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Pseudotumors and High-Grade Aseptic Lymphocyte-Dominated Vasculitis-Associated Lesions Around Total Knee Replacements Identified at Aseptic Revision Surgery: Findings of a Large-Scale Histologic Review

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ABSTRACT

Background: Aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL) development (including pseudotumors) secondary to metal debris generation around total hip arthroplasties is a well-recognized histopathologic phenomenon. Emerging data have highlighted a similar potential concern around TKAs although the body-of-knowledge has largely been limited to individual case reports or small retrospective case series. This study sought to establish the prevalence of pseudotumors or high-grade ALVALs seen at the revision of primary TKAs and to establish the correlation between histologic ALVAL grade and patient-reported functional outcome measures.

Methods: The findings of 321 non-infective (aseptic) patients undergoing unilateral revision knee surgery, at a high-volume tertiary referral center, were reviewed. Each case was independently histologically classified. Complete patient-reported functional outcome measures were available for 134 patients (42%) allowing correlation between functional performance and histopathology results.

Results: Five distinct pseudotumors and a further 18 high-grade ALVALs were histologically identified representing 1.6% and 5.6% of the cohort, respectively. When compared by histologic grade, Oxford Knee Score and Western Ontario and McMaster University's Osteoarthritis Index suggested a high correlation between ALVAL grade and functional knee scores.

Conclusion: These findings suggest a prevalence of pseudotumors or high-grade ALVALs at revision TKA surgery of >7%. This unexpectedly high result may contribute insight into the previously underappreciated significance of metal debris-related local tissue reactions around TKAs. The findings also demonstrate a strong near-linear inverse relationship between patient-reported clinical knee performance and the underlying histologic grade of local tissue reaction. These results have potential management implications for patients with underperforming TKAs and should prompt consideration of an ALVAL secondary to metallosis in the differential diagnosis.

Level of Evidence: This is a retrospective cohort study with Level III evidence.

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As the population continues to age and patient expectations of enduring functional performance continue to rise [1], the prevalence of total knee and hip replacements and their resultant burden on healthcare services increases [2]. Metal alloys remain the mainstay of lower limb arthroplasty device production with cobalt-chrome the most commonly used metallic bearing surface. The potentially toxic cellular effects resulting from local particulate

debris generation—especially cobalt and chromium ions—and the subsequent local innate immune response are well recognized. Adverse local tissue reactions (ALTRs) have been reported extensively following the recent short-lived resurgent spike in popularity of metal-on-metal bearing surfaces in total hip arthroplasty [3] and have been shown to correlate with metal wear [4]. Recently, there has been growing interest in trunnion corrosion and fretting (ie, non-bearing wear) [5] as the precipitant for ALTR responses seen in metal-on-polyethylene bearing surfaces [6-11].

Aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL)—a form of ALTR—is the histologic description of the local tissue reaction to metal debris after arthroplasty. Its hallmark is the peri-vascular accumulation of lymphocytes [12]. Campbell et al [12] described a classification for ALVAL based on 3 key histological features: synovial lining, cellular infiltrate (lymphocytes vs macrophages), and tissue arrangement (peri-vascular or otherwise). This system generates a composite score between 0 and 10, whereby 0-4 is classified as "low," 5-8 as "moderate," and 9-10 as "high" ALVAL scores. A strong inter-observer and intra-observer correlation of 0.7 was reported, with higher ALVAL scores associated with patients with demonstrated pseudotumor lesions or high-grade metal sensitivity reactions [12].

There have been some sporadic reports describing local tissue reactions to particulate metal debris after total knee arthroplasty (TKA) [13-17]. Most of these studies have been limited to case reports or low number case series describing patients with pain of otherwise unknown origin after TKA [18,8]. Thomas et al [19] recently described the immunological analysis of 25 patients with otherwise unexplained pain associated with an in situ TKA, of which 20 were shown to have metal sensitivity responses to TKA components [19]. Common to these studies has been the suggestion that an abundant local immune-mediated lymphocytic reaction to metal debris is the predominant underlying histology feature.

