

HYPERSENSITIVITY REACTIONS TO METAL IMPLANTS: CLINICAL, DIAGNOSTIC AND TREATMENT OVERVIEW

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Abstract

Metal allergy is common in the general population. Cutaneous reactions are elicited by daily life articles such as watch bands, jewellery etc. In contrast little is known regarding metal sensitization following insertion of implants. Implants are commonly used in orthopaedic, gynaecological, dental and endovascular surgeries. With increasing life expectancy, the number of these surgeries has drastically increased. Nickel, cobalt and chromium have been most commonly implicated in the causation of hypersensitivity following metal implants. Clinical manifestation include peri implant eczema, effusion, swelling etc. Although diagnostic tests such as patch testing, histology, radiology and lymphocyte transformation are available, the diagnosis still remains a challenge. The review provides a brief overview of the pathophysiology, clinical features, diagnostic tests and management in a scenario of suspected metal allergy.

Key Words - Metal implant allerg, Cutaneous allergic reaction, Peri implant eczema, Hypersensitivity reaction to metals, Implant failure.

Introduction

Metal implants are widely being used in today's medical practice. These find uses in osteosynthesis materials, endoprosthesis, cardiac stents, cardiac replacements, nose, ear, gynaecological surgeries, dentistry etc. As the ageing population is increasing, so is the incidence of these implant surgeries. Contact allergy to nickel, cobalt and chromium is frequent in the general population. Its incidence has been reported to be as high as 14% in case of nickel and 1-2% with cobalt and chromium. The exposure to these metals occurs by the cutaneous route (exposure to daily life article such as wrist band, jewellery, leather articles etc). The implanted metal devices also form an important cause of metal allergy in today's world. On one hand ample amount of literature is present pertaining to cutaneous contact sensitization to metals, little is known regarding the contact sensitization that follows metal implant insertion. The metal alloys employed in these implants also include these metals as their constituents. The first report of metal sensitivity in an orthopaedic implant was reported in 1966 by Foussereau and Laugier. These metals not only constitute a major part of orthopaedic implants, but are also used in endovascular devices, pacemakers, dental surgery, ear, nose, throat devices and gynaecology practice. Wide variety of manifestation occur due to implant allergy, including eczematous reactions, delayed fracture healing, implant loosening, persistent pain effusion, endovascular restenosis etc. Thus it is important that other differential diagnosis should be ruled out before arriving at the diagnosis of implant allergy. In a report by Australian arthroplasty registry in 2012, "metal sensitivity" was reported to be the cause of implant failure in 0.9% cases following shoulder

endoprosthesis and 5.7% cases following hip arthroplasty. Metal hypersensitivity is difficult to diagnose and its prevalence is thus underreported.

Materials

Usually cobalt-chromium- molybdenum (CoCrMo) and titanium alloys are used in endoprosthesis devices. Stainless steel and titanium alloys are used in osteosynthesis devices. Oxidized Zirconium is a newer metal used primarily in knee prosthesis. The bone cements used are acrylate based. Dental implants are primarily composed of mercury amalgam, gold alloys, chromium based alloy, stainless steel, palladium, titanium and cobalt alloys. Metals alloys used in endovascular surgery in the form of endovascular stents, patent foramen ovale occluders, aortic aneurysm endografts etc use metal alloys such as stainless steel and nitinol. Titanium is commonly implicated in pacemaker induced dermatitis as it is a constituent of pacemaker.

CoCrMo alloys

These alloys are commonly used in shoulder, hip and knee arthroplasty. The composition includes 64% cobalt, 28% chromium, 6% molybdenum and 0.5% nickel.

Stainless steel

This is commonly used in multifilamentary wires, Kirschner wire, intramedullary nails, osteosynthetic plates and screws. It consists of mainly iron along with 18% chromium, 15% nickel and 3% molybdenum

Titanium alloys

Titanium is mainly used in dental and spine surgeries. It consists mainly of titanium along with traces of aluminium, vanadium

and niobium. Table 1 enumerates the metal alloys used in various implants.

First generation metal on metal hip bearings used in 1960s and 1970s were associated with high rate of metal sensitization (28-46%). Use of these prosthesis was associated with increased levels of cobalt, nickel and chromium in the body fluids. These were followed by metal on plastic implants in the 1970s and 1990s. These prosthesis were less likely to induce allergic sensitization as the large polyethylene wear particles did not form the allergenic polymer protein complexes. Later on second generation metal on metal bearings came to be used. These prosthesis had high fracture toughness, lower wear rate, and better postoperative stability.

