Perivascular Lymphocytic Infiltration Is Not Limited to Metal-on-Metal Bearings

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Abstract

Background Perivascular lymphocytic infiltration (PVLI) suggests an adaptive immune response. Metal hypersensitivity after THA is presumed associated with idiopathic pain and aseptic loosening, but its incidence and relationship to metallic wear leading to revision are unclear as are its presence and relevance in non-metal-on-metal arthroplasty.

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Questions/purposes We compared (1) incidence and severity of PVLI in failed hip metal-on-metal (MoM) to non-MoM implants and TKA; (2) PVLI in MoM and non-MoM hip arthroplasty based on reason for revision; and (3) PVLI grade to diffuse lymphocytic infiltration (DLI) and tissue reaction to metal particles.
Patients and Methods We retrospectively examined incidence and severity of PVLI, DLI, and tissue reaction in periprosthetic tissue from 215 THA and 242 TKA revisions including 32 MoM hips.
Results Perivascular lymphocytic infiltration was present in more TKAs (40%) than overall hip arthroplasties (24%) without difference in severity. Compared to non-MoM hips, MoM bearings were more commonly associated with PVLI (59% versus 18%) and demonstrated increased severity (41% versus 3% greater than mild). Histologically, PVLI correlated (r = 0.51) with DLI, but not tissue reaction. In THA, PVLI was most commonly associated with idiopathic pain (70%) and aseptic loosening (54%) in MoM, and infection in all hip revisions (53%).
Conclusions Perivascular lymphocytic infiltration is more extensive in revisions of MoM and in aseptic loosening, idiopathic pain, or infection but is also present in TKA, non-MoM, and different reasons for revision. It correlates with other signs of metal hypersensitivity, but not with histologic measures of metal particulate load.
Level of Evidence Level III, diagnostic study. See the Guidelines for Authors for a complete description of levels of evidence.

Introduction

Metal-on-metal (MoM) bearings have reemerged as a low-wear and large-head-diameter alternative for high-demand

patients [25]. A better understanding of tribology, improvements in implant design, and the recognition of polyethylene (PE) wear debris as a major cause of osteolysis have galvanized a gradual shift away from traditional metal-on-PE (MoP) THA in young individuals. Nevertheless, concerns remain regarding the effects of metal particulate debris and metal ions on patient health and on implant function [29].

There is evidence that metal particles may cause local cytotoxicity and elicit a delayed-type hypersensitivity-like (DTH) reaction, termed aseptic lymphocyte-dominated vasculitis associated lesion (ALVAL) [39]. A spectrum of deep tissue pathology including persistent groin pain [2, 5, 29], joint effusions [39], cystic and fibrotic pseudotumors [10, 11, 19, 31, 35], aseptic loosening [28], and osteolysis [6, 7, 20, 29, 36] have been associated with these findings. Two predominant histologic findings of the adaptive immune response and ALVAL phenomenon are perivascular lymphocytic infiltration (PVLI) and diffuse lymphocytic infiltration (DLI) [39]. Although some authors have described this reaction to be characteristic of and largely limited to MoM bearings [13, 29], it has been previously described with other surface types to a lesser extent [17, 26, 39]. All metallic implants in a biologic milieu corrode and release ions [22], but higher levels are found with MoM compared to MoP bearings [12, 32]. In addition, histologic examination of periprosthetic tissue and neocapsules have found a higher prevalence of PVLI in MoM than non-MoM implants [38]. Nevertheless, its relationship to metallic wear and its incidence leading to revision surgery are unknown [23]. Additionally, the presence and relevance of this phenomenon in non-MoM arthroplasty are unclear.

We therefore compared (1) the incidence and severity of PVLI in failed MoM implants to non-MoM hip arthroplasty and TKA; (2) PVLI in MoM and non-MoM hip arthroplasty based on reason for revision; and (3) grade of PVLI to DLI and tissue reaction to metal particles.

Patients and Methods

We retrospectively reviewed the medical records of all patients who underwent a hip arthroplasty or TKA revision by one of the senior authors (KRB or AVL) between January 2006 and July 2009. The pathology reports for intraoperative periprosthetic soft tissue and neocapsule specimens were reviewed for the grade of PVLI, DLI, and periprosthetic particle storage and tissue reaction. We identified 219 hip arthroplasty and 253 TKA revisions, but four and 11 cases respectively lacked full specification of PVLI grade and were excluded for a total of 215 hip arthroplasties and 242 TKAs. Patient demographics were documented (Table 1), including the diagnosis for revision and bearing surface for hip arthroplasties (Table 2). Among the hips, 11 were second revisions and two were third. Among the TKAs, 26 were second revisions, three were third, and one was fourth. Because not all primary arthroplasties were performed by the authors, a wide variety of implants were the subject of revision. Proceedings were in accordance with the Western Institutional Review Board (Olympia, WA), Study #1063398.

