

RESEARCH ARTICLE

Semi-quantitative histology confirms that the macrophage is the predominant cell type in metal-on-metal hip tissues

Patricia Campbell  | Sang-Hyun Park  | Edward Ebramzadeh 

The J. Vernon Luck, Sr., M.D. Orthopaedic Research Center, Department of Orthopaedic Surgery, Orthopaedic Institute for Children, UCLA, Los Angeles, California, USA

Correspondence

Patricia Campbell, 403 W. Adams Blvd., Los Angeles, CA 90007, USA.
Email: pcampbell@mednet.ucla.edu

Funding information

DePuy Synthes

Abstract

Numerous studies have examined the histology of metal-on-metal hip tissues for evidence of a dose response to metal wear but have often reported inconclusive or contradictory findings. The aim of the present study was to address these discrepancies using multiple histological scoring methods to characterize the tissue features of one large group of revised metal-on-metal total hips. Periprosthetic tissues from 165 metal-on-metal hip revisions were examined for features of aseptic lymphocytic vasculitis associated lesions (ALVAL) as rated using two scoring systems as well as rankings for macrophage and lymphocyte numbers, intracellular wear debris and necrosis. Correlations between histological features and clinical variables including gender and time to revision and implant variables including articular surface wear volume or visual taper corrosion scores were examined. Both ALVAL scores reflected the macrophage dominated histology with average scores of 5.9/10 and 1.5/3. There was a statistically significant correlation between the original ALVAL score and wear rate per year (correlation coefficient = 0.17, $p = .05$) and a moderate correlation between the number of macrophages and wear particles and wear volume. There was no statistically significant correlation between wear and any other feature including lymphocytic inflammation or necrosis. Strong correlations between combined cup and ball wear volume and histological characteristics were not observed, although the number of macrophages was more closely correlated with wear than lymphocytes or necrosis.

KEYWORDS

ALTR, ALVAL, histology, metal-on-metal, wear

1 | INTRODUCTION

The initially promising clinical results of metal-on-metal bearings for total hip and hip resurfacing arthroplasty were followed by increasing rates of revisions for a spectrum of causes including unexplained pain and adverse local reactions such as pseudotumors. The incidence of these failures varied among the different implant

designs, and numerous studies were conducted to examine the roles of clinical, surgical and implant variables in the outcome of metal-on-metal hips. Several studies based on metal ion measurements found an association between component wear and the incidence of pseudotumors^{1,2} although it was not clear whether these adverse reactions were dose-dependent and mediated by an immune response or were a direct toxic effect of the metal debris.³

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2021 The Authors. *Journal of Orthopaedic Research*® published by Wiley Periodicals LLC on behalf of Orthopaedic Research Society.

The results of histological studies which examined correlations between tissue features such as lymphocytic inflammation or necrosis and component wear have typically reported wide ranging tissue scores and highly variable wear results leading to inconclusive results.⁴ For example, Lehtovirta et al.⁵ reported from a study of 85 metal-on-metal hip resurfacings that bearing wear volume correlated with blood metal ion levels and the degree of necrosis and macrophage infiltration in periprosthetic tissues. By contrast, Langton et al.³ did not find a correlation between wear and the number of macrophages or degree of necrosis in a group of 60 revised metal-on-metal hip resurfacings. Grammatopoulos et al.⁶ examined tissues around 56 metal-on-metal hip resurfacings revised mostly for symptomatic pseudotumor formation. The authors reported that histological findings did not strongly correlate with wear depth per year because some hips with relatively low wear had a pronounced lymphocytic response, consistent with a hypersensitivity reaction. This was concluded to reflect variability in the individual response to the amount and, possibly, type of metal debris.

In 2010, the DePuy Articular Surface Replacement (ASR; DePuy) was recalled by the manufacturer following higher than anticipated revision rates. Our research team was contracted by the manufacturer to perform implant retrieval analysis on all available revised ASR implants sourced from multiple surgeons throughout the United States. This provided an opportunity to examine the concept of a dose-response in a much larger group of metal-on-metal retrievals. To maximize the information gained from these samples, we elected to use multiple semi-quantitative histological scoring systems. These included a previously reported cellular ranking⁷ and the original aseptic lymphocytic vasculitis associated lesions (ALVAL) score that we developed.⁸ This is a 10-point ranking that assigns 3 points for the integrity of the synovial lining, 4 points for the type of inflammatory cell infiltrate and 3 points for the general tissue organization. We also used the Oxford-ALVAL score that uses a 0–3 point ranking based on the maximum degree of perivascular lymphocyte cuffing around vessels in the specimen.⁶ In total, rankings for macrophage and lymphocyte numbers, intracellular wear debris, solid corrosion products and necrosis were utilized.^{7,9} Our aim was to apply the data from this tissue analysis to examine correlations with patient and implant factors such as wear.

