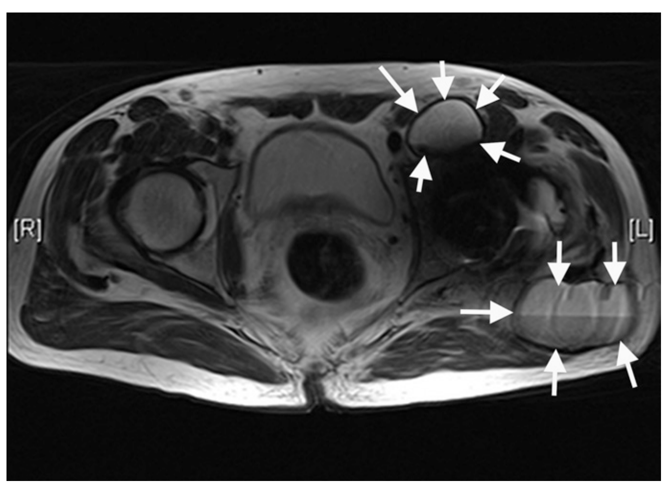

Fig. 3-B

Magnetic resonance images of type-2b pseudotumors (arrows; see Table I for details) adjacent to a metal-on-metal hip prosthesis that was well functioning (**Fig. 3-A**) and to one that was painful (**Fig. 3-B**).

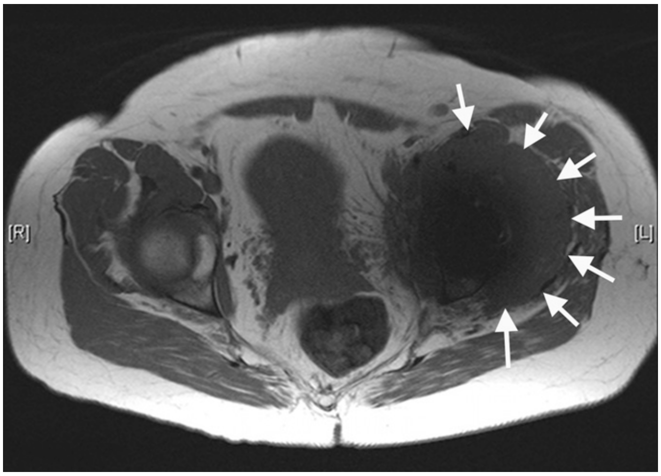

Fig. 4

Magnetic resonance images of a type-3 pseudotumor (arrows; see Table I for details) adjacent to a painful metal-on-metal hip prosthesis.

and eosin. Slides were analyzed according to the criteria established by Willert et al. for the diagnosis of ALVAL[31]. The presence of all three findings of surface necrosis, subsurface macrophage infiltrate, and perivascular lymphocyte infiltrate was defined as diagnostic for ALVAL. The presence of two of these three findings was defined as "suggestive" for the presence of ALVAL. The presence of one or none of the findings was defined as "nondiagnostic" for ALVAL. All samples were further analyzed by a consultant histopathologist for the presence of neutrophils and other features suggestive of infection. Tissue samples were sent for microbiological analysis.

Statistical Analysis

The difference in pseudotumor prevalence between the groups was analyzed with use of logistic regression, adjusting for the known risk factors of sex, age[1], and time since the arthroplasty. The difference in Oxford hip score between the groups was tested with use of the Wilcoxon rank-sum test. A p value of 0.05 (two-sided) was considered significant.

Source of Funding

No external funding was received for this study.

Results

The case group consisted of thirty patients with a painful hip (median age, fifty-five years; interquartile range, forty-six to sixty-four years). The control group consisted of twenty-eight patients with a well-functioning hip (median age, sixty-four years; interquartile range, fifty-four to sixty-nine years). Thirty-four of the patients were men and twenty-four were women. The male:female ratio was 16:14 in the case group and 18:10 in the control group; the difference between groups was

