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## Original article

## Metal Ion Levels Are Not Correlated With Histopathology of Adverse Local Tissue Reactions in Taper Corrosion of Total Hip Arthroplasty

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## ABSTRACT

**Background:** The underlying biological mechanism in the formation of adverse local tissue reaction in taper corrosion of total hip arthroplasty (THA) remains unknown. This study evaluated whether there was a dose-dependent relationship between metal ion levels, intraoperative tissue damage and ALVAL (aseptic lymphocyte-dominated vasculitis-associated lesion) scores in dual taper THA patients who underwent revisions for taper corrosion.

**Methods:** We performed a retrospective review of 31 dual taper THA patients who underwent revision surgery from May 2013 to October 2013. Preoperative serum metal ion levels, intraoperative tissue damage grading, and ALVAL scores were reviewed. Multivariate analysis was performed to determine if an association existed between metal ion levels, intraoperative tissue damage, and ALVAL scores.

**Results:** Findings consistent with adverse local tissue reaction were found in all cases. We noted 10 patients with low, 8 with moderate, and 13 with high ALVAL scores, respectively. For intraoperative tissue damage, we recorded 2 (grade 1), 22 (grade 2) and 7 (grade 3) cases. Preoperatively, there was preferential elevation of serum cobalt (3.8 ng/mL, 2.3–17.0) compared to serum chromium (1.0 ng/mL, 0.2–5.8). There was no correlation between preoperative metal ion levels and intraoperative tissue damage ( $R = -0.06, P = .74$ ) or ALVAL scores ( $R = -0.04, P = .481$ ). There was also no correlation between intraoperative tissue damage and ALVAL score ( $R = -0.06, P = .73$ ).

**Conclusion:** There was no significant correlation between ALVAL scores and prerevision surgery metal ion levels or intraoperative tissue damage, suggesting that the biological mechanism of histologic morphology cannot be solely attributed to elevated metal ion levels and is likely multifactorial, reflecting a complex interplay between implant and patient factors.

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Modularity has played an important role in the design of modern total hip arthroplasty (THA) implants. Initial success with femoral head-neck modularity led to the development of modular dual taper necks to provide additional reconstructive options to aid surgeons in the restoration of normal hip anatomy [1]. Modular dual taper neck stems in THA have interchangeable modular necks, facilitating limb length, femoral offset, and version correction, with the potential of enhancing stability and optimizing hip biomechanical parameters by accurately reproducing the center of rotation of the hip [2, 3]. However, it has been long recognized that modularity will increase the potential for corrosion at the modular junction. [4]

To date, increasing number of studies have reported corrosion-related adverse local tissue reactions (ALTRs) or aseptic lymphocyte-dominated vasculitis-associated lesions (ALVALs)

occurring in modular dual taper THA, which were initially described as a complications of metal-on-metal (MoM) bearings [5–12]. The characteristics of adverse soft tissue reactions detected on metal artifact reduction sequence magnetic resonance imaging (MRI) appear to be similar to those observed in patients with MoM THAs, which include periprosthetic cystic and/or solid lesions and tendon avulsions [6,9]. Furthermore, elevated metal ion levels have also been reported in modular neck THA failures presenting with ALTR [10]. Although ALTR has been linked to modular junction mechanically assisted crevice corrosion and elevated metal ion levels, ALTR has also been observed in the absence of high wear or metallosis [13–15].

The underlying biological mechanism leading to the formation of ALTR in patients with taper corrosion of THA remains largely unknown. Few studies have examined the histologic features in periprosthetic tissues of patients with modular dual taper THA undergoing revision. These studies have demonstrated histologic features that indicate metallic wear and metal hypersensitivity [16, 17]. In addition, several studies have described strong correlations between metal ion levels in serum and positive correlation of elevated metal ion levels and patients with periprosthetic ALTR [18–20]. To our knowledge, however, the potential dose-dependent relationship between metal ion levels, histologic grades (ALVAL scores), and intraoperative tissue damage in taper corrosion-related ALTR reactions has not been previously evaluated. Therefore, the objective of this study was to (1) characterize metal ion levels, intraoperative tissue, histologic features, and immunologic response of ALTRs and (2) determine if there was a correlation between metal ion levels, intraoperative tissue damage, and ALVAL scores in modular dual taper THA patients who underwent revisions for taper corrosion.