The mean age of patients was greater for those who underwent revision TKA (67 years) than hip arthroplasty (64 years) (95% confidence interval [CI], 0.77–5.23) and for non-MoM bearings (65 years) compared to MoM bearings (57 years) (95% CI, 3.1–12.9). There were proportionately more (p = 0.008) women than men with revision TKA (150 women:92 men) than hip arthroplasty (106 women:109 men), but there was no difference between MoM hips (17 women:15 men) compared to non-MoM hips (89 women:94 men).

Table 1. Summary of patient demographics

Surgery type	Number of patients	Number of men	Number of women	Age (years)*
Hip arthroplasty	215	109	106	64 (34–99)
Metal-on-metal hip arthroplasty	32	15	17	57 (38–89)
Metal-on-metal THA	26	9	17	59 (38–89)
Metal-on-metal hip resurfacing	6	6	0	49 (38–58)
Non-metal-on-metal hip arthroplasty	183	94	89	65 (34–99)
Metal-on-polyethylene THA	166	85	81	65 (34–99)
Ceramic-on-polyethylene THA	8	5	3	59 (47–76)
Hemiarthroplasty	9	4	5	70 (53–82)
TKA	242	92	150	67 (38–90)
Total	457	201	256	65 (34–99)

* Values are expressed as means, with ranges in parentheses.

Table 2. Number of cases for each hip implant type, mode of failure, and PVLI grade

Mode of failure	Number of cases (PVLI grade, none:few:many:abundant:excessive)					
	Metal-on-metal THA	Metal-on-metal hip resurfacing	Metal-on-polyethylene THA	Ceramic-on-polyethylene THA	Hemiarthroplasty	Total
Aseptic loosening	11 (5:1:2:2:1)	2 (1:0:1:0:0)	115 (100:14:1:0:0)	5 (5:0:0:0:0)	4 (4:0:0:0:0)	137 (115:15:4:2:1)
Infection	4 (1:1:2:0:0)	2 (1:1:0:0:0)	21 (10:9:2:0:0)	1 (1:0:0:0:0)		28 (13:11:4:0:0)
Dislocation	2 (2:0:0:0:0)		17 (12:3:2:0:0)	1 (1:0:0:0:0)		20 (15:3:2:0:0)
Idiopathic pain (or metal bearing complication in metal on metal)	9 (3:2:3:1:0)	1 (0:0:1:0:0)	2 (2:0:0:0:0)		3 (3:0:0:0:0)	15 (8:2:4:1:0)
Periprosthetic fracture		1 (0:1:0:0:0)	9 (9:0:0:0:0)	1 (0:1:0:0:0)	1 (1:0:0:0:0)	12 (10:2:0:0:0)
Wound healing			1 (1:0:0:0:0)			1 (1:0:0:0:0)
Inadequate offset				1 (0:1:0:0:0)		1 (0:1:0:0:0)
Implant breakage			1 (1:0:0:0:0)			1 (1:0:0:0:0)
Total	26 (11:4:7:3:1)	6 (2:2:2:0:0)	166 (135:26:5:0:0)	8 (7:1:0:0:0)	9 (8:1:0:0:0)	215 (163:35:13:3:1)

PVLI = perivascular lymphocytic infiltration.

Reasons for hip revision included aseptic loosening, infection, idiopathic pain, dislocation, periprosthetic fracture, and implant breakage. Aseptic loosening, which included wear and osteolysis, was diagnosed by continuous radiolucent lines around the implant or migration of the prosthesis, distinct areas of localized bone loss on serial radiographs, or looseness upon intraoperative examination of the component. Infection was diagnosed if one of the following three criteria were present: (1) a sinus tract or abscess that communicated with the joint space; (2) a positive preoperative aspirate culture; or (3) a positive intraoperative culture and obvious intracapsular purulence or two positive intraoperative cultures of the same organism [18]. In cases of negative cultures, an infection was considered present if there was gross purulence within the joint and intraoperative frozen sections demonstrated two or more neutrophil polymorphs on average in each of at least 10 high-power fields ($\times 400$) [33, 34]. Patients were diagnosed with idiopathic pain after a process of elimination. EMGs were performed for suspected radiculopathies. Extraarticular sources of discomfort such as trochanteric bursitis and iliopsoas impingement were ruled out with a corticosteroid injection and local numbing agent. Surgical findings of a well-fixed implant with normal grossly appearing soft tissues and pristine articular surfaces supported the diagnosis of idiopathic pain. Because metal hypersensitivity is primarily a diagnosis of exclusion, patients with MoM bearings who underwent revision for a metal bearing complication, including metallosis, vague pain, or mechanical grinding, were placed in the idiopathic pain category for this study.