To our knowledge, no previous reported work has attempted to define the prevalence of pseudotumors or high-grade ALVAL around in situ TKAs seen at the time of revision surgery. Similarly, a limited body-of-knowledge exists correlating clinical joint function with subsequent histologic tissue grade from specimens collected at the time of revision TKA. Therefore, the purpose of the current study was 3-fold: (1) to determine the percentage of revision TKA cases at which a histologically confirmed pseudotumor or high-grade ALVAL could be identified; (2) to explore the correlation between key patient demographic factors and subsequent histologic tissue grade; and (3) to establish the strength of association between this tissue grade from specimens obtained at the time of revision TKA and patient-reported knee function.

Materials and Methods

Following receipt of institutional human research ethics committee approval, the current study was performed using a retrospective, unmatched, cohort analysis method. Data were collected from a high-volume, dedicated lower limb arthroplasty unit, within a tertiary referral center. Patients deemed eligible for enrollment in the study had undergone their revision TKA procedure during the 10-year period (January 2005 to February 2015). During this time, all TKA revision operations were performed by, or under the direct supervision of, one of the 3 experienced and fellowship trained lower limb arthroplasty surgeons. The main inclusion criterion was that each patient had an available, and complete, formal pathology report from intra-operative specimens collected at the time of their revision surgery. Only adult patients (ie, aged 18 years or older at the time of revision surgery) were considered for inclusion. Patients were excluded if infection, local malignancy, or acute multi-trauma were recorded as the principal reason for their revision, or if intra-operative cultures subsequently demonstrated infection (ie, type 4 infections [20]).

A total of 321 patients (321 knees) who had undergone non-infective (aseptic) unilateral revision TKA during the recruitment period, and for whom complete histopathologic records were available, were identified. Of these, there were 134 (42%) patients for whom corresponding, self-reported, clinical outcome questionnaire datasets were available for review, all of which had been obtained at scheduled pre-operative assessment clinic appointments within 6 weeks of the scheduled revision surgery.

To ensure the clinical representativeness of the final selected "PROMs group" subset, available demographic data for the entire cohort (ie, 321 patients) were collected to allow later statistical analysis. Such criteria included patient age at the time of surgery, gender, operated side, and the documented indication for revision arthroplasty. The demographics of the 134 PROM group cases were independently compared to the entire cohort to ensure sample representativeness and to exclude unintended selection bias.

The mean age at the time of revision surgery for the entire cohort (n = 321) was 70.0 years (range 35-89) (Table 1), compared to the PROMs sample group (n = 134) mean age of 69.3 years (range 41-87) ($P > .05$). There was no statistically significant gender disparity identified comparing the total cohort (55% male) to the PROMs group (49% male) ($P > .05$). In the total cohort, 51% of the revisions were done to the right knee, whereas in the PROMs group, 59% of revisions were done on the right knee ($P = .03$).

Key outcomes were measured both in terms of histology and patient-reported functional status. With regards to histology, patient records with available pathology reports were retrospectively examined and classified into one of the 4 groups. Group 1 had only a local "dendritic response" with no appreciation of lymphocytic infiltration or observed metal debris. Group 2 had at least some mention of metal debris identified among other debris such as cement or plastic, or lymphocyte recruitment. Group 3 comprised patients with significant metallosis or lymphocytosis. Group 4 comprised patients with confirmed presence of a pseudotumor. For the purpose of this study, and as accepted by convention, grade 1

Table 1
Cohort Demographics (Non-Infected Cases With Complete Histopathologic Records Only).

	Total Cohort (N = 321)		PROMs Group (N = 134)	
Age at revision (y)				
Mean ± SD	70.0 ± 10.6		69.3 ± 9.5	
Range (median)	34.8-89.4 (74.2)		41.1-87.2 (69.9)	
Time from TKA to WOSFOX (mo)				
Mean ± SD	–		36 ± 21	
Range (median)	–		1-99 (27)	
Gender				
Raw (%)	Male: 176 (55)	Female: 145 (45)	Male: 65 (49)	Female: 69 (51)
Operated side				
Raw (%)	Left: 156 (49)	Right: 165 (51)	Left: 55 (41)	Right: 79 (59)

PROMs, patient-reported functional outcome measures; SD, standard deviation; TKA, total knee arthroplasty; WOSFOX, cumulative questionnaires containing **W**estern **O**ntario and McMaster University's Osteoarthritis Index + **S**hort **F**orm 12 + **Ox**ford Knee Scores.

Table 2
Etiology for Revision (Infected Cases Excluded).