## Methods

### Study Design and Patient Demographics

After receiving approval from our institutional review board, we retrospectively reviewed 31 hips in 31 THA patients with dual taper femoral stems who underwent revision hip arthroplasty from May 2013 to October 2013. Indications for revision THA included elevated cobalt and chromium serum metal ion levels in symptomatic patients with dual taper modular neck stems in THA with the presence of adverse tissue reaction on cross-sectional imaging. At the time of revision, there were 17 women and 14 men with a mean age of  $57.4 \pm 10.5$  years and a mean body mass index of  $29.1 \pm 5.3$ . These patients described their pain as being diffuse around the hip region or localized to the groin or thigh.

Indications for index primary THA included osteoarthritis (79%), avascular necrosis (9%), femoral neck fracture (3%), hip dysplasia (3%), psoriatic arthritis (3%), and Stickler syndrome (3%). The type of the femoral component, femoral stem size, head size, femoral offset, and bearing surfaces were recorded (Table 1). The bearing surfaces were primarily ceramic on highly crosslinked polyethylene (74%) with the remainder being cobalt chromium on highly crosslinked polyethylene articulations (26%). Femoral stems included the ABG II Modular stem (Stryker Orthopaedics, Mahwah, NJ; 74%) with gas atomized dispersion strengthened cobalt chromium alloy modular necks and Rejuvenate Total Hip System stems (Stryker Orthopaedics) with wrought cobalt chromium alloy modular necks (26%; Stryker Orthopaedics).

### Prerevision Surgery Evaluation

Serum metal ion levels, plain radiographs, and MRI with metal artifact reduction sequence protocol were performed in all patients

**Table 1**  
Demographic Summary.

Parameter	Revision Cases (n = 31)	
Age in years $\pm$ SD	57.4 $\pm$ 10.5	
Body mass index in $\text{kg}/\text{m}^2 \pm$ SD	29.1 $\pm$ 5.3	
Gender (%)	14 Males (45%), 17 females (55%)	
Preoperative blood investigations (normal range)		
WBC (4.5–11.0 WBC/ $\mu\text{L}$ )	6.07 $\pm$ 1.39	
CRP (<8 mg/L)	9.13 $\pm$ 4.03	
ESR (0–13 mm/h)	24.7 $\pm$ 14.1	
Time to revision (mo)	27.5 $\pm$ 9.5	
Parameter	Stryker ABG II (n = 23)	Stryker Rejuvenate SPT (n = 8)
Preoperative implant data		
Stem size	4.2 $\pm$ 1.2	8.5 $\pm$ 1.7
Head size (mm)	31.2 $\pm$ 3.7	38.5 $\pm$ 4.8
Offset ( $^\circ$ )	–1.2 $\pm$ 1.7	0.7 $\pm$ 2.2
Bearing type	CoP 19 MoP 4	CoP 5 MoP 3
Time to revision (mo)	26.8 $\pm$ 8.8	29.4 $\pm$ 11.8
CoP	27.4 $\pm$ 7.1	29.6 $\pm$ 12.9
MoP	25.5 $\pm$ 11.0	29.0 $\pm$ 7.0

SD, standard deviation; WBC, white blood cell; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; CoP, ceramic on highly crosslinked polyethylene; MoP, cobalt chromium on highly crosslinked polyethylene.

at the time of initial presentation. Preoperative erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and white blood cell (WBC) count were collected. There were no infection cases identified based on definition of the musculoskeletal infection society [21]. Primary total hips were revised at a mean of  $27.5 \pm 9.5$  months (Table 1). The revision surgery was performed using “top-out” technique for the femoral stem removal without extended trochanteric osteotomy using high-speed burrs through a posterior approach [22]. Intraoperative tissue damage was determined and graded intraoperatively by the operating surgeon in accordance with a previously published grading system as follows: grade 0 = normal tissue; grade 1 = fluid collection  $\pm$  mild synovial reaction  $\pm$  pseudocapsular dehiscence; grade 2 = grade 1 + moderate-to-severe synovial reaction  $\pm$  metallosis; or grade 3 = grade 2 + abductor damage and/or bone loss [23].

