New insights on metal allergy in total joint arthroplasty

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Metal allergy is an uncommon and not completely understood cause of failure in total joint arthroplasty (TJA). However, either immunopathology neither histologic studies clarified the mechanisms through which the metal ions could lead to the complications related to them. The lack of evidence around this topic also reflects the difficulties to diagnose the MRP in TJA. In fact, the diagnosis is generally based on the exclusion of other causes. Currently, skin-patch testing and lymphocyte transformation test (LTT) are being commonly used to investigate about metal hypersensitivity and a delayed type-IV hypersensitivity is the immuno-histologic response to metals involved in TJA loosening. A review of the recent publications about this topic has been made focusing on immunology, histopathology, and clinics to better understand a still debated topic in orthopedic practice.

Contact allergy to metals (i.e. nickel, cobalt and chromium) is a common disease in everyday life (1) case-control study in Germany, we performed patch tests with 25 standard allergens in 1141 adults (50.4% female, age median 50 years. Total joint arthroplasty (TJA) could be a relevant source of metal ions that leads to both cutaneous (i.e. dermatitis, vasculitis like reactions, urticaria) and non-cutaneous (i.e. pain recurrence, joint effusion, TJA loosening, reduced range of motion) manifestations. Particularly, a high rate of metal sensitization was observed in patients with complicated TJA (2). Immuno-response to metals is extremely frequent in case of metal-on-metal bearings used in hip arthroplasty, but several other sources of metal ions might be observed in TJA. The relevance of this topic is clearly demonstrated by the appearance of the terms "metal sensitivity" and "metal-related pathology" (MRP) as a diagnostic code in the Australian arthroplasty registry since 2012.

In the last report, the cumulative incidence of MRP over a 15year period was 3.9%. The MRP represents one of the principle reasons for revision in some specific types of TJA (i.e. hip resurfacing) (3). Considering that the sensitization to metals seems to be related also to the metal alloys and to the modularity of TJA (3), M represents a relevant issue to both the manufacturer and the orthopedic surgeon. However, the effective relationship between metal allergy (MA) and some TJA complications is still debated (3). The aim of the present study was to describe the red line that connects the immuno-response to the clinical manifestations to metal debris.

The immune response to metals

The immune response to a foreign body is characterized by a granulomatous reaction with the activation of several macrophages and only few lymphocytes (4). It has been observed that few patients develop a specific immune response against corrosion products such as Cobalt (Co), Chrome (Cr) or Nickel (Ni) ions (4, 5). Ni and Co are components of the TJA and known allergens in

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skin hypersensitivity. Patients with hip arthroplasties present a high degree of reactivity to metals probably due to a sensitizing effect of metal debris (6). Indeed, high levels of metal particles was detected in patients with both MA and failed implants (5). However, Christiansen et al, observed a significant increase in the levels of IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, GM-CSF, IFN-γ and TNF-α, in patients with aseptic loosening, but without correlating it with MA (5).

On the other hand Hallab et al. (6), found a linear correlation between serum metal ion levels and an oligo-/monoclonal T-cell infiltrate around the implant, demonstrating an antigen-driven reaction that indicated a release of metal directly associated with MA in vivo (6). Allergies are hypersensitivity reactions characterized by an exaggerated immune response of the human body against substances. This concept implies a delayed type IV hypersensitivity (DTH), exemplified by the allergic contact dermatitis to metal ions (5). DTH is mediated by T cells and is independent from antibody reaction as opposite to type I-III responses.

In DTH an antigen-presenting cell (APCs) recognizes an allergen, binds and presents it to the T helper lymphocytes (Th1), activating an inflammatory response with the migration of cells to the inflammation site and promoting the production of antibodies from B cells. Metal ions are incomplete antigens (haptens) because of their low molecular weight and to form an antigen capable of triggering a DTH must interact with proteins (5).

During the first phase (the sensitization) the APCs activate the Th1 that proliferate and produce long-life memory T cells capable of a stronger response when encountering the same antigen. The Th1-type inflammatory response might be dominant in the reaction of lymphocytes to metals in patients with TJA. In fact, a predominance of Th1 over the Th2 response was observed in aseptically loosened TJA, as demonstrated by the higher expression of the cytokines Th1 than Th2 observed at the bone -prosthesis interface (6). The Th1 activity could be relevant in the pathogenesis of periprosthetic osteolysis. The particles engulfed by macrophages and the metal-protein complexes presented to lymphocytes lead to the production of both autocrine and paracrine factors that could lead to the periprosthetic bone resorption or bone ingrowth impairment (6).

It has been supposed that Th1, might be sensitized by the contact with metals debris from implants inserted before and distally from the joint replaced. This could lead to a reaction to the metal haptens of the subsequent TJA. Moreover, in association to this mechanism, the allergic response could also be related to naive lymphocytes activated by the metal particles released from the TJA itself.

Pro-inflammatory cytokines, like Il-1, IL-2, IL-6, INF-γ, and TNF, play a fundamental role in the DTH reaction to metals. Some cytokines, and especially IL-5, presents a significant increase after contact with Ni and therefore it was proposed as a marker for allergies (8). However, considering the high inter-individual and intra-individual variability of cytokine expression, the effective role of this cytokine in the identification of MA is debated.

