Roberts Conference Presentation: Metal Hypersensitivity and Orthopaedic Implants

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INTRODUCTION BY DR. THOMAS THORNHILL

In 1980 the Robert Breck Brigham Hospital merged with the Peter Bent Brigham Hospital and Boston Hospital for Women into what is now known as the Brigham and Women's Hospital. The Robert Breck Brigham Hospital was a unique institution entirely devoted to the treatment of patients with musculoskeletal disorders. A weekly conference was held at the Robert Breck Brigham Hospital where specific clinical problems were discussed. This case based conference had participation from students, residents, attendings, and fellows.

The current Roberts Conference at the Brigham and Women's Hospital is a weekly meeting held to preserve the tradition of the Robert Breck Brigham Hospital. It is a case based clinical and translational conference where current cases are discussed. When specific topics of great interest arise a resident usually prepares and presents a literature based review on the subject. The following article by Dr. Raneer is an example of one such case.

SUMMARY OF A ROBERTS CONFERENCE PRESENTATION GIVEN ON JANUARY 27, 2005

The field of Orthopaedic Surgery is characterized by the extensive use of metal implants with only rare instances of hypersensitivity reactions. True metal allergies are uncommon but they constitute just one type of hypersensitivity reaction. Various types of hypersensitivity reactions exist, and knowledge of them may become increasingly more important with the rising use of metal-on-metal bearings in joint arthroplasty.

"Hypersensitivity" refers to a state of heightened reactivity to antigen [1]. "Hypersensitivity reactions" are defined as immune responses to innocuous antigens that lead to symptomatic reactions upon reexposure [1]. The term "allergy" is often used broadly by clinicians and lay people. However, in proper use "allergy" refers to a specific type of hypersensitivity reaction known as type I hypersensitivity (Fig. 1). Type I hypersensitivity reactions are those in which a soluble antigen reacts with immunoglobulin E (IgE) leading to mast-cell activation. Common examples of this type are allergic rhinitis, asthma, and systemic anaphylaxis. Type II hypersensitivity reactions are those in which antigens associated with cells or with the extracellular matrix are bound by immunoglobulin G (IgG) leading to activation of phagocytic cells. The common reaction to penicillin is an example of this type of hypersensitivity reaction. IgG is also involved in type III hypersensitivity reactions but in that case binds to soluble antigens and leads to activation of either phagocytic cells or the complement cascade. The classic serum sickness reaction is an example of a type III hypersensitivity reaction. The first three types of hypersensitivity reactions are all antibody-mediated. Type IV hypersensitivity reactions are different in that they are T-cell mediated. The T-cell mediator can be either a helper T-cell (T_H1 or T_H2) or a cytotoxic T-cell. Soluble antigens can bind to T_H1 cells leading to macrophage activation or they can bind to T_H2 cells leading to eosinophil activation. Contact dermatitis and the tuberculin reaction are examples of the former, while chronic asthma and chronic allergic rhinitis are examples of the latter. Contact dermatitis can also arise from cell-associated antigens activating cytotoxic T-cells.

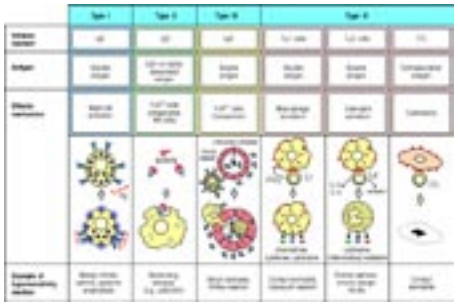

Figure 1.
Types of hypersensitivity reactions [1].

Various case reports over the years have linked immunogenic reactions with metallic implants in cardiothoracic surgery, plastic surgery, orthopaedics, and dentistry [2]. Reactions such as severe dermatitis, urticaria, and/or vasculitis have been linked with the relatively general phenomena of metallosis, periprosthetic fibrosis, and muscular necrosis. Barranco and Solomon reported a twenty year old female who developed extensive eczematous dermatitis five months after having stainless-steel screws implanted for chronic patellar dislocation [3]. She was treated with topical corticosteroids for a few years

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with minimal effect. Ultimately, the screws were removed and the eczema completely resolved within seventy-two hours. The unbelieving orthopaedist applied a stainless steel screw to the patient's back, and within four hours there was a return of generalized pruritus and erythema. Patch testing elicited reactions to nickel, nickel sulfate, and the steel screw. Halpin reported a forty-five year old woman who presented with forearm swelling, periprosthetic fibrosis, and patchy muscular necrosis seven years after ORIF of a both bones forearm fracture with cobalt-alloy plate and screws [4]. The implants were removed and all of the patient's symptoms eventually disappeared. From the general surgery literature comes a fifty year old female who had urticaria and abdominal pain after a cholecystectomy [2]. She had temporary relief with plasmapheresis but not with corticosteroids or antihistamines. Ultimately, the tantalum metal clips used during the cholecystectomy were removed and the patient had permanent symptom resolution. The clips showed visible signs of corrosion. While these reports leave little doubt that some patients become sensitized to metallic implants, they cast little light on the mechanism by which this occurs.