2 | METHODS

Institutional IRB approval was given for this study. Between early 2011 and the end of 2017, nearly 600 revised ASRs were submitted from hundreds of small and large hospitals around the United States. All of the revision cases that were accompanied by tissue samples were included in this histological review. One hundred and sixty-five tissue specimens were suitable for inclusion after 15 were excluded as too small or consisting only of bone or blood clot. The reasons for revision were provided for 135 cases by the revising hospital. Typically, multiple reasons were listed; up to six were listed in some cases. Pain ($n = 86$) and/or elevated ions ($n = 62$) were the most common descriptors listed as causes for revision. “Litigation alleges [multiple reasons]” was the second most common term and was listed as the

reason for revision in 34 cases. The term loosening was used in 21 case descriptions, metallosis in 19 case descriptions, pseudotumor, cyst or fluid in 14, osteolysis in 6, infection in 4 and hypersensitivity in 2 case descriptions. In the absence of radiological imaging reports, metal level reports or case specific details, the listed reasons for revision could not be confirmed and was, therefore, not included in the multiple variables examined in this study. The vast majority of revisions involved the ASR XL total hip replacement and only three were ASR hip resurfacings. There were 80 female patients, 83 male patients and 2 unknowns. The median age at the time of implantation was 56.2 (range: 21.3–88.3, unknown in 15 cases) and the median time to revision was 4.8 years (range: 1.1–9.5 years, unknown in 17 cases).

3 | HISTOLOGY

The size, location or number of tissue specimens was not standardized and was highly variable. The majority of the 165 tissue samples either had no information as to the tissue source, or were described as [left/right/hip] tissue. When a descriptive term was used, it was most commonly capsule or synovial tissue. Only six tissues were labeled as being from a cyst, bursa or pseudotumor. For each retrieval, multiple tissues were sampled to histologically examine a wide selection of tissues. The specimens were routinely processed into paraffin wax, sectioned and stained with haematoxylin and eosin.

An experienced investigator examined the slides for specific histological features without reference to the clinical details or implant retrieval results, using several different ranking methods as shown in Table 1, including two ALVAL scores. Using the previously developed 10-point ALVAL scoring system, hereafter called the C-ALVAL score,⁸ the integrity of the synovial lining, the macrophagic and/or lymphocytic inflammatory cell infiltration and general tissue organization were each ranked for a total of 10 points. In this method, low scores reflect preservation of the synovial lining, macrophage-dominated infiltration and capsule-like tissue arrangements. By contrast, the highest score reflects complete loss of the synovial lining, lymphocyte-dominated inflammation and loss of capsule-like arrangement, often with extensive necrosis. The estimated percentage of tissue necrosis per slide was separately recorded.

In the second ALVAL method, hereafter called the Oxford ALVAL score,⁶ the degree of perivascular lymphocytic inflammation was ranked from 0 to 3, and tissue necrosis was scored as shown in Table 1.

3.1 | Statistical analysis

SPSS Version 19.0 (IBM) was used. The clinical variables of interest included patient gender, age at revision and time to revision. The implant variables of interest included femoral ball diameter, ball taper Goldberg score,¹⁰ cup and ball volumetric bearing wear volume and annual volumetric wear rate. The 4 point visual Goldberg score was used as a ranking of femoral ball taper corrosion.

TABLE 1 Summary of histological features examined and the scoring methods used to rank them

Feature (citation)	Score of 0	Score of 1	Score of 2	Score of 3	Score of 4
C-ALVAL synovial surface ⁸	normal, intact	focal loss of surface	moderate loss of surface, fibrin attachment	marked or total loss of surface and abundant attached fibrin	predominantly lymphocytes
C-ALVAL inflammatory infiltrates ⁸	none	predominantly macrophages	macrophages and diffuse lymphocytes or few small aggregates of lymphocytes	mix of macrophages and lymphocytes, large aggregates	predominantly lymphocytes
C-ALVAL organization score ⁸	normal capsule -like organization	normal with synovial hyperplasia, small focal necrotic areas	marked loss of normal arrangement, distinct cellular and acellular areas	predominant lymphoid aggregates at the rear, thick acellular areas present	
Oxford ALVAL ⁶	none	minor, cuffs <5 cells thick	severe perivascular aggregates 5–10 cells thick	numerous perivascular aggregates, >10 cells thick	
Macrophages ⁷	none	1–5 cells per hpf	6–49 cells per hpf	>50 or more cells per hpf	
Solid corrosion products ⁹	none	1–5 per slide	6–10 per slide	>10 per slide	
Fine metal in most cells ⁷	none	<10 particles per cell, "slate blue/grey"	10–100 particles per cell, "dusty" with debris	>100/numerable visible particles per cell, black, stuffed with debris	
Lymphocytes ⁷	none/rare	1–9 cells per hpf	10–49 cells per hpf	50 or more cells per hpf	
Plasma cells	none/rare	<10 per hpf	10–20 per hpf	>21 per hpf	
Giant cells	none/rare	1 per hpf	2–4 per hpf	>5 per hpf	
Oxford necrosis ⁶	none	scattered small necrotic areas	up to 25% tissue	>25% tissue	

Abbreviation: hpf, high powered field.