IL-1β, IL-6, IL-8, TNF-α secreted by the activated macrophages and IFN–γ, together with the activation of the NF-κB pathway, affect bone formation and play an important role in the periprosthetic osteolysis as demonstrated by the high concentration in the tissues close to an aseptic loosened implant. These substances induce the differentiation of osteoclasts into mature cells, promotes osteoclast activation and osteoblast inhibition, with the result of an improvement in bone resorption. TNF-α is one of the first proinflammatory cytokine produced in response to wear particles and stimulates the production of both IL-1β and IL-6 from macrophages. The IL-6 seems to be important in the late phase of osteolysis, while IL-1β and TNF-α are critical mediators in the acute phase of inflammation. IL-8 is produced by macrophages as well as by osteoblasts, and osteoclasts. It has chemotactic properties on neutrophils and T cells and promotes the formation of osteoclasts.

Therefore, high levels of IL-8 in patients with aseptic loosening is probably related not only to the innate immune response, but also to the osteolytic process. IFN-γ is a produced by several immune cells and present both a pro and an anti-inflammatory activity. The prevalence of one or the other, depends

on secretion levels and pathogenesis. IFN-γ activates macrophages stimulating the expression of both class I and class II major histocompatibility complex (MHC), the production of cytokines (including IL-1, IL-6 and TNF-α) and surface molecules (e.g. ICAM-1, B7 and CD40) (6). The action of IFN-γ on bone resorption is unclear. Some studies showed a protective effect of on osteolysis, possible due to an inhibition effect on the early differentiation of osteoclasts, while others showed that IFN-γ promotes the formation of osteoclasts. Moreover, it seems that IFN-γ while having an inhibitory effect in the early stages of osteoclast differentiation, can improve their maturation in the late stages (5). Other cytokines involved in allergic responses have been detected in periprosthetic aseptic loosening (IL-4, IL-7, IL-9, IL-10) (7).

Recently a high concentration of both Th2 and Th17 had been observed in patients with MA in TJA (8). Therefore, a role of Th17 was hypothesized in the peri-implant inflammatory allergic reaction to Ni, making this similar to that observed in autoimmune diseases (i.e. chronic inflammatory bowel disease) or inflammatory arthritis and it was linked to the osteolytic process. Summer et al. showed that patients with a complicated TJA and a concomitant positivity to nickel patch, present a surprisingly high concentration of IL-17 and low levels of IFN-γ. On the other hand, patients with asymptomatic TJA with positive nickel patch test had a moderate IFN-γ expression without producing IL-17 (8). These contrasting observations further underline the extreme variability of the individual immune response and the need for further studies to better explain the mechanism of MA in TJA.

Histologic findings of periprosthetic metal reactions

The histological examination might help to clarify the different pathogenesis of implant loosening. An emerging concept in this field is the "Synovial-like interface membrane" (SLIM) (9). This is a term that indicates both the synovial tissue and the bone-implant interface membrane and could be studied to clarify the mechanism that led to implant loosening. For this purpose, a SLIM consensus-based classification had been developed, based on both histological and histochemical criteria (9). This classification differentiates seven patterns of adverse local tissue reactions to orthopedic implants.

Among these, SLIM type VI includes the "adverse local tissue reactions to implant materials (ALTRs) or to metallic debris (ARMD)". It represents an extension of the aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL) (9). It may be difficult to differentiate between particle toxicity and an allergy because of limited knowledge of mechanisms of reactions and properties of the particulate. Moreover, it must be considered that some of the described reactions might be mixed and overlapped. Three main histological patterns were found in SLIM type VI: (1) a macrophagic predominantly pattern with none or minimal lymphocytic response; (2) a mixed inflammatory pattern (both macrophagic and lymphocytic) with a variable presence of plasma cells, eosinophils, and mast cells and (3) a granulomatous pattern, that might be predominant, or associated with the mixed one .

Patterns 2 and 3 showed a population of T cells, or mixed T and B cells. The concomitant observation of a high concentration of mast cells and eosinophils, with or without formation of perivascular lymphocytic germinal centers, suggested a reaction to toxic wear with allergic/hypersensitivity response. The interpretation of the histological findings of a loosened implant should take into account the patients' clinical, radiological, microbiological, and allergology data (9). Moreover, data from the implants would be useful also to evaluate the corrosion patterns and wear particle characterization using transmission/scanning electron microscopy of the peri-prosthetic tissue.

However, high-grade lymphocytic infiltration in regardless the presence of tissue necrosis, suggest MA. In a histological evaluation of periprosthetic tissues obtained from patients with complicated metal-on-metal arthroplasty a cell-mediated DTH was observed (9). The samples showed a vasculitis with perivascular and intramural lymphocytic infiltration (CD3- positive T lymphocytes and CD20-positive B lymphocytes) of the postcapillary venules, swelling of the vascular endothelium, recurrent localized bleeding, necrosis, fibrin exudate and the

accumulation of inflammatory macrophages, typical of the cell-mediated immune reaction (variable dimensions drop like inclusions) and in some cases eosinophilic granulocytes and mast cells (10).