In each patient, one to three samples of periprosthetic tissue from the surrounding joint capsule were used for pathology. Two to three slides were produced from each sample, and three to four sections were analyzed from each slide. Histologic analysis was performed in a fashion similar to that of previous authors [39]. Briefly, all samples were formalin-fixed and 5- to 10-μm microtome sections were stained with hematoxylin and eosin. All sections were reviewed twice by an experienced musculoskeletal pathologist (SB) and subsequently graded according to the scheme described by Willert et al. [39] for PVLI, DLI, and periprosthetic particle storage and tissue reactions.

Paired t tests were used to compare mean ages, with 95% CIs. Two-sided Fisher's exact tests were used to determine differences in the presence and grades of PVLI between MoM, non-MoM, hip arthroplasty, and TKA groups. The Pearson correlation coefficient (r) was used to analyze the relationship among histologic evidence of PVLI, DLI, and tissue reaction to wear. All data were compiled on a Microsoft® Excel® spreadsheet (Microsoft Corp, Redmond, WA).

Results

PVLI was found in implants of every bearing type (Fig. 1) in varying frequency and severity (Fig. 2). It was present in more ($p < 0.001$) TKAs (40%) than overall hip arthroplasties (24%) with no difference in severity. Compared to non-MoM hip arthroplasty, MoM bearings were more commonly ($p < 0.001$) associated with PVLI (59% versus 18% positive) and demonstrated increased severity (41% versus 3% greater than grade +) ($p = 0.02$–0.04).

Regarding diagnoses for revision hip arthroplasty, aseptic loosening was the most common, followed by infection and dislocation (Table 2). The highest proportions of hip revision cases associated with the presence of PVLI were found in infection (53%) and idiopathic pain (47%), followed by dislocation (25%), fracture (17%), and aseptic loosening (16%). However, when bearing surfaces