Table 1: Enumerates the metal alloys used in various implants

	Metal Alloy	Uses
1.	Stainless Steel SAE 316 L	Cardiac devices, orthopaedic prosthesis, pins, plates, nails, screws, fixators, surgical clips
2.	Cobalt–chromium–molybdenum steel	Dental implants, orthopaedic prosthesis, pins, plates, nails, screws, fixators, surgical clips
3.	Vitallium	Orthopaedic prosthesis, plates, nails, screws, fixators
4.	Titanium alloy	Orthopaedic prosthesis, pacemakers, surgical clips
5.	Titanium–tantalum–niobium	Orthopaedic devices
6.	Nitinol	Intravascular devices, septal defect devices and implants, contraceptive device, urological implant
7.	Oxinium	Orthopaedic joint prosthesis

Bone cement

It consists of two reacting components, liquid component constituted by methyl methacrylate and powder component constituted by polymethylmethacrylate. Other additives present includes dibenzoyl peroxide, N, N dimethyl-p-touludine and 2-(4-(dimethylamino-phenyl) ethanol. Other constituents are X ray contrast agents, colorants, and antibiotics (gentamycin).

Mechanism of hypersensitivity

Following implant surgery metal ions increase in the circulation. Hypersensitivity response is mounted against these released particles in the circulation. This increase is attributed to corrosion, wear and tear. Osteoclastic activity over the implant also cause release of metal ions into the circulation and subsequent implant loosening. The released metal ions elicit a local inflammatory process. Increased metal levels have also been demonstrated in periprosthetic tissue as well as liver, spleen, lymph nodes, serum and urine. The released metal particles (haptens) complex with proteins to form complexes which in turn stimulate the circulating lymphocytes. The haptens induce a type I, II, III type of immune response following exposure, but most importantly they induce a type IV hypersensitivity response following stimulation of CD4+ Th 1 lymphocytes. Stimulation of Th 1 lymphocytes, causes release of pro inflammatory cytokines such as IL-1, IL2, TNF alpha, TNF gamma. These cytokines in turn recruit macrophages to the

site of implant. A study by Vermes et al concluded that that metal hypersensitivity was related to the duration of metal exposure, with number increasing from 12 to 18% from 6 to 36 months after surgery.

Another proposed mechanism for implant loosening involves haptogenic stimulation of toll like receptors in periprosthetic tissue. Studies have shown nickel to stimulate TLR 4 in the periprosthetic tissue.

Clinical manifestation

The clinical manifestation of implant allergy varies from skin lesions to impaired wound healing. Recurrent pain, loosening and reduced range of motion have been documented following knee arthroplasty. Other causes of implant failure such as infection etc must be excluded before making a diagnosis of implant allergy. In a study comparing 200 symptomatic patients who had undergone arthroplasty to 100 symptom free patients, it was found that the group with complications had a higher rate of metal sensitization. The common complications included reduced range of motion, recurrent effusion and aseptic loosening. In a study by Krecisz et al 14 patients were followed up with symptoms of suspected implant allergy such as skin lesions and sterile fistula formation. Eight of these 14 patients had reported cutaneous lesions within a year of surgery, among these three were found to be symptom free following revision surgery.

Most common skin manifestation is eczema seen following osteosynthetic implants, containing nickel, cobalt and chromium. These present as itchy, eczematous lesions in the vicinity of the implant. Other clinical manifestations include erysipelas like erythema, urticaria, swelling and vasculitis like lesion. Metal sensitivity has also been shown to cause symptoms of chronic fatigue syndrome, fibromyalgia, etc. Fistulas, eczema and local redness has been reported following bone cement allergy. Allergic reaction to bone cement have been reported in 24.8% in a series of 239 patients. Bircher et al reported complications in five patients following knee and shoulder replacement, who were eventually found to be allergic to benzyl peroxide. Complaints noted among these patients were pain, swelling, pruritus. Metal particles remaining following use of saw/drilling instruments have been shown to cause local allergy related complications. Figure 1 (a and b) demonstrates eczematous lesions over lower limb, buttocks and back in a patient 6 months following total hip replacement surgery. Diagnostic criteria proposed for metal induced allergic dermatitis are listed in Table 2.

Table 2: Proposed diagnostic criteria for metal allergy

1.	Chronic eczema beginning weeks or month after implant
2.	Eczema severe around the implant site
3.	Absence of other contact allergen or systemic cause
4.	Patch test positive or strongly positive for one of the metals in the alloy
5.	Complete recovery after total removal of foreign metal implant

A broken drill tip causing dermatitis, redness and swelling in the overlying skin in close proximity to the tibia have been reported in a nickel allergic patient. In a report by Maldonado-Naranjo et al patient developed erythema, itching, macroglossia and pain



Figure 1: Itchy eczematous lesions over lower limb, buttocks and back in patient undergone total hip replacement (6 months post surgery)

due to polyetheretherketone following spinal surgery.