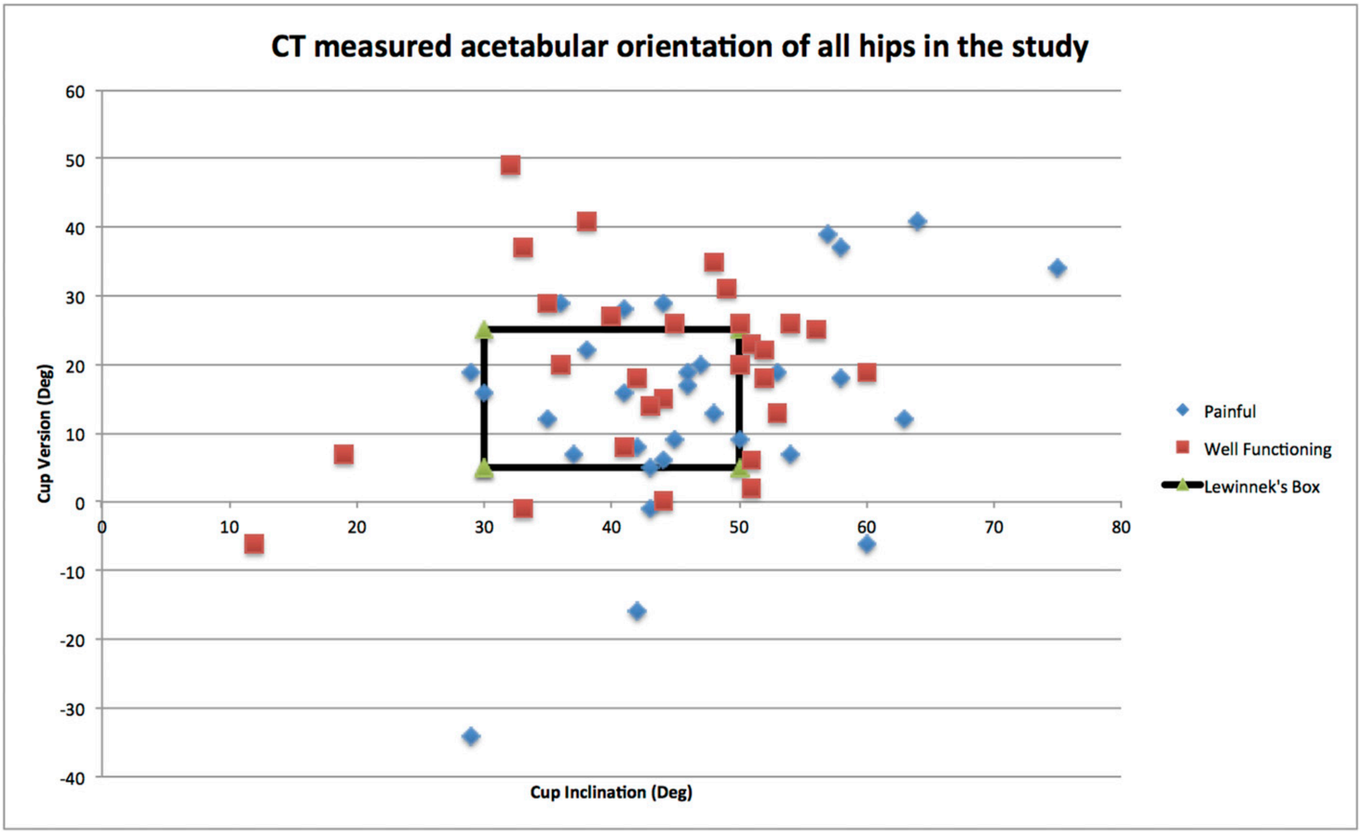

Fig. 5

Scatter plot of acetabular cup version and inclination (measured with use of computed tomography) of all patients with well-functioning and painful metal-on-metal hip prostheses. The Lewinnek safe zone has been added to draw attention to one of the many combinations of orientations that surgeon aim for during total hip arthroplasty.