TABLE 2 Descriptive statistics of histology features in all slides for all cases

	Macrophages	Lymphocytes	C-ALVAL	Oxford ALVAL	% Necrosis	Oxford necrosis score
Mean	2.3	1.1	5.9	1.5	16.8	1.1
SD	0.7	1.1	1.7	1.1	25.7	1.2
Median	2.0	1.0	5.7	1.0	5.0	1.0
Mode	2	0	5	0	0	0
Minimum	0	0	3	0	0	0
Maximum	3	3	10	3	100	3

Abbreviation: ALVAL, aseptic lymphocytic vasculitis associated lesions.

In almost all cases, multiple sections were available for histological evaluations. Graphs and tables reporting histological features were therefore based on the average value of each histological feature among the multiple sections for a given case. In this way, each case was represented by one data point for each feature, representing the average of the sections for that case. All of the graphs and tables are based on these average values. However for correlation analyses, described below, the maximum value of each histological feature for each case was used.

The majority of the histological variables showed skewed distributions and therefore nonparametric statistical analysis was used. Specifically, the Spearman correlation coefficient was calculated to find any correlations between the maximum values of the histological variables for each tissue versus patient and implant wear-related variables

4 | RESULTS

4.1 | Histology

The number of slides examined for each case ranged from 1 to 7 (median 2) for a total of 345 slides. Of these, 7 lacked a tissue edge suitable for evaluating the synovial lining score but the cellular ratings, presence and amount of necrosis and wear debris were still ranked in those slides. Tables 2–4 summarize the histological findings.

TABLE 3 Descriptive statistics for histological features, using average scores of each case

	C-ALVAL	Oxford ALVAL	% Necrosis	Oxford necrosis score
Mean	5.9	1.5	15.1	1.0
Median	5.7	1.0	5.0	1.0
SD	1.7	1.1	22.5	1.0
Minimum	3.0	0.0	0.0	0.0
Maximum	10.0	3.0	96.7	3.0

Abbreviation: ALVAL, aseptic lymphocytic vasculitis associated lesions.

Macrophages were the most prominent cell type and the most commonly applied score for all slides was 2 (6–49 cells per high powered field, in 145 slides). Macrophages were most commonly rated as having a slate blue color and fewer than 10 visible particles per cell, but dusty or black cells packed with innumerable particles were present in 39 cases. Diffuse and/or perivascular lymphocytes were present in the majority of cases ($n = 116$ cases, 70.3%) but typically at fewer than 10 lymphocytes per high power field. The average lymphocyte cell score was less than 1 in 67 cases (42%) while an average high score of 3 was assigned in 23 cases (14%). Plasma cells were only present in 55 cases (40.7%), usually in small numbers that were mixed with macrophages and lymphocytes. However, extensive numbers of plasma cells were observed in 11 cases (6.6%) in which they often dominated the perivascular aggregates. Eosinophils and polymorphonuclear neutrophils were only observed in 2 (1.2%) cases each.

A wide range of C-ALVAL and Oxford ALVAL scores was found (Table 3). The most commonly assigned ALVAL scores (i.e., the mode for each rated tissue slide) was 5/10 and 0/3 for the C-ALVAL and Oxford-ALVAL scores, respectively. The averaged C-ALVAL scores ranged from 3/10 (3 cases) to 10/10 (5 cases), mean 5.9. The averaged Oxford ALVAL score ranged from 0/3 (28 cases) to 3/3 (41 cases), mean 1.5.

The majority of the slides consisted of viable tissue but where present, the estimated tissue necrosis averaged 15.1%, SD 22.5%, median 5.0%. Two cases were found to consist only of necrotic tissue but a necrosis score of 0 was assigned to 50 cases (30%), including

TABLE 4 Descriptive statistics for histological features, using maximum scores of each case

	C-ALVAL	Oxford ALVAL	% Necrosis	Oxford necrosis score
Mean	6.2	1.8	20.3	1.3
Median	6.0	2.0	7.5	1.0
SD	1.9	1.1	28.0	1.1
Minimum	0.0	0.0	0.0	0.0
Maximum	10.0	3.0	100.0	3.0

Abbreviation: ALVAL, aseptic lymphocytic vasculitis associated lesions.