### Histologic Analysis and Flow Cytometry

In all cases, soft tissue surrounding the implant was taken intraoperatively and fixed in 10% formalin immediately after removal. Multiple sections were obtained from 10 different sites in each retrieved sample and embedded in paraffin blocks for routine staining with hematoxylin and eosin. Hematoxylin and eosin stained tissue sections were examined and evaluated by 2 observers, who reviewed up to 45 slides per case. The tissue sections were evaluated for the quality of synovial lining, type of inflammatory infiltrate, and tissue organization based on the ALVAL scoring system [24]. The ALVAL scoring system is a 10-point histologic score used to semi-quantify the degree of ALVAL by examination of synovial lining integrity, inflammatory cell infiltrates, and tissue organization. Based on this system, a score of <4 is considered low, between 5 and 8 moderate, and >9 high. As there were considerable morphological variations across tissue sections from the same case, the highest observed score in each case was used as its ALVAL score. The tissue sections were also examined for the presence of wear debris and for any other significant histologic findings.

Flow cytometry of the samples were performed to assess the immune response. Hip capsule lymphocytes were obtained by

manually scraping tissue and purging cells into a liquid suspension. Using established laboratory methods [25], cells were then washed in phosphate buffered saline (PBS) and resuspended in 0.5 mL PBS 2% Flow Cytometry Standard and stained with titrated volumes of CD56 Pacific Blue, CD45 FITC, CD33 PE, CD3 PE-Cy7, CD19 APC, and CD8 APC-Cy7 (Becton-Dickinson, San Jose, CA) for 15 minutes, washed with PBS, and resuspended in 1% paraformaldehyde PBS. Using single color compensation controls, cells were then run on an 8-laser (LSR) flow cytometer [26] using the 488-, 532-, 406-, and 640-nm excitation wavelengths to develop the appropriate fluo-chrome and analyzed on FlowJo, version 8.8.6, software (Tree Star Software, Ashland, OR).

### Statistical Analysis

Data are expressed as mean  $\pm$  standard deviation, except where noted. Differences in preoperative and postoperative metal ion levels (nonparametric data) were compared using the Mann-Whitney rank sum test with statistical significance determined if  $P < .05$ . Multivariate analyses using multiple linear regression were performed to determine if there was an association between metal ion levels, intraoperative adverse tissue grading, and ALVAL scores. Correlations between 2 groups were made using the Spearman's rank correlation coefficient. All analyses were conducted using Statistica software (Statsoft, Tulsa, OK)

## Results

### Prerevision Surgery Laboratory and MRI

The ESR was elevated in 26.3% of patients ( $24.7 \pm 14.1$ ; range, 4.1–131; normal  $<27$  mm/h), whereas CRP was elevated in 42.1% of patients ( $9.13 \pm 4.03$ ; range, 0.9–75; normal  $<8$  mg/L). Mean serum WBC count was  $6.07 \pm 1.39$  WBC/ $\mu$ L (range, 4.7–13.5; Table 1). All patients with elevated ESR and/or CRP underwent hip joint aspiration. Cell counts remained below 500 WBC/ $\mu$ L, and cultures were negative in all cases. There were no infection cases identified based on definition of the musculoskeletal infection society [21].

Preoperatively, there was a greater elevation in median serum cobalt 3.8  $\mu$ g/L (range, 2.3–17.0) than serum chromium 1.0  $\mu$ g/L (range, 0.2–5.8). The median Co/Cr ratio was 3.8 (range, 3–22.0). Postoperatively, there were statistically significant reductions in Co, Cr, and Co/Cr ratios at a mean of  $5.5 \pm 2.2$  months (Table 2). There was no correlation between preoperative Co ( $R = 0.22, P = .24$ ), Cr ( $R = -0.06, P = .74$ ), Co/Cr ratio ( $R = 0.27, P = .14$ ) and intraoperative tissue damage grading. Preoperative MRIs revealed either a complex fluid collection and/or complex solid soft tissue masses (pseudotumors) (Fig. 1).