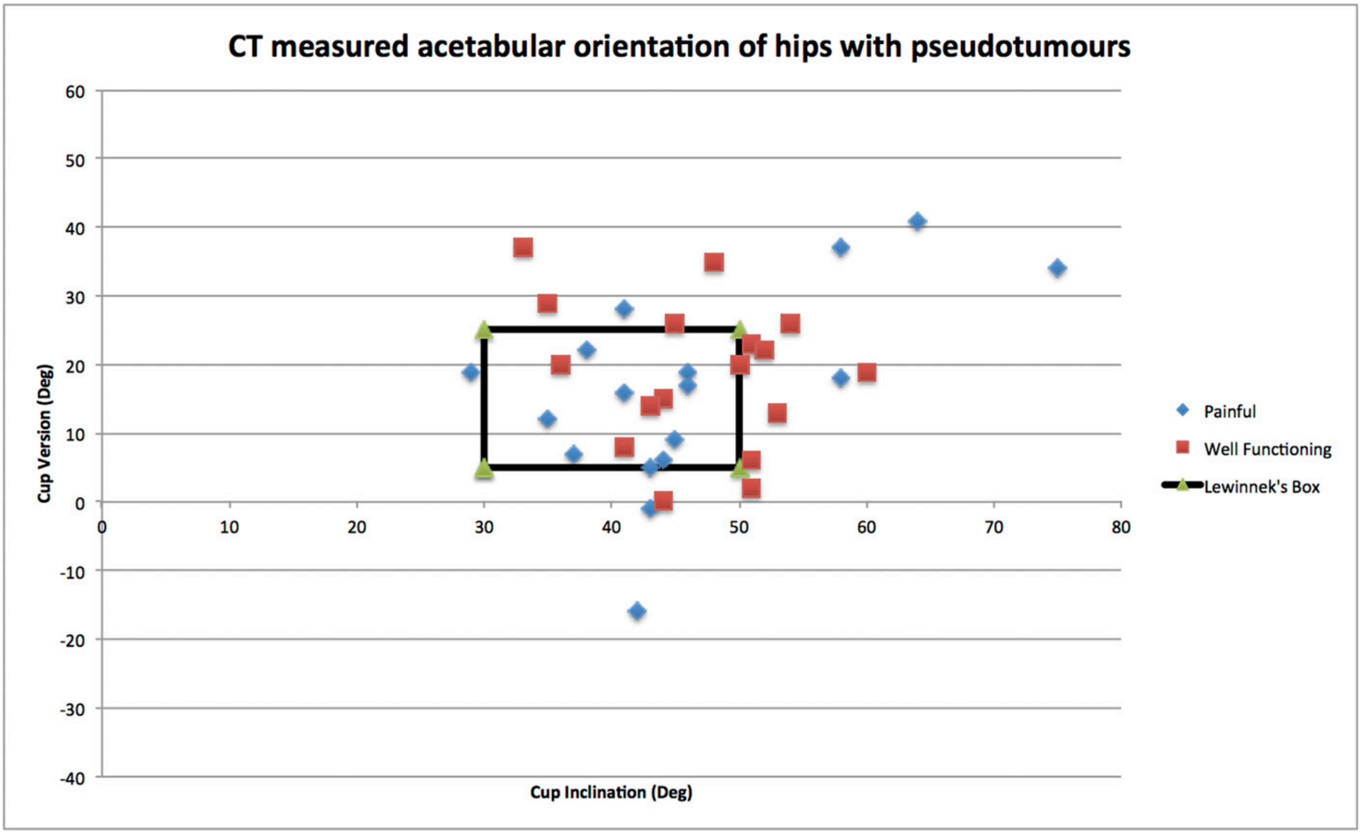

Fig. 6

Scatter plot of acetabular cup version and inclination (measured with use of computed tomography) of those patients with well-functioning and painful metal-on-metal hip prostheses who had a pseudotumor diagnosed on MRI. The Lewinnek safe zone has been added.

not significant (chi-square = 0.791 with 1 degree of freedom, $p = 0.397$).

Additional characteristics of the patients in the two groups are shown in Table II. The mean Oxford hip score was 20.2 (95% confidence interval, 12.7 to 45.8) in the case group and 41.2 (95% confidence interval, 18.5 to 45.8) in the control group ($p \leq 0.0001$). The functional score in the case group was significantly poorer than that in the control group (Mann-Whitney U = 773.5 with $n_1 = 30$ and $n_2 = 28$, $p < 0.0001$).

Logistic Regression Model

A logistic regression model to detect differences between the groups with painful and well-functioning hip prostheses was constructed as described. Sex was removed from the final model because of lack of significance ($p > 0.1$). The results from this model are shown in Table III. The groups did not differ significantly with regard to the prevalence of pseudotumors, age at the time of the primary arthroplasty, or time since the arthroplasty.