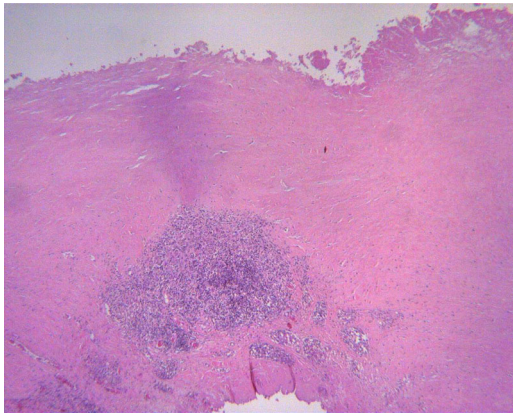


FIGURE 3 Light micrograph of tissues from a 66-year-old woman, revised after 3 years. The average C-ALVAL score of 3 tissue sections was 9, maximum 10. This score reflects the complete loss of the synovial lining and loss of capsule-like organization and the formation of large lymphocytic aggregates in the deep layers of the tissue. The average Oxford-ALVAL score of 3 reflects the large lymphocyte aggregates. Necrosis averaged 65%, and was rated 3 on the Oxford necrosis score. H&E, $\times 40$. ALVAL, aseptic lymphocytic vasculitis associated lesions; H&E, haematoxylin and eosin [Color figure can be viewed at wileyonlinelibrary.com]

7 | DISCUSSION

In our previous study of ASR tissue features using only the C-ALVAL score, a range of scores reflected a spectrum of histology from minimal macrophage infiltration to extensive lymphocytic inflammation.¹¹ The results of the present study were similar, and each of the multiple scoring methods gave comparable ranges in the cell and tissue features. Predominantly macrophagic tissue responses have been associated with an innate immune reaction to wear

TABLE 5 Statistically significant ($p < .05$) correlation coefficients and p values of maximum histological variables and component wear

Feature	Correlated with	C. coefficient	p Value
Macrophage numbers	Ball wear volume	0.19	.02
Fine metal	Ball wear volume	0.2	.01
	Total wear	0.19	.02
Giant cells	Ball wear volume	0.2	.01
Solid corrosion products	Goldberg score	0.23	.00
C-ALVAL total	Wear rate	0.17	.05
Oxford necrosis	Ball wear volume	0.16	.04
	Goldberg score	-0.16	.05

debris¹²⁻¹⁴ while a predominantly lymphocytic inflammatory reaction has been linked to an adaptive immune response¹⁵⁻¹⁸ but there is a lack of consensus regarding the clinical significance of these findings and their relationship with wear debris. The application of semi-quantitative histological rating scores has been proposed to improve the reporting of these reactions⁸ and many studies now report histology using such data.

In studies which also report component wear measurements, researchers have evaluated correlations between tissue reactions and wear for evidence of a dose-response. Campbell et al.⁴ reviewed 12 English-language studies from a systematic review of papers in PubMed and Embase databases that reported the results of wear measurements from revised metal-on-metal implants and the