All metals in contact with biological systems corrode. Serum levels of cobalt, chromium, and titanium are significantly increased in patients with normal functioning metal-on-metal hips [5]. Released ions themselves are not immunogenic - they are so called haptens. However, they can activate the immune system by forming complexes with native proteins. Nickel is the most common sensitizer in humans, followed by cobalt and chromium [2]. The prevalence of dermal hypersensitivity to metal in the general population is 10-15% [6]. In general, metal implant related hypersensitivity reactions are thought to be type IV hypersensitivity reactions.

There are essentially three ways to test for metal sensitivity. The first, and most used, is skin (patch) testing. This testing is quick and there are commercial kits of common antigenic substances. However, patch testing does have drawbacks including numerous concerns about the applicability of skin testing to *in vivo* sensitivity. First, skin testing involves only a short (2-3 day) exposure while typical reports of eczemic reactions to orthopaedic implants occur after weeks or months of constant exposure. Second, dermal Langerhans cells are the primary effector cells with skin testing, while the dominant antigen presenting cell (if any) responsible for mediating implant related hypersensitivity remains unknown. Third, the haptenic potential of metals on open testing dermal contact is likely different than that *in vivo*. In fact, whether or not a skin reaction occurs can depend on the type of preparation (eg. titanium salt solution vs. titanium ointment). A further concern with skin testing is that it could potentially induce hypersensitivity in previously non-sensitized patients. A second method for metal sensitivity testing is lymphocyte transformation testing (LTT). LTT involves measuring the proliferative response of lymphocytes following activation. A radioactive thymidine marker is added to lymphocytes and they are exposed to the challenge agent. Dividing cells incorporate the radioactive thymidine marker into their cellular DNA. Thus, the amount of radioactivity at the end of the test is a measure of the proliferative response of the lymphocytes. Few implant-related metal sensitivity investigations with LTT have been done to date. However they seem to indicate that LTT is better than patch testing. The final way to test for metal sensitivity is with leukocyte migration inhibition. Leukocytes in culture actively migrate in a random fashion, but they can be preferentially attracted to chemoattractants. In the presence of a sensitizing agent, leukocytes migrate more slowly and lose the ability to recognize chemoattractants. Leukocyte migration inhibition techniques quantify the migration of leukocyte populations along various media in the presence and absence of antigen. Few investigators have applied leukocyte migration inhibition testing and there have been few improvements in the assays since they were first used nearly thirty years ago.

The link between *in vitro* metal hypersensitivity and implant function comes from multiple cohort studies in the late 1970s and 1980s [2]. These studies included heterogeneous patient populations and testing methodologies. The common link was that all patients were tested for sensitivities to one or a combination of metals after they received a metal implant. Averaged across all the studies, the average prevalence of metal sensitivity among patients with a well functioning implant was roughly 25% while the average prevalence among patients with a failed/poorly functioning implant was roughly 60% [2]. Both of the values are higher than the 10-15% quoted for the prevalence in the general population. However, by no means does this data prove a causal effect. After all, were patients sensitized because the device failed, did the device fail because the patient had a pre-existing metal sensitivity, or did something else (like autoimmunity) cause both? Ultimately what is needed is a study where multiple hypersensitivity tests are performed on individual patients: 1) before implantation, 2) during the service of the device, and in the case of an adverse outcome, both 3) before and 4) after removal of the device.

The major question left unanswered is whether metal hypersensitivity is an extreme complication in only a few highly susceptible patients (as in the case reports), or a common subtle contributor to implant failure (as the cohort studies suggest). Two recently published studies address this question to some degree.

Willert et al. performed a study of the clinical data and periprosthetic tissues associated with metal-on-metal implants retrieved at revision [7]. They looked at their first 24 consecutive metal-on-metal revisions with 5 being excluded for infection. They compared these to 3 control groups of revisions done for aseptic loosening. Control group I consisted of 18 non-cemented titanium alloy stems with an alumina head articulating against polyethylene. Control group II was composed of 11 all-cemented Müller-Charnley prostheses consisting of a monobloc Co-Cr-Mb stem articulating with polyethylene. Finally, group III consisted of 15 cemented classic metal-on-metal McKee-Farrar Co-Cr-Mb implants. Histological examination of the study group tissue was remarkable for diffuse and perivascular infiltrates of lymphocytes, plasma cells, high endothelial venules, fibrin exudation, macrophages (many recently invaded), and

