Clin Orthop Relat Res (2015) 473:3915–3917 / DOI 10.1007/s11999-015-4571-8

Clinical Orthopaedics and Related Research®
A Publication of The Association of Bone and Joint Surgeons®

Published online: 13 October 2015

CORR Insights

CORR Insights®: Do Patients With a Failed Metal-on-metal Hip Implant With a Pseudotumor Present Differences in Their Peripheral Blood Lymphocyte Subpopulations?

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Where Are We Now?

The study by Catelas and colleagues adds to the current scientific consensus that adaptive immune responses to metals occurs in a subset of all people with metal implants. The study authors also found that the incidence of pseudotumors correlates with systemic evidence of metal-related delayed-type hypersensitivity (DTH) responses and elevated metal ion levels. The current study identifies alterations in circulating adaptive immune cells in people with elevated levels of metal debris and pseudotumors. These findings support past histological and T-cell function studies, indicating pseudotumors are more prevalent in people with DTH-type immune reactivity. This highlights the growing recognition of these phenomena as central to implant performance in some individuals/implant designs.

Case and group studies [4, 5] indicate that once locally activated, adaptive immune inflammation to metal contributes to (if not, mediates) the pathogenesis of poor implant performance. Metal DTH reactivity is a lymphocyte mediated response, similar to a Type IV DTH reaction. Metal-on-metal (MoM) hip failures have been associated with classic DTH responses including periimplant activated lymphocyte accumulations (aseptic lymphocytic vasculitis-associated lesions, [ALVAL]), and dermal and functional lymphocyte hypersensitivity responses to metals [2, 7, 11]. Elevated metal exposure can also cause different forms of toxicity responses in tissue, bone, and immune cells, including cobalt-induced hypoxia-like responses, postulated as causing pseudotumors [10]. Lymphocyte reactivity (metal DTH responses/ALVAL) and pseudotumors can be caused separately [6, 8]. Currently, there are no accepted thresholds for systemic metal ion levels that necessarily indicate for pseudotumor formation or immune reactions [1, 7]; it remains an increased risk association.

This CORR Insights® *is a commentary on the article* "Do Patients With a Failed Metal-on-metal Hip Implant With a Pseudotumor Present Differences in Their Peripheral Blood Lymphocyte Subpopulations?" *by Catelas and colleagues available at:* DOI: 10.1007/s11999-015-4466-8.

The author certifies that she, or any members of her immediate family, has no funding or commercial associations (consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

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This *CORR* Insights® comment refers to the article available at DOI: 10.1007/s11999-015-4466-8.

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Therefore, we still do not know whether metal sensitization can be predictive or causative of pseudotumor formation in patients with MoM hips.

The current study purports that under conditions of elevated metal, systemic changes in adaptive immune cells can occur that are consistent with metal DTH responses and pseudotumor formation. These changes in systemic memory cells are consistent with the results found in functional lymphocyte transformation testing in similar pseudotumor versus nonpseudotumor populations, and therefore support the use of diagnostic testing [8]. However, it remains unclear if the utility of diagnostic testing extends beyond those with a history of metal sensitivity and/or have an implant with idiopathic aseptic inflammation and symptoms consistent with metal DTH reactivity.

Where Do We Need To Go?

One unresolved issue pertains to how men and women differ in terms of the processing of (and the reaction to) the corrosion products from metallic arthroplasties. The current study indirectly supports previous reports that females have greater immune reactivity to orthopaedic metal debris [9] and experience a greater incidence of autoimmune disease [3] than males. However, it is unclear how much of the current study's findings are due to inherent gender difference and not pseudotumor metal-related immune response. It is clear that a subset of the general population is more predisposed to metal-DTH and pseudotumor formation and that predictive testing of these individuals is needed. But these tests are hard to develop, harder to standardize across laboratories, and still harder to validate; development, standardization, and validation all must be performed before any new test can be considered clinically useful. Functional DTH testing of lymphocytes, cytokine analysis, and others immune assays matched to groups with systemic adaptive immune system alterations in nonpseudotumor, and DTH-metal-positive gender-matched cohorts is needed to further determine the extent and implications of the current findings. Moreover, further research is needed to predict individual susceptibility (whether toxic or hypersensitive) to elevated metal ion concentrations, given that individual susceptibility to metal toxicity has virtually not been investigated at all.

How Do We Get There?

To fully understand the relationship between elevated metal levels, pseudotumors, and systemic alterations in adaptive immune cells, we need further studies to relate flow cytometry analysis to functional lymphocyte study; these studies need to include sufficient numbers of patients, graphical depiction of raw flow data (gating), and absolute counts of different cells numbers of per volume of blood.

Additionally, we need to confirm through animal models or carefully controlled clinical experiments that indeed elevated metal ion levels even cause the immune reactions we suspect they cause (eg, systemic alterations in immune cell frequency). Ideally, long-term prospective analysis of patients with MoM hips would be required where a comprehensive set of outcome measures are collected. However, the number of endpoints of interest, the expense, and the (appropriately) decreasing number of MoM hips being done all preclude the performance of such large, prospective studies. Instead, targeted, smaller investigations, such as the current study, can help us to reach consensus as to how systemic and local DTH responses are causally linked to pseudotumors.

It is clear that adaptive immune reactivity to metals is prevalent in more than a few highly susceptible individuals and that postoperative screening of metal-sensitization may result in early detection of pathology reducing complications of metal implant failure, like MoM hips, due to pseudotumors and/or excessive immune responses; however, more study is needed prior to widespread use of any new screening protocols.

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