MRI

Pseudotumors were identified in thirty-four patients with use of MRI. A pseudotumor was diagnosed in seventeen (57%) of the thirty patients with a painful hip (the case group) and in seventeen (61%) of the twenty-eight asymptomatic patients (the control group). The fluid-filled pseudotumors in the case group had similar characteristics to those in the control group (see Appendix for classification). Eight of the fourteen women and nine of the sixteen men in the case group had a pseudotumor, compared with four of the ten women and thirteen of the eighteen men in the control group.

Examples of periprosthetic pseudotumors of types 1, 2a, and 2b in well-functioning and painful hips are shown in Figures 1, 2, and 3, respectively. One solid pseudotumor was identified in a patient in the case group (Fig. 4). Pseudotumors were present in patients with the following implants: ADEPT (Finsbury Orthopaedics, Surrey, United Kingdom), ASR (Anatomic Surface Replacement; DePuy Johnson & Johnson, Warsaw, Indiana), BHR (BIRMINGHAM HIP Resurfacing System; Smith & Nephew, Memphis, Tennessee), Cormet (Corin, Cirencester, United Kingdom), and Durom (Zimmer, Warsaw, Indiana). The median pseudotumor volume was 25.1 cm^3 (range, 0.9 to 594.0 cm^3). The pseudotumor volume was significantly larger in the patients with a painful hip (median, 79.2 cm^3; range, 5.6 to 594.0 cm^3) than in the patients with a well-functioning hip (median, 15.7 cm^3; range, 0.9 to 75.6 cm^3; $p = 0.016$).

Cup Orientation Measured with Use of CT

Figure 5 shows that the acetabular inclination and version angles varied widely among the patients in each group. Fourteen (47%)

of the thirty hips in the painful group and six (21%) of the twenty-eight hips in the well-functioning group were within the so-called "safe zone" described by Lewinnek et al.[32]. However, a greater number of hips in the painful group were furthest from the Lewinnek safe zone; for instance, all three acetabular cups that had an inclination angle of >60° and all three cups that were more retroverted than −5° were in the painful group. Figure 6 shows the cup orientation of only the patients with a pseudotumor; the acetabular cup was positioned within the Lewinnek safe zone in nine of the seventeen patients in the case group and in five of the seventeen patients in the control group.

Histology

Eighteen patients in the painful group underwent revision arthroplasty, and all had negative microbiological culture results. Samples from thirteen of these patients, including six patients with a visible pseudotumor on MARS MRI, were available for histological analysis. Eight of the samples were "diagnostic" for ALVAL, one was "suggestive," three were "nondiagnostic," and the remaining sample was entirely necrotic and was not analyzed further. Five of the six histological samples from patients with a pseudotumor were "diagnostic" for ALVAL and one was "nondiagnostic." None of the patients in the control group underwent revision arthroplasty.

Discussion

To our knowledge, this is the first study to compare MRI findings between patients with well-functioning and painful metal-on-metal hip prostheses. The 61% pseudotumor prevalence in the well-functioning (control) group was unexpectedly high, and both this prevalence and the characteristics of the pseudotumors were similar to those in the painful (case) group. This high prevalence is probably due to use of the term pseudotumor for a spectrum of lesions—ranging from small, fluid-filled cysts (Fig. 1) to large, complex, and destructive lesions with solid components (Fig. 4)—surrounding metal-on-metal hip prostheses[7]. Prior to this study, we had been concerned by the presence of any cystic mass that was visible adjacent to a metal-on-metal hip prosthesis on MARS MRI because previous researchers had included cystic masses in their definition of pseudotumors and had reported a poor clinical outcome associated with the presence of pseudotumors[2]. As a result of our study, we now place less clinical importance on the presence of a fluid-filled lesion visible on MARS MRI. However, we recognize the variability in proposed definitions of the term pseudotumor, and we recommend that the natural history and longitudinal imaging findings of these lesions be more fully analyzed.

We continue to use MRI in diagnosing the cause of a painful metal-on-metal hip arthroplasty and also find it useful when planning revision arthroplasty (for instance, to determine the extent of intrapelvic debridement required and to avoid neurological structures during the debridement). We remain concerned about the solid pseudotumors (Fig. 4), but we are seeking an alternative term, or a more restrictive use of the term pseudotumor, to describe the spectrum of fluid-filled lesions that is observed. We suggest that surgeons and radiologists consider the status of the tissues surrounding the fluid lesion—specifically, the destruction of adjacent muscle and other soft tissue.