Diagnosis	Total Cohort (N = 321)		PROMs Group (N = 134)	
	n	Percent (%)	n	Percent (%)
Aseptic loosening	116	36.1	46	34.3
Poly/bearing wear	44	13.7	23	17.2
Instability/maltracking	43	13.4	15	11.2
Osteolysis	36	11.2	16	11.9
Pain/stiffness	32	10.0	9	6.7
Other	26	8.1	15	11.2
Fracture[a]	24	7.5	10	7.5

PROMs, patient-reported functional outcome measures.
[a] Catastrophic implant failure and peri-prosthetic fracture not associated with infection, multi-trauma, or local malignancy.

and 2 ALVALs were considered "low grade" and grade 3 and 4 "high grade" lesions. With regards to patient-reported clinical outcomes, what we refer to as the 'WOSFOX' cumulative questionnaires—containing Hip and Knee Satisfaction Scale, **W**estern **O**ntario and McMaster University's Osteoarthritis Index (WOMAC), **S**hort **F**orm 12, **Ox**ford Knee Score (OKS), University of California-Los Angeles Activity Score, and Charnley Comorbidity Classification—were retrieved from the hospital electronic medical record system. For the purpose of this study, only the components of the questionnaire using the WOMAC [21] and the OKS [22] were sub-selected to determine the patient-reported functional knee status. These evaluation tools have been validated and are widely used in the setting of osteoarthritis and arthroplasty [21,22].

All collected data were entered into a Microsoft Excel (Microsoft Corporation, Richmond, WA) spreadsheet and exported for statistical analysis using R (Adelaide University, Adelaide, Australia). The correlation between the histologic grade of intra-operative specimens and the patient-reported outcomes was then determined by comparing each group as an independent discrete variable to their OKS and WOMAC scores as dependent variables. Since no assumption about the underlying normality of distribution could be made, statistical analysis was carried out using non-parametric testing. The Jonckheere-Terpstra test was used to determine if there is a statistically significant trend between the ordinal independent variables and the continuous dependent variables. The resultant degree of final correlation was determined using Spearman's rho method. Average WOMAC and OKS from each group were also correlated using Spearman's rho method. All data were analyzed on an intention-to-treat basis.

Results

In total, 5 cases of histologically proven pseudotumor (grade 4 ALVALs) and 18 grade 3 lesions were identified, representing 1.6% and 5.6% of the total cohort, respectively. Considering grade 3 and 4 lesions together as "high-grade ALVALs," this represented an overall prevalence of 7.2% seen at the time of revision surgery.

The documented principal indication for revision was recorded and categorized for each patient (Table 2). Eight distinct diagnostic groups were identified. To ensure consistency in interpretation for the purposes of the study, "osteolysis" was defined as local peri-prosthetic loss of bone stock without convincing evidence of component migration or loosening, and "aseptic loosening" was defined as component migration or radiographically defined loss of implant-host bone interface integrity, with or without subjacent local bone loss, in the absence of infection. In instances where both contributory diagnoses of "aseptic loosening" and "osteolysis" were documented, the patient was categorized under "aseptic loosening." In total, there were only 7 (2.2%) cases in which both key diagnoses were listed. The majority of cases from the PROMs group were revised for aseptic loosening (34%), polyethylene and/or bearing wear (17%), or osteolysis (12%). Cases listed as a "fracture" included fracture of in situ components (ie, catastrophic implant failure) or peri-prosthetic fracture not related to acute multi-trauma, infection, or local malignancy. For 26 cases in the whole cohort (8.1%), a clear principal indication for revision could not be confidently established from the retrospective case note review. The indication for revision in these cases was subsequently recorded as "other" (Table 2).

Analysis of initial pathology reports for each of the cases in the PROMs sample group was carried out and classified by the pathologist's comments according to the rubric presented in Table 3. Over the inclusion time period, specimens were reported independently by one of the 7 staff pathologists—3 of whom collectively reported over 80% (257/321) of the cases. After each case was classified into one of the 4 previously defined groups according to the available histology report, the 'WOSFOX' data were gathered and tabulated. Graphical representation of these data can be seen in Figure 1. The average OKS for each group is displayed in Figure 1A. The mean pre-operative OKS scores ranged from 33.2 for grade 1 ALVALs to just 9.1 for grade 4 lesions, respectively. Linear regression for the average OKS using the least squares method yielded an R^2 value of 0.82. The average WOMAC score for each group is displayed in Figure 1B. The mean pre-operative WOMAC scores ranged from 49.9 for grade 1 ALVALs to 63.1 for grade 4 lesions, respectively. Linear regression for the average WOMAC score using the least squares method yielded an R^2 value of 0.77.