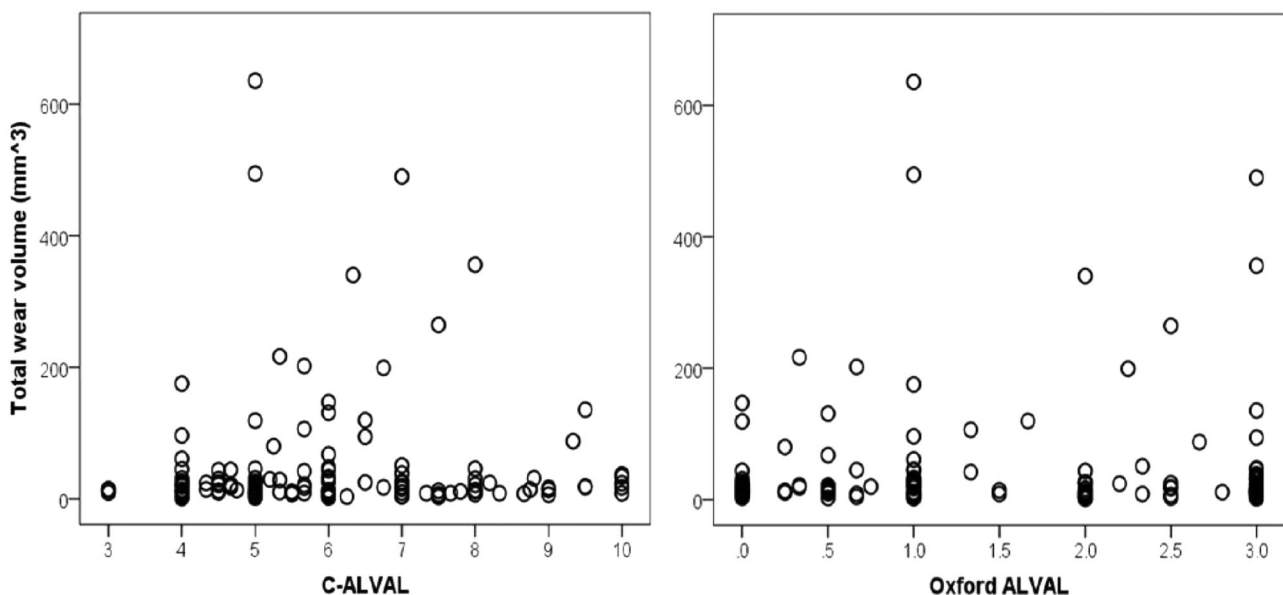


FIGURE 4 Scatter plots indicating the distribution of volumetric wear as a function of C-ALVAL scores and Oxford ALVAL scores. ALVAL, aseptic lymphocytic vasculitis associated lesions

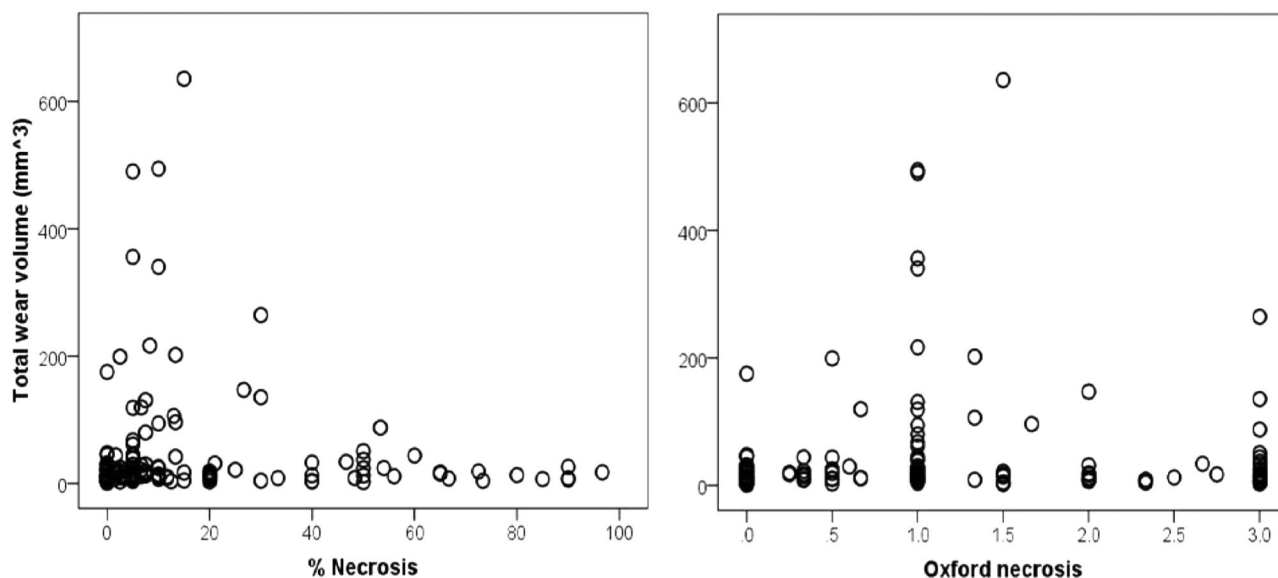


FIGURE 5 Scatter plots indicating the distribution of volumetric wear for tissues with a range of percent-necrosis and Oxford necrosis scores

histopathology of the periprosthetic tissues. Notably, there was a wide range of wear depth and volumetric wear data reported in patients revised for suspected wear-induced problems such as a pseudotumor, and no evidence of a dose response. Reports that pseudotumors occur in association with well-positioned, low wearing metal-on-metal bearings, possibly as a result of metal sensitivity, as well as variable host-specific factors helps to explain the lack of correlation between component wear and the occurrence of pseudotumors.^{2,5,8,19,20} Lehtovirta et al.⁵ studied 85 ASR hip resurfacings revised for adverse reactions to wear debris. They used two semi-quantitative histopathology scores including the C-ALVAL score, and CMM to measure bearing wear. Similar to the findings in the present study, they noted that macrophage infiltration occurred to some degree in all tissues, while many tissues lacked or had very few lymphocytes, even though the tissues were all from ASRs that were revised for adverse reactions to metal debris. The median cup and ball total wear volume was 39 mm^3 (range: $7\text{--}541 \text{ mm}^3$) which was much higher than the median total wear volume in the present study, 15.4 mm^3 (range: $1.2\text{--}635.8 \text{ mm}^3$) but notably, the ranges in measured wear were very large in both studies. They found that total wear volume showed a moderate correlation with surface tissue necrosis, macrophage sheet thickness, tissue organization score and total ALVAL score, while wear rate was found to correlate with tissue organization score and total ALVAL score. In the present study, ball wear volume but not cup wear or total wear volume showed statistically significant correlations with macrophage numbers and with Oxford necrosis but not estimated necrosis amounts. Thus, not all of the wear measurements showed correlations with tissue features. Neither the study by Lehtovirta et al.⁵ nor the present study found correlations with any of the wear variables and the lymphocytic histological variables, although high ALVAL scores occurred in a small number of patients. In our previous studies, the highest ALVAL