necrosis. The plasma cells and massive fibrin exudation are not characteristic of a type IV hypersensitivity reaction. Rather, they support the diagnosis of a hypersensitivity reaction that can be described as an aseptic lymphocyte-dominated vasculitis-associated lesion or as a lymphocyte-dominated immunological answer (LYDIA). Furthermore, the new macrophages suggest a chronic inflammation with a continuous recruitment of inflammatory macrophages from the peripheral blood. Control group I showed primarily polyethylene wear particles and a foreign body reaction, with predominantly old macrophages and few lymphocytes. Control group II tissues were also remarkable for primarily a foreign body reaction to polyethylene, with lymphocytes seen in roughly one-third of cases. Control group III also showed a foreign body reaction but in this case it was to cement. There were lymphocytes in about two-thirds of cases in this Co-Cr-Mb metal-on-metal group but interestingly they were lower in number than in the study group. Finally, there was no correlation between the amount of metal particles seen and the intensity of the lymphocytic infiltrate. These histological findings support the possibility of a lymphocyte dominated response to metallic implants and to metal-on-metal bearings in particular. The reason for the different intensity of the reaction in the different generation metal-on-metal bearings is unclear. Clinical analysis of the 19 revisions in the study group showed that 12 were revised to alumina-on-poly, 2 were revised to metal-on-poly, and 5 were revised to a new Co-Cr-Mb metal-on-metal articulation. At a range of 1 to 7 years follow-up, all 14 hips revised to either alumina-on-poly or metal-on-poly had total relief of pain, while hip and thigh pain persisted in all 5 revised to a second metal-on-metal articulation. Of the 5 still with pain, 2 had a second revision, this time to a non metal-on-metal articulation and had symptom relief. These findings suggest that an immunological response persisted after the first revision and that the patients had been sensitized to the components of the metal-on-metal bearing.

Davies et al studied the histological appearance of periprosthetic tissues retrieved from metal-on-metal and metal-on-poly hip replacements and compared these with control tissues retrieved at the time of primary arthroplasty from patients with osteoarthritis [8]. In the study group there were 25 Co-Cr on Co-Cr hips with 14 being total hip replacements and 11 being surface replacements. Of these 25, 22 were retrieved at the time of revision (19 aseptic loosening, 2 impingement, and 1 heterotopic ossification) while 3 were retrieved from autopsy specimens. The study group also consisted of 19 metal-on-poly (10 titanium, 9 Co-Cr) surface replacements all of which were revised for aseptic loosening. There were 9 control specimens from primary total hip replacements performed for osteoarthritis. The results were remarkable for a greater extent and severity of surface ulceration of the periprosthetic neocapsule in the metal-on-metal bearings than in the metal-on-poly bearings. Within the 25 metal-on-metal bearings, there was a greater extent/severity of surface ulceration amongst the 19 aseptic revisions than in the other 6 hips (2 impingement, 1 heterotopic ossification, 3 autopsy). Overall, 17 of the 25 had a significant perivascular lymphocytic cuff. In addition to having a less ulcerated surface, the tissues from the metal-on-poly bearing specimens showed none with a perivascular lymphocytic cuff. In these tissues, macrophages and fibroblasts predominated. The data of Davies et al support those of Willert et al and lend further support to the existence of a novel form of immunological reaction. In addition, they demonstrate a further correlation between histology and implant function.

Howie and Vernon-Roberts demonstrated that intra-articular injection of Co-Cr wear particles in rats produced synovial surface ulceration and a dense infiltrate of small lymphocytes in the subsurface tissue layer [9]. These data support the hypothesis that the primary insult is to the surface of the tissue and that the perivascular lymphocytic infiltrate is the secondary phenomenon. Furthermore, the findings of Howie and Vernon-Roberts indicate that, at least in rats, exposure of tissue to debris is sufficient to provoke a reaction even in the absence of a loose prosthesis.

CONCLUSIONS

The current state of knowledge regarding metal hypersensitivity reactions in patients with metallic implants is still evolving, but a number of points can be made at this time. First, numerous case reports have shown that some patients clearly have hypersensitivity reactions directly associated with implanted metallic materials. Second, recent histological studies appear to show that metal-on-metal bearings induce a novel immunological response. Third, intra-articular Co-Cr wear particles are sufficient to produce this response in rats. Fourth, a correlation has not been observed between the amount of metal particles seen histologically and the histological extent of the response. Lastly, the recent clinical studies show some correlation, albeit weak based on numbers, between the histological extent of the response and the function of the implant.

While the prevalence of true hypersensitivity reactions in patients with metal-on-metal joint replacements appears to be low, metal sensitivity should certainly be considered in the event of cutaneous signs of allergic response temporally related to implant placement. Patients with such a reaction should be sent for hypersensitivity testing. At the same time, the recent clinical data showing some correlation between lymphocytic response and implant function lend support to the idea of immunological reaction as a contributing factor to implant failure. Ultimately, when implant failure is associated with possible hypersensitivity or immunological reaction, optimum treatment is early exchange to non-metal bearing surfaces.

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