Testing for homogeneity of variance in both OKS and WOMAC datasets was carried out using Levene's test. The *P*-value for each test was .12 and .21, respectively. Non-parametric testing to elucidate data trends and associated correlation was carried out using Jonckheere-Terpstra and Spearman's correlation testing. When compared by histologic grade according to group, the Jonckheere-Terpstra test yielded *P*-values of .02 and .03 for the OKS and WOMAC datasets, respectively, suggesting significant differences between the group means. The Spearman's correlation test returned a rho value of 0.20 and a *P*-value of .02 for the OKS data, as well as a rho value of 0.19 and a *P*-value of .03 for the WOMAC data, also suggesting significant differences between the group means. The results of non-parametric testing are shown in Table 4.

Table 3
Histologic Classifications.

Group	Description	All Available Histopathology Reports	Non-Infected Revision Cases With Clinical Questionnaires
1	Dendritic synovitis	281 (87.5%)	119 (88.8%)
2	Synovitis with metal, plastic, or cement debris or lymphocytes present	17 (5.3%)	6 (4.5%)
3	Metallosis and/or marked lymphocyte infiltration	18 (5.6%)	8 (5.9%)
4	High-grade ALVAL or pseudotumor	5 (1.6%)	1 (0.74%)
		321	134

ALVAL, aseptic lymphocyte-dominated vasculitis-associated lesion.

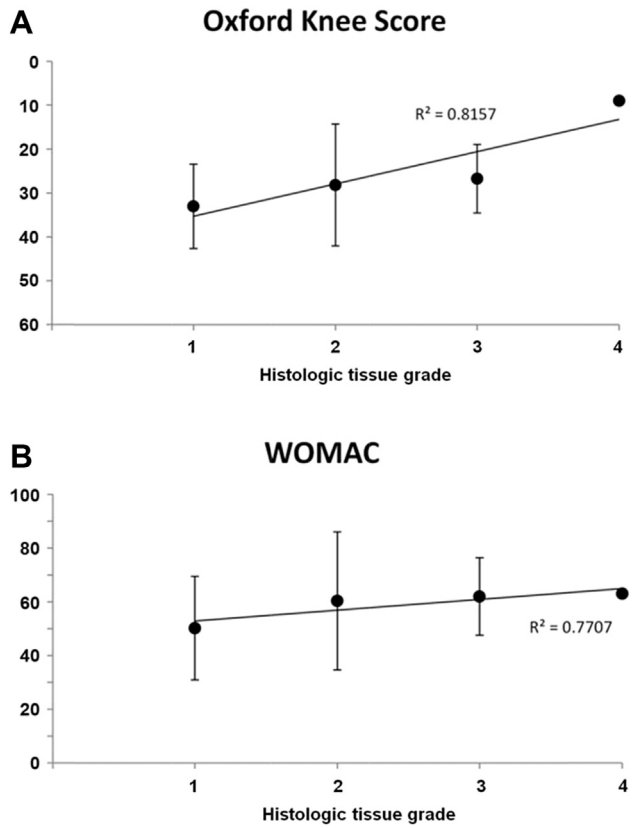

Fig. 1. Functional knee scores vs histologic grade. (A) Oxford Knee Score and (B) WOMAC.

Discussion

The overall prevalence of high-grade ALVAL (7.2%) and distinct pseudotumors (1.6%) seen in this study was much higher than anticipated, and has not been previously reported. There is little published evidence exploring the true rate of pseudotumors seen around TKA at the time of revision of primary implants, and much of the work to date has reflected single case examples or very small case series. To our knowledge, this study, drawn from a cohort of 321 patients with complete histopathologic datasets, represents the largest single investigation into the occurrence of pseudotumors around knee replacements so far reported.