The high prevalence of fluid-filled lesions in both groups may simply reflect the fact that the capsulotomy required during implantation of a hip prosthesis results in potential points of weakness within the capsule[27]. A complete capsulotomy is routinely performed to enable acetabular exposure during hip resurfacing, in which the femoral head is retained, whereas a partial capsulotomy is sufficient during a conventional hip arthroplasty, in which the femoral head is removed. The location of the fluid collections may be related to pathways of low resistance created by the capsulotomy, rather than to the surgical approach, which would explain the occurrence of collections in the iliopsoas.

A small number of fluid collections had atypical fluid signal characteristics in the core of the lesion, with a high signal on both T1 and T2-weighted images (Fig. 3). It is not clear whether this is due to the presence of proteinaceous material or a high concentration of metal ions. These fluid collections may represent a more clinically problematic group of lesions, although there was no difference in their prevalence between the two groups in this study. Therefore, although the classification of lesions into fluid-filled and solid types appears to be clinically relevant, we were unable to demonstrate the clinical importance of differences among the fluid-filled lesions.

This study also examined the histology of the lesions in a small number of patients who underwent revision arthroplasty. Consistent with the findings reported by other groups[5,7], we noted that five of six patients with a pseudotumor had histological results that were diagnostic for ALVAL. However, it was also evident that the remaining patient with a pseudotumor did not have features of ALVAL, and three patients without a pseudotumor had histological results that were diagnostic for ALVAL. We therefore caution that ALVAL-type histology was not pathognomonic for the presence of a pseudotumor, and we encourage future work to determine whether an immunological mechanism is responsible for these lesions.

We also investigated the relationship between acetabular component position, hip function, and pseudotumor occurrence. Unsurprisingly, we found that extremes of malpositioning were associated with poor hip function. However, we also noted that 41% (fourteen) of the thirty-four pseudotumor occurrences were associated with components positioned within the Lewinnek safe zone.

Other Studies Involving MARS MRI in Patients with Metal-on-Metal Hip Prostheses

A number of series have provided details of MARS MRI findings in a smaller number of patients[1,7,27,33,34]. One previous study indicated that women were at greater risk of developing a pseudotumor than men were[1]. However, we did not find evidence to support this in our study. In our population, pseudotumors were more common in male patients, but this difference was not significant. This finding is consistent with the similar pseudotumor prevalence in men and women in other reports[27,33,34].

Limitations

One limitation of our study is the inability to accurately classify patients as having either a well-functioning or a painful hip on the basis of the Oxford hip score, even though the Oxford hip scores differed substantially and significantly between the groups. For instance, one of the patients in the well-functioning group had a relatively low Oxford hip score (31 of a possible 48 points) but was satisfied with the results of the hip arthroplasty and regarded the procedure as successful. In such cases, other areas of the body (commonly the lumbar spine) may reduce the overall Oxford hip score. In contrast, one of the patients in the painful group was dissatisfied with the results of the hip arthroplasty despite a high Oxford hip score (43 of 48 points) because he was unable to sail and play tennis.

Another limitation is that our MRI and clinical assessments took place at a single follow-up time point. It is therefore possible that the pseudotumors observed in the well-functioning group will develop into symptomatic lesions. Investigation of this possibility will require longitudinal study of these lesions to understand their natural history, but to our knowledge such a study has not yet been reported. For instance, variation in the size of the lesion over time may be relevant; if small lesions are detectable on MRI but not on ultrasonography, this may explain the lower prevalence (six [10%] of sixty-one women) in a recently reported study involving ultrasonographic screening[26].

Summary

A periprosthetic cystic pseudotumor was commonly diagnosed (in 59% of the entire study cohort) with use of MARS MRI in patients with a metal-on-metal hip prosthesis, and the prevalence was similar regardless of whether the hip was functioning well or poorly. A pseudotumor was also commonly found in patients with a well-positioned acetabular component. Although MARS MRI is useful for surgical planning, the presence of a fluid-filled periprosthetic lesion (pseudotumor) may not necessarily indicate the need for revision arthroplasty. Further correlation of clinical and imaging data is needed to identify the natural history of pseudotumors to guide clinical practice.

Appendix

eA A table summarizing the MARS MRI findings in the patient groups is available with the online version of this article as a data supplement at jbjs.org. ■

NOTE: The authors acknowledge Gwynneth Lloyd, Angus Lewis, and the patients who contributed to this study.

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