Diagnostic workup

The clinician can be faced with two scenarios . A patient with known metal allergy may approach prior to an planned implant surgery or a patient can present post surgery with suspected implant allergy. The clinician should first exclude other causes for the skin eruption before making a diagnosis of metal allergy. In a review by Schalock and Thyssen, they stated that pre surgery testing should only be considered in patients with definitive metal allergy. The role of patch test as a prophetic testing has not been encouraged . The proposed reason for the same could be “ de novo” sensitization from the metal following continuous corrosion. Prophetic testing in these cases would lead to negative results. Carlsson and Moller followed 18 patients with confirmed pre surgery metal allergy for a mean of 6.3 years. None of these patients developed systemic or cutaneous reactions. The role of allergy testing in patients with failed implants is limited.

Patch test

Patch test is the gold standard test for delayed hypersensitivity reactions, however its role in cases of suspected implant allergy is not clear. Many studies have concluded that patch test does not establish a causal role cutaneous allergic reaction and implant failure. Patch test with 2+/3+ readings are considered more consistent with complications compared to the milder reactions. The unreliability of the patch testing method is further highlighted by the observation that patients with previous metal hypersensitivity become desensitized following implant surgery. Rooker and Wilkinson demonstrated that among six patients who tested positive for metal hypersensitivity via patch testing, five were found to be negative post operatively at 3-19 months . Metal hypersensitivity in patients with failed implants is six times more common compared to general population, and about three times commoner in those with known metal allergy . The diagnosis is arrived by ruling out other causes, positive patch test findings, presence of the metal as a constituent of the implant, disappearance of the lesions on implant removal.

For a suspected case of metal allergy, patch testing with single/handful of allergens is not recommended, a more comprehensive testing should be performed. Extended series such as extended North American standard series, international comprehensive baseline series are indicated. The patch test battery should include the metals currently being used in orthopaedic implants and should be continuously updated. Prosthesis series have been suggested by many authors .

Radiology

Radiological findings of patients with implant failure include periprosthetic osteolysis and aseptic loosening due to the inflammatory response mounted against the metal particles. Imaging studies also show pseudotumor formation around the prosthesis due to collection of inflammatory cells . None of these findings are however specific for metal hypersensitivity.

Histology

Histology of the peri implant tissue has a adjuvant role in the diagnosis of implant allergy. Four reaction patterns have been described in the histological evaluation of periprosthetic membrane in case of endoprosthetic loosening. Type 1 is foreign body like, type 2 granulocyte dominated infectious type, type 3 is a combination type and type 4 is fibrotic type. Neutrophils number exceeding 23/10 high power field is indicative of infection . The criteria for implant allergy reaction pattern is not yet established. Although histology is included in the diagnostic workup of suspected implant allergy patient, its efficacy is unproven. Lymphocytic infiltrate is seen predominantly in cases of suspected allergy. Histological appearance in cases of suspected metal allergy includes localized areas of necrosis, bleeding and fibrin exudation along with perivascular lymphocytic and plasma cell collection. The evaluation of local cytokine pattern may also add on to the diagnosis of metal allergy. Rarely aseptic lymphocyte dominated vasculitis associated lesions (ALVAL), which represents a delayed hypersensitivity reaction mediated by T lymphocytes have been described . Locally destructive pseudotumors have also been reported specially in females with hip surgeries .

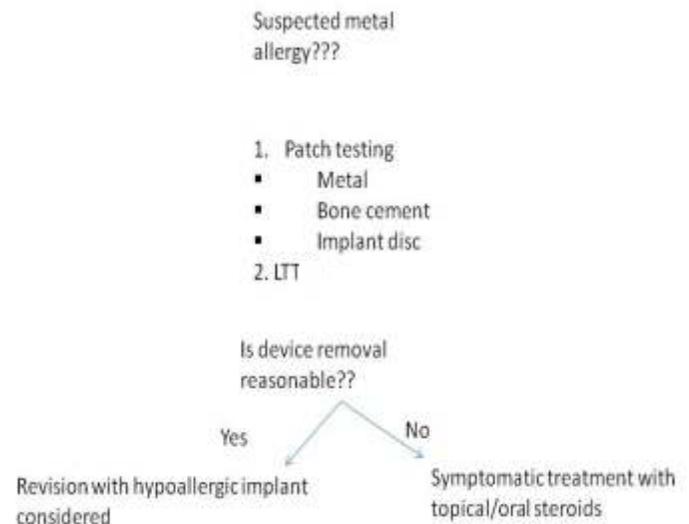


Figure 2: Algorithm for a case of suspected metal allergy

Lymphocyte transformation test

It is an in vitro test that measure the proliferation of lymphocytes from patients blood in presence and absence of antigens. The result is expressed as an stimulation index of proliferation in relation to an antigen vs baseline proliferation. Stimulation index >3 is kept the limit for sensitization in most settings . It is mostly used as a complementary test, when results of the patch test are equivocal. The quality assessment of this test are very rare even for nickel allergy. The specificity and sensitivity of this test are yet to be established by studies in the future. Issues faced by this test include limited availability, pricing and inability to test for certain metals. Currently it is impractical to be used routinely.