However, a recent study on joint exposure to metal ions showed a higher increase in macrophages rather than lymphocytes (11)but can also be disseminated to remote organs. Periprosthetic tissues harvested during revision surgeries mainly reflect end-stage failure but may not adequately reveal initial biological reactions and systemic side effects. Therefore, primary reactions caused by metal particles and ions were investigated in an established murine model. Left knee joints in three groups, each consisting of ten female BALB/c mice, received injections of metal ions (MI. The inflammation cascade activated by wear particles might decrease the osteoblast activity while increase the osteoclast one. Moreover, an impairment in the mesenchymal stem-cell differentiation into functional osteoblasts might be observed. Finally, particles can inhibit the collagen synthesis by mature osteoblasts and induce their apoptosis (10). As a result, particles led to an increase in periprosthetic bone resorption and therefore to implant loosening.

The clinical manifestation of MA in TJA Clinics

Patients with MH to TJA may have a clinical presentation, quite difficult to be interpreted. The onset of symptoms might occur between two months and two years post-operatively (12). A comprehensive patients' history and clinical evaluation are needed (13). Patients might complain of both joint and skin manifestations, including local rash, erythematous papular lesions surrounding the skin incision, or throughout the entire body (14). Regarding the joint symptoms they represent the greatest challenge for surgeons. Patients typically present joint effusion, stiffness or limited range of motion (1, 14), and very often this presentation is not distinguishable from a low-grade infection (14).

Therefore, the diagnosis of MH after TJA requires the exclusion of other painful TJA causes including aseptic loosening, infection, or implant mispositioning, crystal arthropathy or psychological disorders (8, 15). However, especially after total knee arthroplasty (TKA), a considerable percentage of patients had residual pain without a clear explanation (16). Standard x-rays are necessary to investigate on periprosthetic loosening, malalignment and component mal-positioning (15). Laboratory is important to evaluate that inflammatory markers (i.e. ESR, CRP) necessary to rule out infection (14, 16, 17). Secondary level modalities (i.e. CT Scan) might be useful to further evaluate sings of component loosening or malposition (18). If these studies are inconclusive, preliminary exams for MA can be conducted (19).

Patch test (PT)

PT is the most commonly utilized test for suspected MA considering the low cost and easy to use (16). It is conducted placing cutaneous patches containing specific allergens and observing the development of a dermatitis, related to a delayed hypersensitivity at regular intervals (20). However, this test has some disadvantages including: the subjective nature of the immune response to an antigen, and the lack of a clear demonstration that the cutaneous response to an allergen reflects the process that occurs within the joint. In fact, the Langerhans cells (skin tissue APCs) could not be detected in the joint. Therefore, the use of patch test for the identification of a MA after TJA had been questioned.

Granchi et al. indicated that neither pre-operative either post-operative screening for MA are recommended, considering the lack of predictive value of both positive or negative results (21). Caicedo et al (22) demonstrated that a sensitivity to Ni or MA was not directly correlated to a hypersensitivity of implant materials. A recent study on 161 TKA, demonstrated the absence of a correlation between pre-operative positive PT and the rates of complications, reoperations or revisions (23). This observation was in contrast to that by Granchi et al, that reported a shorter median survivorship in patients with a positive skin patch (78 months with 120 months, respectively), although a direct relationship was not defined (24).

Lymphocyte Transformation Testing (LTT)

This test is performed by exposing blood

lymphocytes and monocytes to a variety of metal salts and evaluating their proliferation during the following 7 days (22). Stimulation index represent the ratio of lymphocytes proliferation with and the proliferation without allergen exposition (20). This test is an alternative to PT and eliminates the confounder of Langerhans cells. Obviously, LTT has some disadvantages including: high costs, limited availability, inter-laboratory variability, lack of standardization, high rate of false-negative when the test processing is delayed, and the difficulties to maintain an appropriate sample (16, 19). Moreover, this test still needs to be validated (25). However, in a recent study comparing symptomatic and asymptomatic TJA, 17% of patients with a well-functioning implant had reactivity to Ni, while this percentage went up to 36% in case of a poorly functioning prosthesis. In a systematic review conducted by Granchi et al, the probability of a positive LTT was more than double for patients who had a loosened TJA compared with those with a stable one (21). Although promising, it is important to underline that a positive LTT in a patient with a poorly functioning arthroplasty does not imply a causality and, therefore, the diagnosis of MA in TJA is still excluded.

CONCLUSIONS

MA in TJA is a relevant cause of concern. The mechanism that underlines the immune response to metals are similar to those that control periprosthetic bone resorption. Particularly, DTH response seem to play a key role in both activities. However, the exact path that links the MA to its clinical manifestation is still unclear and further studies are needed to clarify the immune response that could be observed into a replaced joint. Considering the open questions around MA, its diagnosis as a causative factor of a complicated TJA is still excluded.

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