### Revision Surgery Intraoperative Findings

At the time of revision, all cases demonstrated black metallic material at the base of the modular neck taper as well as bore of the modular stem representing corrosion debris from neck-stem junction (Fig. 2). Findings consistent with ALTR were found in all cases. Two cases (6.5%) were described as grade 1, 22 cases (71.0%)

**Table 2**  
Preoperative and Postoperative Co, Cr, and Co/Cr Ratio Laboratory Values.

Parameter	Preoperative Median (Range)	Postoperative Median (Range)	P Value
Co (ng/mL)	3.8 (2.3–17.0)	0.4 (0.2–2.6)	$<.001$
Cr (ng/mL)	1.0 (0.2–5.8)	0.6 (0.1–1.5)	.002
Co/Cr Ratio	3.8 (3.0–22.0)	1.0 (0.3–3.5)	$<.001$

Co, cobalt; Cr, chromium.



**Fig. 1.** A large pseudotumor (white arrow) surrounded the THA on coronal T1 MRI sequence using metal artifact reduction technique. THA, total hip arthroplasty; MRI, magnetic resonance imaging.

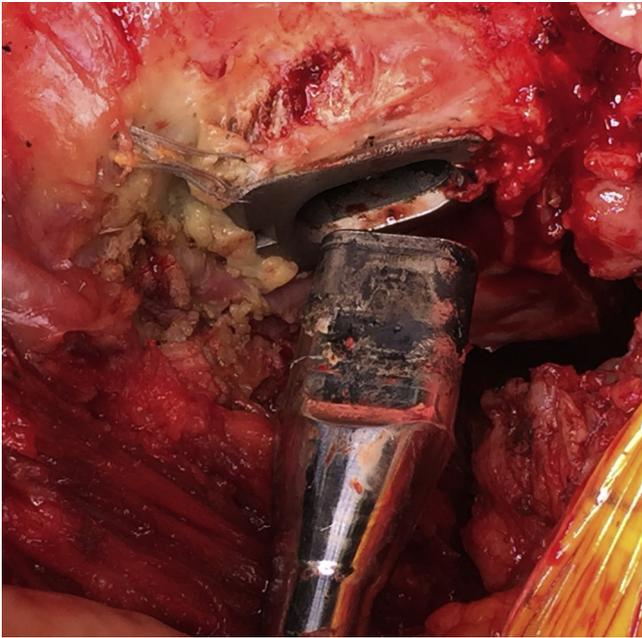
as grade 2, and 7 cases (22.5%) as grade 3 (Fig. 3). A large amount of fluid was observed after entering the capsule in most cases (88%). Particulate debris was often observed (52%), and there were 2 cases with heterogenous solid lesions. However, no loosening of femoral or acetabular components was noted.

### Histology ALVAL Scores

Histologic semiquantitative ALVAL scores demonstrated there is a histologic spectrum observed at the time of revision. All 31 cases showed positive morphologic findings with 10 cases scoring low (Fig. 4), 8 cases scoring moderate, and 13 cases scoring high (Fig. 5). Wear debris was identified in 19 of the 31 cases, and a low-to-moderate ALVAL score was frequently associated with the presence of wear debris (79%). We noted a spectrum of partial ALVAL score components (synovial lining, inflammation, and tissue organization) and the total ALVAL score (Fig. 6). There was no correlation between Co serum levels to total histologic ALVAL score ( $R = -0.04, P = .481$ ), Cr serum levels to total histologic ALVAL score ( $R = 0.10, P = .505$ ), or the ratio of Co/Cr serum levels to total histologic ALVAL score ( $R = -0.08, P = .368$ ). There was also no correlation between ALVAL score ( $R = -0.06, P = .73$ ) and intraoperative tissue damage grading. Of the 13 cases that had a high ALVAL score, only 4 showed histologic wear debris. Four cases showed additional findings; 2 showed hemosiderotic synovitis, 1 showed nonnecrotizing granulomas, and 1 showed a predominantly lymphoplasmacytic infiltrate.