Figure 2 outlines the diagnostic algorithm for suspected cases of implant allergy.

Treatment

If a case of implant failure is suspected due to metal allergy (all causes excluded) further contact with the allergen warrants termination. Alternative materials in implant allergic patients includes titanium, oxinium and ceramide based/coated materials . In instances of bone cement allergy, the suspected allergen is omitted when considering revision of the implant . Amini et al stated in a review that currently there are no FDA cleared “hypoallergic implant” .

Dental implants

Metals are extensively used in dentistry in artificial teeth, implants, restorative materials etc. These are exposed to variations in temperature, pH inside the oral cavity. Cases of allergic contact dermatitis following dental prosthesis placement have been reported in the literature. A case of generalised allergic dermatitis in the setting of Nickel Chromium denture was reported in 1966 by Fousereau and Langier . The patient was found to be allergic to Nickel and Chromium on patch testing and the skin lesions settled completely following denture removal .

Most common manifestation of allergic contact dermatitis in the oral cavity is lichen planus like lesions. These are commonly placed near to the dental implant and include reticular, plaque like, atrophic and erosive variants. Lichenoid eruption have been reported most commonly in association with dental amalgam and gold . Other clinical manifestations of metal allergy in the oral cavity include loss of taste, oral swelling and dryness . Other manifestation of oral allergy include erythema of oral mucosa, purpuric patches on palate, labial edema, perioral eczematous eruption, lichenoid eruption and angular cheilitis . Swelling of the oral and pharyngeal cavity are some of the manifestations of type I hypersensitivity in the oral cavity .

Mercury amalgam are commonly used in dental practice as restorative material. Metal ions release cause allergic reactions in the oral cavity. The use of mercury amalgam has been abandoned largely in the recent years. Mercury amalgam are also implicated in the formation of amalgam tattoos. Amalgam tattoos are the result of small metal particles being implanted in the oral soft tissue . Gold allergy is also a common cause of contact dermatitis in patients undergoing dental restoration procedure. One series have reported its incidence to be as high as 33.8%. Patients having confirmed patch test positivity to gold, have been shown to tolerate gold containing dental restoration . Lower rates of allergic dermatitis have been reported with nickel containing restorative materials .

Cardiac implants

Allergic contact dermatitis have been reported following intravascular placement of implants. Two common types of intravascular stents used are bare metal and drug eluting stents. The metal alloys in the bare metal stents cause expression of intercellular adhesion molecule on the surface of endothelial cells. This stimulates neointimal hyperplasia due to recruitment of inflammatory cells, which leads to intravascular restenosis. Drug eluting intravascular stents are coated with polymer impregnated with drug, which inhibits the intimal hyperplasia and thus have a lower rate of allergic reaction . Nickel, chromate, manganese are among the metals which are frequently implicated in inducing an allergic contact dermatitis.

Initially gold plated stents were used because of higher stability and lesser allergic reactions. However studies have shown a higher risk of contact dermatitis following insertion of gold plated intravascular stents . Three cases of allergic contact dermatitis have been reported following patent foramen ovale occluders. All three patients were patch test positive and improved on device removal . Titanium is the most common metal implicated in allergic reactions following implantable pacemakers. The first case was reported in 1970 . The use of polytetrafluoroethylene wraps in pacemakers have shown to decrease the incidence of allergic dermatitis .

Gynaecological implants

Metals are used in contraceptive devices in gynaecological practice. Three cases of allergic contact dermatitis have been reported in literature following insertion of copper containing IUCD, which resolved on removal . Copper containing IUCD are contraindicated in patients with copper allergy, while nitinol (alloy of Ni and Ti) is contraindicated in Ni allergic subjects.

Conclusion:

With the recent advancement in medical science and healthcare, the number of implant surgeries has been on a rise. However little is known about the metal allergies that these implants may cause and the possible clinical manifestations. The scenario of implant allergy still remains a challenge to diagnose as well as treat. This review aims at highlighting few important aspects pertaining to metal hypersensitivity. A systematic approach is provided for workup of patients with suspected implant allergy. Carefully interpretation of the medical history, clinical examination, patch testing and lymphocyte transformation test(LTT) help to establish the diagnosis of metal sensitization. A collaborative effort by the dermatologist, allergists and the surgeon is necessary for the patient care.

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