Fig. 1 Representative examples of absent, mild, and severe PVLI are shown for TKA, MoP THA, and MoM THA. Low-power (×40) photomicrographs with hematoxylin and eosin stain demonstrate large, dense perivascular infiltration of lymphocytes in mild and severe PVLI.
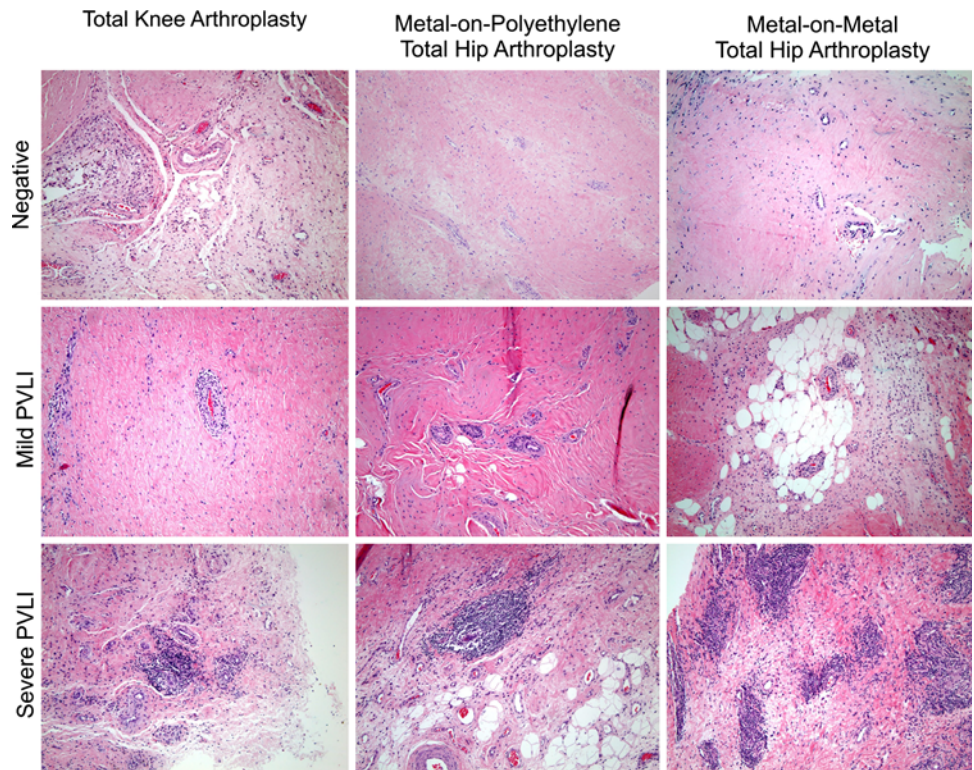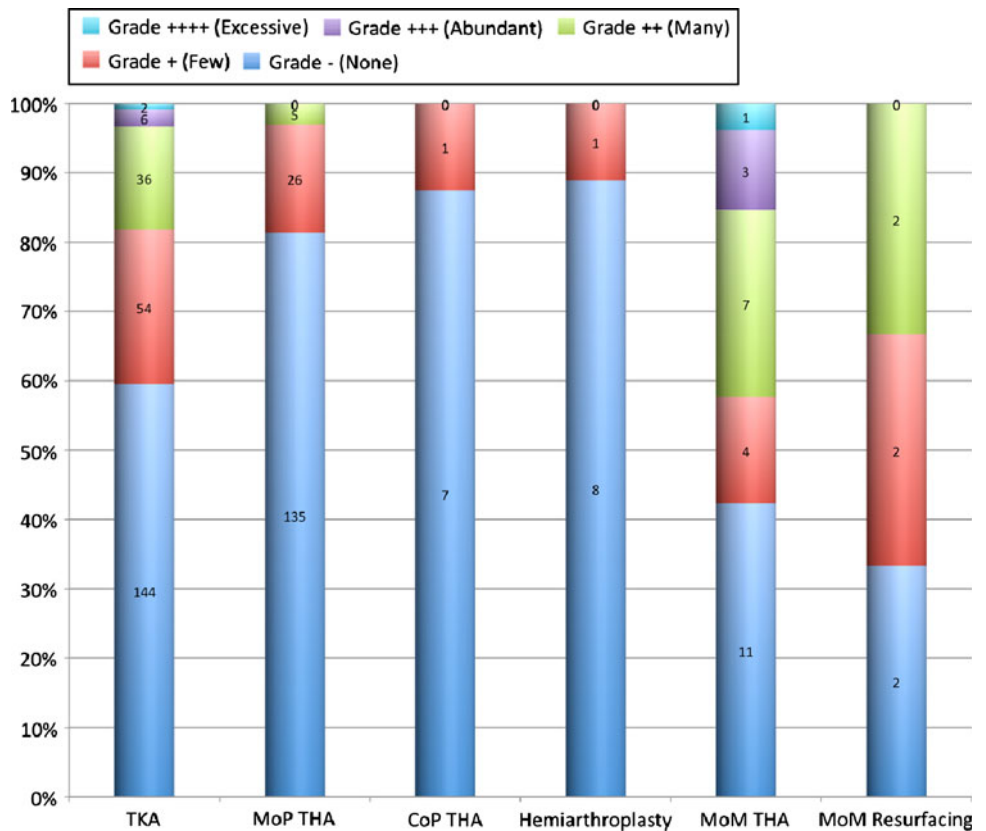

Fig. 2 Grading of PVLI for bearing surfaces according to number of perivascular agglomerations per field of view under ×4 magnification [39] is shown. None = 0; few = 1 to 2; many = 3 to 6; abundant = 7 to 10; excessive > 10. CoP = ceramic on polyethylene.

were evaluated separately for aseptic loosening, PVLI was present more often (p < 0.001) in MoM hips (54%) than non-MoM hips (12%) and demonstrated more extensive involvement. In MoM hips, six of the seven cases of aseptic loosening with PVLI were rated greater than "few/ +"; in non-MoM hips, all but one of the 15 cases were

rated as "few/+". For idiopathic pain, PVLI was present in 70% of the MoM hips, but none of the non-MoM hips.

Histologically, the extent of PVLI demonstrated no correlation to the extent of periprosthetic particle storage and tissue reaction in TKA, MoM, or non-MoM hip arthroplasty. On the other hand, the grade of PVLI was correlated to the grade of DLI in TKA (r = 0.46) and MoM hip (r = 0.61) revisions and weakly correlated in non-MoM hip revisions (r = 0.33).