### Immunocytochemistry Analysis

The data from flow cytometry analysis revealed that most leukocytes obtained from the submitted specimens were CD45+CD3+ T cells (50 + 27%) with a slight trend toward more

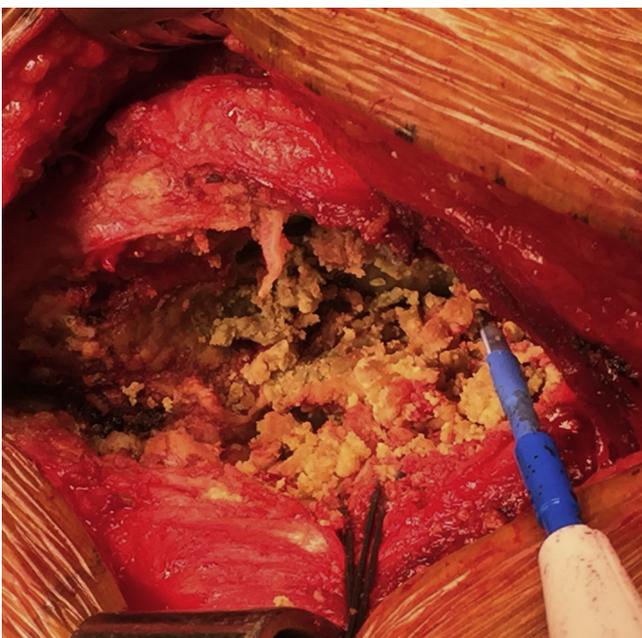


**Fig. 2.** Black metallic material at the base of the modular neck taper as well as bore of the modular stem representing corrosion debris from neck-stem junction.

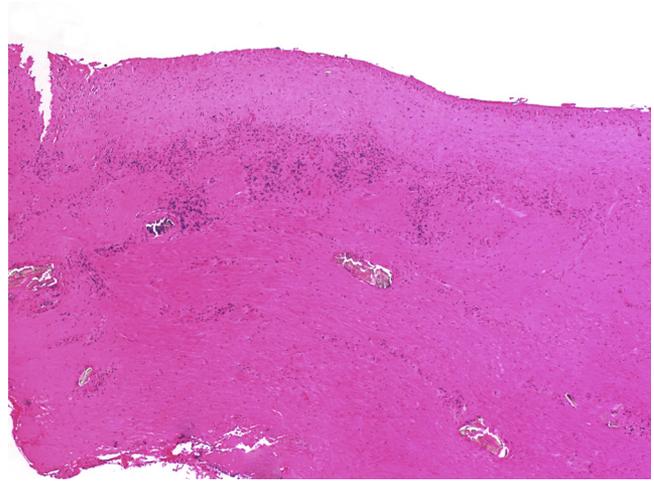
CD3+8+ (34 + 16%) cells over CD3+4+ (26 + 14%) cells. Very few CD45+CD19+ B cells were detected (2+2%) while far more CD45+CD56+CD3- NK cells (13 + 7%) were identified.

### Discussion

Recently, there have been increasing concerns with occurrence of ALTR or pseudotumor formation due to corrosion at the modular taper junctions [5,27-29]. Our study evaluated the metal ion levels, intraoperative tissue damage grades, histologic features, and immunologic response of dual modular neck THA patients who had