A clear association between histologic ALVAL grade and patient-reported knee functional performance was seen using widely accepted and utilized clinical scoring systems. When the average of each OKS and WOMAC score was taken for each ALVAL grading group, a strong near-linear inverse correlation was clear—that is, higher ALVAL grade corresponded to a poorer patient-reported functional performance—with R^2 values of 0.82 and 0.77, respectively. Levene's test, performed to establish data homogeneity, returned *P*-values of .12 and .21 for the OKS and WOMAC, respectively. Non-parametric testing using the Jonckheere-Terpstra returned *P*-values of .02 and .03 for the OKS and WOMAC, respectively. Combined, these results suggest a strong association between patient-reported functional knee outcome scores and the categorized histologic grade. To further determine the strength of the correlation between the patient-reported clinical outcomes and histologic grade, a Spearman's correlation test was used. Spearman's test returned rho values of 0.20 and 0.19 for the OKS and WOMAC, respectively. The associated *P*-values of .02 and .03 respectively indicate that these correlations are statistically significant. The absolute magnitude of the mean differences between lower grade lesions (ie, grade 1) and frank pseudotumors (ie, more than 24 points for OKS and 13 points for WOMAC scores, respectively) contextualizes the clinical meaningfulness and relevance of the disparities demonstrated. This result highlights the true negative impact of progressive ALVAL grade on patient-reported knee function and associated quality-of-life.

Table 4
Statistical Analyses (Patient-Reported Knee Function vs Histologic Grade).

	Levene's Test (*P*-Value)	Jonckheere-Terpstra Test (*P*-Value)	Spearman's Correlation Rho (*P*-Value)
Oxford Knee Score	.12	.02	0.20 (.02)
WOMAC	.21	.03	0.19 (.03)

WOMAC, Western Ontario and McMaster University's Osteoarthritis Index.

Although little difference existed between the demographic characteristics of the overall cohort and the sample group, the small bias toward the need for revision of right-sided TKAs compared to left-sided TKAs remains an interesting and noteworthy disparity, the clinical significance of which remains unclear. This may perhaps simply reflect a sample size confounder but may provide an interesting opportunity for further investigation.

The authors acknowledge several limitations associated with the current work. First, the retrospective nature of the investigation is recognized. The quality and accuracy of the extrapolated data collected, especially the formal pathology reports, relied heavily on the precision with which records were generated at the time of revision surgery and primary pathologic analysis, and the manner with which such records were safely stored thereafter. Also, the lack of formal pathology specimen analysis for all revision cases is also acknowledged. Although intra-operative solid tissue specimen collection for subsequent microbiological and pathology examination is now standard-of-care at our institutions during revision procedures, this was not the case during the entire period from which cases were recruited.

The self-reported nature of the patient-derived functional outcomes scores is also a potential area for the introduction of bias given the uncontrolled and unsupervised environment of data collection. Whether this potentially confounding variable strengthened or undermined the association with the documented pathology findings is unclear.

Finally, it is important to reiterate the contextualization of the findings of the current study—while we report the prevalence of high-grade ALVALs and pseudotumors around primary TKA components at the time of revision surgery, our findings do not allow us to confidently attest to what degree these lesions actually contributed to the need for revision surgery—if at all. Similarly, given the setting within which the patient cohort was drawn—a high-volume regional referral center—our work does not allow us to extrapolate these findings to suggest an overall incidence of high-grade ALVAL in the setting of primary TKA, or even confidently the incidence at revision surgery, given the likely skewed patient demographic referred to us. We recognize that the majority of revision procedures performed on primary TKAs occur in the non-tertiary referral center setting and are usually safely performed and managed in smaller centers.

Conclusions

In conclusion, the results of the current work suggest a prevalence of histologically confirmed pseudotumor or high-grade ALVAL formation around in situ primary TKAs, seen at the time of revision surgery, in the order of 7%-8%. This is markedly higher than had been anticipated. These findings also demonstrate a strong

near-linear inverse relationship between patient-reported clinical knee performance and the underlying histologic ALTR grade of local tissue reaction to implant-derived particulate metal wear debris. These results have potential diagnostic and management implications for clinicians responsible for the care of patients with painful or underperforming in situ TKAs, particularly in the referral center setting. We hope these results might prompt consideration of pseudotumor formation, or a lesser grade of ALVAL secondary to local metal reaction, in the differential diagnosis of such knees. Furthermore, ideally prospective, investigations are warranted to confirm the results seen in this study and to elucidate the optimized diagnostic and management pathways for such patients, although it is likely that much of the work done in investigating similar lesions around total hip arthroplasties may be translatable here. The preliminary findings presented herein do perhaps shed light on a reasonable new consideration for the widely reported 15%-20% of patients who suffer with ongoing, otherwise previously unexplained, pain and dissatisfaction associated with their TKA.

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