scores occurred in a small percentage of patients with suspected metal hypersensitivity.⁸ However, in the present study, we did not have sufficient clinical information to examine this variable. Reito et al.²¹ observed that ASR tissues showed four differing histopathological patterns that occurred both due to excessive wear and to immunological hypersensitivity and low wear. They suggested that in a subset of patients, there was a certain threshold of wear required after which a traditional lymphocyte dominated reaction starts to develop but this amount of wear is still unknown.

The majority of ASR tissues studied to date were selected on the basis of being classified as revised for adverse reaction to metal debris, which includes intraoperative metallosis or pseudotumors or histological lymphocytic inflammation.^{5,6,21} By contrast, every suitable tissue specimen available from the submitted revision cases was examined in the present study. It should be noted, however, that the choice to submit tissue specimens lay with the revising surgeons and it is possible that only tissues with unusual features such as metallosis or necrosis or from patients with unusual symptoms or suspected high wear were submitted. Indeed, we found that the median wear of the tissue group was slightly higher than the median wear of the larger revised ASR group.¹¹ Thus, one of the limitations of this study is that the tissues provided for examination may not be representative of the entire revised ASR cohort. Another limitation was that, while basic demographic information was available, detailed individual information such as cup position, blood metal levels and symptom history were not generally available.

While the wear volume of each bearing surface was measured, and taper corrosion features were visually ranked, the contribution of taper corrosion products to the tissue characteristics cannot be accurately assessed from this method. However, our correlation analysis was nonparametric, and therefore the addition of any hypothetical value of wear debris to all cases would not substantially

change any of the correlation coefficients or associated *p* values. Therefore, if the amount of taper wear debris was uniformly distributed among the cohort, there would be no change in the results and conclusions drawn in the study. Notably, although the majority of the tapers in this study were rated as 4 on the Goldberg visual scale, this rating does not necessarily mean that large amounts of material loss occurred in those tapers. Hothi et al.²² used the visual rating scale and also measured material loss in 150 metal-on-metal hips, including 61 ASRs. They reported a wide range of material loss (ranging from approximately 0.1–26 mm³) within tapers but the median amount in tapers with the highest Goldberg rating was 1.52 mm³. Overall, they found a moderate correlation between taper corrosion scores and material loss. A strong correlation was found between the Goldberg visual score and taper material loss by Matthies et al.²³ who found a median volume of 2.02 mm³ in 110 large diameter femoral balls. In both the present study and that of Lehtovirta et al.,⁵ which was based on resurfacings, a correlation was found between wear volume and C-ALVAL score. These similar findings suggest that the influence of taper wear on histology was not a large one.

Periprosthetic tissues are commonly reported to display a high degree of heterogeneity from site to site and obtaining multiple samples for histopathological examination is recommended. In addition to processing multiple specimens, we collated the histological scores for each slide as well as calculating the average for multiple slides and the maximum value for each variable. Our initial correlation analysis (not presented) was based on the average score of each histological feature among the multiple slides for each tissue, but found very few correlations with clinical or implant related variables using these average scores. Therefore, we chose to use the maximum score for each tissue, since this may better represent the histological state of that particular tissue.

Reporting the histopathological findings of periprosthetic tissues using one or more of the semi-quantitative scores is becoming more common.^{6,14,16,17,24,24,25} The C-ALVAL score has been criticized for emphasizing necrosis while not including macrophagic exfoliation²⁶ and for not providing sufficiently well-defined or discriminatory criteria to permit distinction between high-wear and low-wear metal-on-metal hip replacements.⁶ Smeekes et al.²⁷ reported low intra-class reproducibility of both the C-ALVAL and the Oxford ALVAL scores and called for the development of a simpler score.²⁷ However, over-simplifying the quantification of a wide number of histopathological variables that reflect complex biological processes that are clearly affected by multiple patient, implant and surgical factors may be self-defeating. In fact, some authors have used more complicated scoring methods and/or multiple scoring methods.^{26,28,29} Regardless of the scoring method, the key to understanding the complex interrelationships between the periprosthetic tissues and component wear and corrosion products is to have sufficient samples from as wide a variety of material combinations and failure modes as possible. We recommend surgeons submit all of the removed periprosthetic tissues and implants to the Pathology

department for examination regardless of appearance or the suspected failure mode.

