Introduction: T cell-mediated type IV hypersensitivity reaction to metal has been suggested to play an important role in an etiology of adverse reactions to metal debris (ARMD) including pseudotumors following metal-on-metal total hip arthroplasty (THA) [1]. Other study showed cytotoxicity response to metal wear debris could be the cause of ARMD [2]. Our hypothesis was that T cell-mediated type IV hypersensitivity could be a major cause of ARMD. This hypothesis was studied by lymphocyte stimulation test and immunohistochemistry in patients with ARMD.

Methods: Thirteen patients with pseudotumors underwent revision surgery following metal-on-metal THA (15 hips). The patient population consisted of one man and 12 women with a mean age of 65 years and a mean body mass index of 24.9 kg/m$^2$. Cormet (Corin, Cirencester, UK) was used in 12 hips and Pinnacle (DePuy, Warsaw, IN) was used in three hips for the primary THA. The mean time to revision was three years and seven months. Lymphocyte stimulation test to metal was conducted before revision surgery. A stimulation index > 200% was considered positive. In six unilateral THAs, serum cobalt and chromium ion concentrations were measured before and after revision surgery. The periprosthetic tissue specimens in patients who underwent revision were stained with hematoxylin & eosin and examined by light microscopy, and the ALVAL (aseptic lymphocyte-dominated vasculitis-associated lesion) score was analyzed [3]. They were also analyzed with immunohistochemistry using antibodies to T cells (CD3; DAKO, Glostrup, Denmark) and B cells (CD20; DAKO) to characterize the immunophenotype. The predominant lymphocyte was determined based on whether T cells or B cells were dominant. The Wilcoxon signed rank test was used for differences in serum cobalt and chromium ion concentrations before and after revision surgery. The Mann-Whitney U test was used to compare ALVAL scores between patients with and without positive lymphocyte stimulation tests. Statistical significance was set at a P value less than 0.05.

Results: Lymphocyte stimulation test showed that five patients were nickel-sensitive, and one patient was also cobalt-sensitive before revision. No reactivity to chromium was detected. The mean cobalt levels were elevated to 4.4μg/L before revision and then decreased significantly to 0.8 μg/L after revision (p=0.028). The median chromium levels dropped significantly from 3.0 μg/L (before revision) to 0.7 μg/L (after revision, p=0.043). The mean ALVAL score was 7 points (5 - 9 points). The ALVAL score showed no significant difference between patients with and without positive lymphocyte stimulation tests. Immunohistochemical studies showed that CD3-positive T cells were dominant in five hips with ARMD, and CD20-positive B cells were dominant in 10 hips with ARMD (Fig. 1). Centrally placed B cell aggregates were loosely surrounded by T cells. In four of the five patients with positive lymphocyte stimulation tests, T cells were dominant, suggesting type IV hypersensitivity.
Discussion: T cells play a crucial role in metal hypersensitivity reactions. Testing for metal hypersensitivity has been historically conducted in vivo using skin patch testing. The patch test is considered the reference method for diagnosing contact allergy, but its use in detecting hypersensitivity to implant materials is controversial. [4] Lymphocyte stimulation test has been used to investigate metal sensitivity related implant failure.

In four patients with positive lymphocyte stimulation test and dominant T cell infiltration, the cause of ARMD could be suggested to be type IV hypersensitivity. Since B cell infiltration is not characteristic of a type IV hypersensitivity reaction, the major cause of ARMD could not be type IV hypersensitivity in the remaining nine patients.

The B and T cell-containing aggregates seen in ARMD bear a remarkable resemblance to tertiary lymphoid organs that arise in chronically inflamed adult tissue. Features associated with tertiary lymphoid organs include centrally placed B cell aggregates, loosely surrounded by T cells. In addition to the well-described T cell-mediated type IV hypersensitivity response, an under-recognized immunological reaction to metal wear debris involving B cells and the formation of tertiary lymphoid organs could occur in a distinct subset of patients with ARMD [5].

The limitations of this study include the small number of patients studied and the relevance of nickel exposure, which is present in only a small percentage in cobalt chromium alloys.

In conclusion, the cause of ARMD could be metal hypersensitivity in some patients; however, the majority of patients with ARMD had no evidence of metal hypersensitivity and our hypothesis was not verified.

Significance: Metal hypersensitivity was not the dominant biological reaction involved in the occurrence of ARMD.
Fig. 1. Immunohistochemical staining showing numerous CD20 positive B cell infiltration in periprosthetic tissue (original magnification x100).

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