Discussion

Metallic debris is not benign. Highest during the initial running-in process and eventually reaching an asymptotic level after 6 months to 2 years, metallic abrasive wear particles are smaller, yet more numerous [17, 37] than PE wear particles [27]. Ions can be generated from not only corrosion but also repassivation, modular components, delaminated metal coatings, impingement, and fixation screws [24, 30]. Although metal ions disseminate throughout the reticuloendothelial system at less than toxic levels [1, 8], metal particles can concentrate locally in the periprosthetic soft tissue [16] causing metallosis [9] and frank tissue necrosis [3]. Histologic studies of MoM periprosthetic tissue have identified a characteristic pattern of DLI in the inner neocapsular layer and PVLI in the intermediate vascular layer [39, 40] suggestive of a DTH reaction. Although some authors have described these findings to be limited to MoM bearings [13, 29], careful review of the literature demonstrates prior descriptions of these chronic inflammatory cells in non-MoM implants [17, 26, 39]. The prevalence and role of this phenomenon in revision hip arthroplasty, both MoM and non-MoM, are not clear. It is thought metal-stimulated lymphocytes, as part of the adaptive immune response, can release osteolytic cytokines and contribute to aseptic loosening [23]. Whether this process is related to the innate immune response and particle-stimulated macrophages [23, 39] or the local cytotoxicity and ulceration from metallic wear particles [13, 29] is unknown [31]. We compared the incidence and severity of PVLI in failed hip metal-on-metal implants to non-metal-on-metal implants and TKA, PVLI in metal-on-metal and non-metal-on-metal hip arthroplasty based on reason for revision, and grade of PVLI to DLI and tissue reaction to metal particles.

There are several weaknesses in this study. First, it was not practical to include a control group of well-functioning implants to evaluate the presence of PVLI in surgical samples. Only autopsy samples could provide these data. Noninvasive tests for metal hypersensitivity such as dermal patch testing and lymphocyte transformation testing do not replicate the periprosthetic milieu [14], lack clinical validation [23], and are not widely accepted in the orthopaedic community [2, 21]. While the amount of metal released through corrosion by non-MoM implants would not likely change substantially based on implant integrity, well-positioned MoM implants are associated with lower wear rates and less metallosis [15, 16]. With fewer metallic particles, the prevalence of metal hypersensitivity reactions and PVLI may be reduced, but this correlation is not necessarily supported by this or other studies [40]. Undoubtedly, a histologic study of healthy MoM and non-MoM implants would help determine whether ALVAL is a naturally occurring reaction to metal that only pathologically manifests itself in some patients or an indicator of problematic implants requiring revision. Second, only PVLI was the focus of this study. Although DLI, plasma cells, and macrophages with droplike inclusions similarly are components of ALVAL [39], PVLI was the prominent feature in first describing this phenomenon and associating it with a DTH reaction in contemporary literature [13]. Third, histologic specimens were examined by a single pathologist only. While interobserver and intraobserver variability in histologic grading of ALVAL are known to exist (κ = 0.71, 0.68) [4] and could have potentially affected significance levels in this study, they are unlikely to alter the general trends found here.

In this study, PVLI occurred in 59% of MoM hip revisions, most extensively in cases of aseptic loosening and idiopathic pain. This supports the findings of previous authors [5, 31, 36]. In MoM failures, histologic findings of PVLI correlated strongly with the presence of DLI, another component of ALVAL, but did not correlate with periprosthetic particle storage and tissue reactions, indicators of metal particulate load. Several studies have similarly reported correlation between the extent of PVLI and DLI [5, 40] but not with local metallic particle burden [28, 36, 39, 40] or the extent of necrosis [40]. Periprosthetic tissue from non-MoM bearings for a variety of reasons displayed an 18% rate of PVLI. Infectious diagnoses were associated with PVLI in 53% of all hip implants, and its prevalence may contribute to a higher rate of PVLI in TKA (40%) than hip arthroplasty (24%) as a whole. The association of PVLI and septic loosening is not new [34], but to the authors' knowledge, the prevalence of PVLI in revision TKA has not been published.

Based on these findings, mild PVLI is present in a substantial proportion of failed total hip and knee prostheses, but higher levels of PVLI are most prominent in revised MoM bearings and TKA. Aseptic loosening and idiopathic pain in MoM hips are associated with PVLI, but metal particulate load is not. Additional studies are necessary to further elucidate the cause of PVLI in TKA and to prove whether these histologic characteristics suggestive of

a DTH reaction in joint arthroplasty are primary instigators, secondary changes or merely incidental findings to adverse clinical processes.

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