8 | CONCLUSIONS

In this cohort of 165 revised ASR hip replacements, there was a high degree of variability in histological scores for inflammatory cell types, wear debris, and necrosis. Regardless of the scoring method, the majority of the tissues were ranked with moderate levels of macrophage-dominated inflammation and necrosis. The wear of these 165 cases also covered a spectrum of low and high wear and strong correlations between combined cup and ball wear volume and histological features were not observed, although the number of macrophages was more closely correlated with wear than lymphocytes or necrosis.

ACKNOWLEDGEMENTS

The authors are grateful to Dr Zhen Lu for the CMM analysis and to Mr Matthew Day for assistance with the figures. This study was conducted with funding from DePuy Synthes. The funder played no role in the study design, data interpretation or manuscript preparation.

CONFLICT OF INTERESTS

The author Patricia Campbell is a medico-legal consultant for DePuy Synthes.

AUTHOR CONTRIBUTIONS

Patricia Campbell: research design, data acquisition, analysis and interpretation of data, review and revision of manuscript. **Sang-Hyun Park:** data acquisition, analysis and interpretation of data, review and revision of manuscript. **Edward Ebramzadeh:** analysis and interpretation of data, review and revision of manuscript. Each author has read and approved the final submitted manuscript.

ORCID

Patricia Campbell  <http://orcid.org/0000-0002-3652-7264>

Sang-Hyun Park  <https://orcid.org/0000-0002-5812-831X>

Edward Ebramzadeh  <http://orcid.org/0000-0001-5282-8465>

REFERENCES

1. Kwon YM, Glyn-Jones S, Simpson DJ, et al. Analysis of wear of retrieved metal-on-metal hip resurfacing implants revised due to pseudotumours. *J Bone Joint Surg Br.* 2010;92:356-361.
2. Glyn-Jones S, Roques A, Taylor A, et al. The in vivo linear and volumetric wear of hip resurfacing implants revised for pseudotumor. *J Bone Joint Surg Am.* 2011;93:2180-2188.
3. Langton DJ, Joyce TJ, Jameson SS, et al. Adverse reaction to metal debris following hip resurfacing. *J Bone Joint Surg Br.* 2011;93:164-171.
4. Campbell PA, Kung MS, Hsu AR, Jacobs JJ. Do retrieval analysis and blood metal measurements contribute to our understanding of adverse local tissue reactions? *Clin Orthop Relat Res.* 2014;472:3718-3727.

