Lymphocyte Proliferation Responses In Patients With Pseudotumours Following Metal-on-metal Hip Resurfacings

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Introduction: Recently, a series of ‘pseudotumour’ (soft-tissue mass relating to the joint) has been reported in patients following metal-on-metal hip resurfacing arthroplasty (MoMHRA) [1]. Although the reported incidence of symmetrical pseudotumours is 1%, they were found be locally destructive, requiring revision surgery in a high percentage of patients. The aetiology remains unknown. Based on the common histological features of extensive necrosis with lymphocytic infiltration observed in ‘pseudotumours’, a delayed hypersensitivity reaction to nickel (Ni), chromium (Cr) or cobalt (Co) has been suggested to play a role in its aetiology. The aim of this study was to investigate the incidence and level of hypersensitivity reaction to metals in patients with ‘pseudotumour’.

Materials and Methods: A total of 24 patients were investigated in this Institutional Review Board approved study. There were 3 patient groups: (1) Groups 1 – MoMHRA patients with ‘pseudotumour’, a cystic or solid mass relating to the resurfaced hip, detected on the ultrasound and confirmed with MRI (n=6, 5 female, 1 male, a mean age 53 years, range 45-62); (2) Group 2 – MoMHRA patients without pseudo-tumours detected on US and MRI (n=13, 7 female, 6 male, a mean age 55 years, range 40-69); and (3) Group 3 – age-matched healthy control patients without metal implants (n=5, 3 female, 2 male, a mean age 54 years, range 50-58). The first 2 groups were a part of ongoing MoMHRA surveillance study and were recruited on an all-comer basis with a mean follow-up of 58 months (range 13-88). A detailed clinical history of metal allergy was obtained from all patients.

Lymphocyte transformation tests (LTT) were used to measure lymphocyte proliferative responses to metals [2]. Peripheral blood mononuclear cells (PBMC) were isolated from heparinized blood samples using standard Ficoll-Hypaque® (Pharmacia, Uppsala, Sweden) densities gradient centrifugation. The PBMC were cultured in microtitre plates at a cell density of 10^5 cells/mL in an enriched RPMI1640 culture medium (Sigma, Deisenhofen, Germany) supplemented with 10% human AB serum (CC Pro, Neustadt, Germany). Stimulation assays were done in triplicate in 96-well microtiter plates (Greiner, Frickenhausen, Germany; 2×10^5 cells/well). Culture was set up in the presence of either: (1) medium alone as a negative control; (2) phytohaemagglutinin (PHA) (Biochrom, Berlin, Germany; 2 μg/mL), which activates lymphocytes as a positive control; (3) nickel chloride (NiCl2) (Sigma N-4882, Germany; 10^-4M, 10^-5M, and 10^-6M); (4) cobalt chloride (CoCl2) (10^-4M, 10^-5M, and 10^-6M); and (5) chromium chloride (CrCl3) (10^-4M, 10^-5M, and 10^-6M). After 5 days of culture, cells were labelled with [3H]-thymidine and proliferation was assessed by scintillation counting of incorporated radioactivity. The stimulation index (SI) was calculated by the ratio of mean counts per minute (cpm) of stimulated to unstimulated (culture medium only) cultures. The SI stimulation index was used to compare lymphocyte proliferative response. A SI value of greater than 2.0 was interpreted as a positive result.

Results: A clinical history of metal allergy manifested as a dermal reaction to metal jewellery was reported in 2/6 (33%) in Group 1, 2/13 (15%) in Group 2, and none in Group 3. In the pseudo-tumour group, the incidence of reactivity to Ni, Co and Cr was 60%, 17% and 0%, respectively. Within Group 2, the reactivity to Ni, Co and Cr was 69%, 8% and 15%, respectively. Although there was no positive reactivity to Co and Cr in the healthy control Group 3, one subject, who has not reported metal allergy, had reactivity to Ni. Among the patients with metal-reactivity in all three groups, the majority were reactive to Ni. Inter-group comparisons of mean SI values for PHA, No, Co and Cr calculated using Kruskal-Wallis non-parametric analysis of variance showed no significant differences with p > 0.05. (Figure 1)

Discussion: The histological features of pseudotumours, characterized by the presence of B cells, T lymphocytes and plasma cells, are similar to ALVAL (aseptic lymphocyte dominated vasculitis associated lesion) as described by Willert et al. [3], suggesting that pseudotumours may represent a delayed hypersensitivity reaction to nickel, chromium or cobalt. The incidence of enhanced lymphocyte response to metals in patients with MoMHRA was more common than the control group, in agreement with previous reports [4]. However, in comparison with non-pseudotumour MoMHRA patients, there was no significant difference in the incidence and the level of lymphocyte reactivity to metal, as measured by LTT, in patients with pseudotumour. Thus, the current data demonstrates that lymphocyte responses to metal, especially to Co and Cr, are not elevated in pseudotumour. We conclude that patients with MoMHRA have an enhanced lymphocyte response to metal ions, reflecting exposure and immune reactivity to metal ions. However, patients with pseudotumours have a similar proliferative response to those without pseudotumours, which suggests that type IV hypersensitivity may not be the cause of the pseudotumours.


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