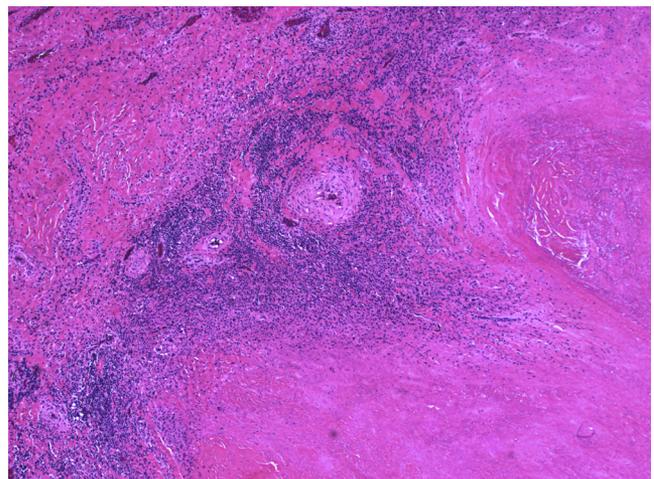


**Fig. 3.** A representative case of intraoperative tissue damage grading 3.



**Fig. 4.** A “low” ALVAL score. Synovial tissue organization is retained, and the synovial lining is intact. There is a mild inflammatory infiltrate consisting predominantly of small lymphocytes, but without organized perivascular aggregates (hematoxylin and eosin, 4× magnification). ALVAL, aseptic lymphocyte-dominated vasculitis-associated lesion.

revisions for taper corrosion. Although several studies have noted higher ALVAL scores in MoM hips with lower wear rates, suggesting that ALTR was associated with metal hypersensitivity [15, 24], other studies have also attributed adverse tissue reactions in patients without MoM bearings to possible metal hypersensitivity [30-32]. In our study, wear debris was identified in 79% of cases with a low-to-moderate ALVAL score, which is consistent with existing literature for MoM bearing THA. Conversely, patients with absence of wear debris had higher ALVAL scores, suggesting the possibility of inherent metal hypersensitivity. The histopathology features from ALTR associated with modular taper stem corrosion in the present study demonstrated a spectrum of ALVAL scores, likely reflecting a complex underlying biological mechanism involving implant and patient factors.



**Fig. 5.** A “high” ALVAL score. The tissue organization is diffusely effaced, with a thick band of necrotic debris and fibrin deposition at the surface. No residual synovial lining is present. The inflammatory infiltrate is dense, with a dense lymphocytic infiltrate and large (>50% of high-power field) perivascular aggregates (hematoxylin and eosin, 4× magnification).

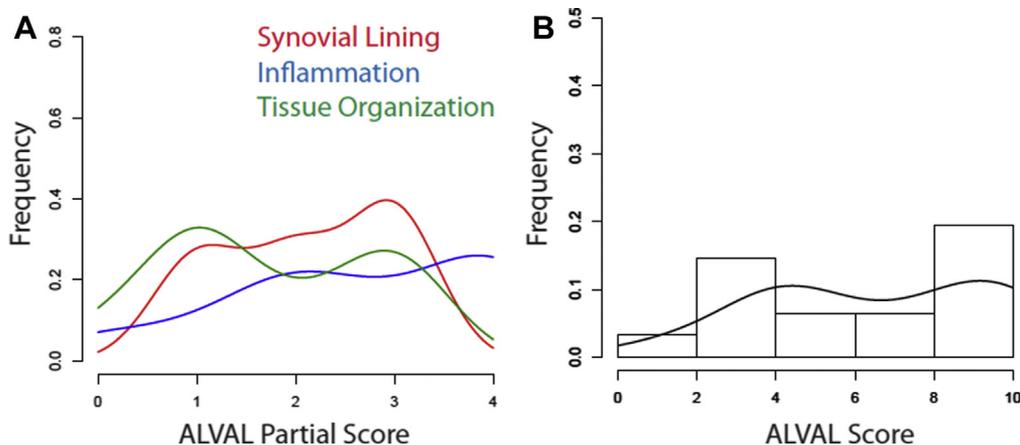


Fig. 6. Histogram of (A) partial and (B) total ALVAL score.