5. Lehtovirta L, Reito A, Parkkinen J, et al. Analysis of bearing wear, whole blood and synovial fluid metal ion concentrations and histopathological findings in patients with failed ASR hip resurfacings. *BMC Musculoskelet Disord*. 2017;18:523. <https://doi.org/10.1186/s12891-017-1894-5>
6. Grammatopoulos G, Pandit H, Kamali A, et al. The correlation of wear with histological features after failed hip resurfacing arthroplasty. *J Bone Joint Surg Am*. 2013;95(12):e81. <https://doi.org/10.2106/JBJS.L00775>
7. Doorn PF, Mirra JM, Campbell PA, Amstutz HC. Tissue reaction to metal on metal total hip prostheses. *Clin Orthop Relat Res*. 1996;329: S187-S205.
8. Campbell P, Ebramzadeh E, Nelson S, Takamura K, De Smet K, Amstutz HC. Histological features of pseudotumor-like tissues from metal-on-metal hips. *Clin Orthop Relat Res*. 2010;468:2321-2327.
9. Huber M, Reinisch G, Trettenhahn G, Zweymüller K, Lintner F. Presence of corrosion products and hypersensitivity-associated reactions in periprosthetic tissue after aseptic loosening of total hip replacements with metal bearing surfaces. *Acta Biomater*. 2009;5: 172-180.
10. Goldberg JR, Gilbert JL, Jacobs JJ, Bauer TW, Paprosky W, Leurgans S. A multicenter retrieval study of the taper interfaces of modular hip prostheses. *Clin Orthop Relat Res*. 2002;401:149-161.
11. Park SH, Lu Z, Hastings RS, Campbell PA, Ebramzadeh E. Five hundred fifty-five retrieved metal-on-metal hip replacements of a single design show a wide range of wear, surface features, and histopathologic reactions. *Clin Orthop Relat Res*. 2018;476:261-278.
12. Gallo J, Goodman SB, Konttinen YT, Raska M. Particle disease: biologic mechanisms of periprosthetic osteolysis in total hip arthroplasty. *Innate Immun*. 2013;19:213-224.
13. Grammatopoulos G, Munemoto M, Pollalis A, Athanasou NA. Correlation of serum metal ion levels with pathological changes of ARMD in failed metal-on-metal-hip-resurfacing arthroplasties. *Arch Orthop Trauma Surg*. 2017;137:1129-1137.
14. Phillips EA, Klein GR, Cates HE, Kurtz SM, Steinbeck M. Histological characterization of periprosthetic tissue responses for metal-on-metal hip replacement. *J Long Term Eff Med Implants*. 2014;24:13-23.
15. Goodman SB. Wear particles, periprosthetic osteolysis and the immune system. *Biomaterials*. 2007;28:5044-5048.
16. Munemoto M, Grammatopoulos G, Tanaka Y, Gibbons M, Athanasou NA. The pathology of failed McKee-Farrar implants: correlation with modern metal-on-metal-implant failure. *J Mater Sci Mater Med*. 2017;28:66. <https://doi.org/10.1007/s10856-017-5882-y>
17. Pelt CE, Erickson J, Clarke I, Donaldson T, Layfield L, Peters CL. Histologic, serologic, and tribologic findings in failed metal-on-metal total hip arthroplasty: AAOS exhibit selection. *J Bone Joint Surg Am*. 2013;95(1-11):e163. <https://doi.org/10.2106/JBJS.L01446>
18. Willert HG, Buchhorn GH, Fayyazi A, et al. Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study. *J Bone Joint Surg Am*. 2005;87:28-36.
19. Matthies AK, Skinner JA, Osmani H, Henckel J, Hart AJ. Pseudotumors are common in well-positioned low-wearing metal-on-metal hips. *Clin Orthop Relat Res*. 2012;2012(470):1895-1906.
20. Ebramzadeh E, Campbell PA, Takamura KM, et al. Failure modes of 433 metal-on-metal hip implants: how, why, and wear. *Orthop Clin North Am*. 2011;42:241-250.
21. Reito A, Lehtovirta L, Parkkinen J, Eskelinen A. Histopathological patterns seen around failed metal-on-metal hip replacements: Cluster and latent class analysis of patterns of failure. *J Biomed Mater Res B Appl Biomater*. 2020;108:1085-1096.
22. Hothi HS, Matthies AK, Berber R, Whittaker RK, Skinner JA, Hart AJ. The reliability of a scoring system for corrosion and fretting, and its relationship to material loss of tapered, modular junctions of retrieved hip implants. *J Arthroplasty*. 2014;29(6):1313-1317.
23. Matthies AK, Racasan R, Bills P, et al. Material loss at the taper junction of retrieved large head metal-on-metal total hip replacements. *J Orthop Res*. 2013;31:1677-1685.
24. Duggan PJ, Burke CJ, Saha S, et al. Current literature and imaging techniques of aseptic lymphocyte-dominated vasculitis-associated lesions (ALVAL). *Clin Radiol*. 2013;68:1089-1096.
25. Nawabi DH, Gold S, Lyman S, Fields K, Padgett DE, Potter HG. MRI predicts ALVAL and tissue damage in metal-on-metal hip arthroplasty. *Clin Orthop Relat Res*. 2014;472:471-481.
26. Ricciardi BF, Nocon AA, Jerabek SA, et al. Histopathological characterization of corrosion product associated adverse local tissue reaction in hip implants: a study of 285 cases. *BMC Clin Pathol*. 2016; 16:3. <https://doi.org/10.1186/s12907-016-0025-9>
27. Smeekes C, Schouten BJM, Nix M, et al. Pseudotumor in metal-on-metal hip arthroplasty: a comparison study of three grading systems with MRI. *Skeletal Radiol*. 2018;47:1099-1109.
28. Natsu S, Sidaginamale RP, Gandhi J, Langton DJ, Nargol AVF. Adverse reactions to metal debris: histopathological features of periprosthetic soft tissue reactions seen in association with failed metal on metal hip arthroplasties. *J Clin Pathol*. 2012;65:409-418.
29. Krenn V, Perino G, Rütter W, et al. 15 years of the histopathological synovitis score, further development and review: A diagnostic score for rheumatology and orthopaedics. *Pathol Res Pract*. 2017;213:874-881.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Campbell P, Park S-H, Ebramzadeh E. Semi-quantitative histology confirms that the macrophage is the predominant cell type in metal-on-metal hip tissues. *J Orthop Res*. 2022;40:387-395. <https://doi.org/10.1002/jor.25040>