A potential mechanism in the histologic response may be the dose-dependent response to metal ion levels. Cobalt and chromium are trace elements essential for normal biological functions, which may have deleterious occupational health adverse effects in elevated levels [33–35]. Excessive release of these metallic particles and their corrosion by-products from dual taper THA implants represents an internal exposure to metals that may result in dose-dependent adverse effects. A strong correlation between elevated metal ion levels and patients with periprosthetic ALTR has been demonstrated [10]. However, in our study, we found no significant correlation between ALVAL score and metal ion levels ( $R = -0.08$ ,  $P = .368$ ) and intraoperative tissue damage grading ( $R = -0.06$ ,  $P = .73$ ), respectively. Although the pathogenesis of ALTR is not yet well defined, a wide spectrum of necrotic and inflammatory changes involving the periprosthetic tissues have been reported [33]. However, we did not find significant correlation between intraoperative tissue damage and ALVAL score. This could be attributed to the fact that ALVAL score may be an indication of the developmental stage of the ALTR rather than its severity [16]. Our findings support that the ALVAL score may not be directly related to the severity of ALTR. This may explain, in part, the reason for preoperative metal ion levels and intraoperative tissue damage were not found to be predictive of histologic ALVAL scores. Nevertheless, this spectrum of histologic findings may suggest the importance of patient factors such as systemic hypersensitivity in the occurrence of adverse tissue reactions and a complex underlying biological mechanism that is not dependent on metal ion exposure alone. Metal ion levels should not be relied on as the sole parameter to determine revision surgery indication. Evaluation of taper corrosion-related adverse tissue reactions in patients with dual modular taper THA should include a systematic approach considering patient clinical symptoms, physical examinations, implant type, radiographs, and cross-sectional imaging as outlined in recently reported systematic risk stratification algorithms [36].

In our study, we noted 2 cases with hemosiderotic synovitis. The presence of hemosiderotic synovitis has been associated with early implant loosening; however, its significance is yet to be understood [34, 35]. Additionally, we noted histologic findings of florid papillary hypertrophy, dense giant cell-mediated lymphocytic infiltrate, and tissue necrosis in peri-implant capsular tissues of modular dual taper neck stem THA, which resembles the disease processes seen in rheumatologic disorders [7, 16, 17]. Elevated levels of interferon gamma inducible chemokines MIG/CXCL9 and IP-10/CXCL10 have been recorded from periprosthetic tissue of ALTR patients and are also commonly elevated in rheumatoid arthritis patients [17,37–39].

For immunochemistry analysis in the present study, although each patient's circulating blood cells were not available for direct comparison, the values obtained from hip capsule specimens suggested the potential presence of inflammatory reaction, as the average CD4 to CD8 ratio was 0.9, distinctly below that of normal circulating cells. Similarly, the percentage of B cells was relatively low and the percentage of NK cells elevated, compared with normal circulating cells. These results are consistent with a principally T lymphocytic activity with variable B cell response seen in MoM total hip surfacing and arthroplasty [24, 33,40–43]. Despite these similarities, as there are implant based difference between MoM and modular taper THA with qualitative differences in the appearance of corrosion products, lymphocyte distributions, and macrophage morphology [16], the present study findings may not be generalized for MoM THA or hip resurfacing adverse reactions.

This study has several limitations. First, our study was retrospective with a relatively small number of patients. However, this study describes one of the larger cohorts which have attempted to characterize and correlate histologic findings with metal ion levels and intraoperative tissue damage. Second, ALVAL score used in this study remains a non-standardized and non-validated scoring system for evaluating hypersensitivity reactions. However, it is a useful system currently available to semiquantify histologic features. Third, each patient's circulating blood cells were not available for direct comparison with flow cytometry. However, the results were consistent with a principally T lymphocytic activity with variable B cell response seen in MoM bearings.

In summary, there is a spectrum of histologic features associated with taper corrosion of hip arthroplasty revised for adverse tissue reactions. There was no significant correlation with pre-revision surgery metal ion levels or intraoperative tissue damage, suggesting that the biological mechanism governing histologic morphology cannot be solely attributed to dose-dependent metal ion levels and is likely to be multifactorial, reflecting a complex interplay between implant and patient factors. Further research is required to elucidate the potential biological mechanisms.

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