Allergy to Surgical Implants

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Surgical implants have a wide array of therapeutic uses, most commonly in joint replacements, but also in repair of pes excavatum and spinal disorders, in cardiac devices (stents, patches, pacers, valves), in gynecological implants, and in dentistry. Many of the metals used are immunologically active, as are the methacrylates and epoxies used in conjunction with several of these devices. Allergic responses to surgical components can present atypically as failure of the device, with nonspecific symptoms of localized pain, swelling, warmth, loosening, instability, itching, or burning; localized rash is infrequent. Identification of the specific metal and cement components used in a particular implant can be difficult, but is crucial to guide testing and interpretation of results. Nickel, cobalt, and chromium remain the most common metals implicated in implant failure due to metal sensitization; methacrylate-based cements are also important contributors. This review will provide a guide on how to assess and interpret the clinical history, identify the components used in surgery, test for sensitization, and provide advice on possible solutions. Data on the pathways of metal-induced immune stimulation are included. In this setting, the allergist, the dermatologist, or both have the potential to significantly improve surgical outcomes and patient care. © **2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;3:683-95)**

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ORTHOPEDIC IMPLANTS

Case

Donald Taylor is a 68-year-old man referred by his orthopedic surgeon for an "allergy evaluation." The patient reports persistent joint pain and swelling that began about 6 weeks after his right total knee replacement was performed 15 months earlier. Joint aspiration performed 3 months ago showed 5000 white blood cells (WBCs), with a differential of 74% lymphocytes, and 26% neutrophils. Cultures held for 2 weeks showed no growth. A complete blood cell count was normal with normal WBC counts, the C-reactive protein level was minimally elevated, but the erythrocyte sedimentation rate was normal. These findings indicate that the patient does not have an infection as the cause of his knee failure. An X-ray of the knee showed good alignment of the implant, with only minor lucency noted along the tibial plate. The alignment and size are noted to be appropriate, suggesting that a mechanical problem is not the cause of the patient's knee failure. A triple-phase bone scan showed increased uptake in the right knee, slightly more than would be expected after a recent knee implant. The surgeon requests an allergy evaluation to determine whether this may be the cause of the patient's joint failure. (In this review, the terms "sensitization: and "allergy" will be used interchangeably. Although this is incorrect from an immunological standpoint, these terms are frequently substituted in other specialties, to whom this review may also be useful.)

Differential diagnosis

Joint failure is defined in orthopedic terms as a replaced joint that does not function well. A good deal of research has investigated the causes of joint failure, and, interestingly, the current orthopedic literature does not consider sensitization to implant components as a frequent reason for joint replacement failure. In a review of 781 total knee arthroplasties requiring revision, the most common failure mechanisms that were listed included loosening (40%), infection (27.5%), instability (7.5%), periprosthetic fracture (4.5%), and arthrofibrosis (4.5%).[1] Revision for infection occurred early, less than 2 years from implant surgery, and aseptic loosening was the most common cause reported for late revisions.[1] Causes of total hip arthroplasty failure, based on 1272 patients (1366 hips) who required revision of their hip implant between 2000 and 2007 from the same institution,[2] implicated aseptic loosening (51%), instability (15%), wear (14%), infection (8%), fracture (5%), and miscellaneous (7%).[2] Obesity is a known risk factor for poor outcome in both primary hip[3] and knee[4] replacements. Other risk factors for joint failure include hemarthrosis[5] and microbleeding into the joint,[6] osteopenia and osteoporosis,[7] and cigarette smoking.[8,9] Trauma to the joint from replacement surgery can rarely trigger complex regional pain syndrome (ie, reflex sympathetic dystrophy). An expert opinion survey of the members of The Knee Society published in 2013[10] listed total knee arthroplasty complications and adverse events in order of importance as bleeding, wound complications, thromboembolic disease, neural deficit, vascular injury, medial collateral ligament injury, instability, malalignment, stiffness, deep infection, fracture and dislocation, bearing surface wear, osteolysis, reoperation, revision, and

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Abbreviations used
LPT- lymphocyte proliferation test
MMA- methyl methacrylate
PMMA- polymethyl methacrylate
SI- stimulation index
TLR4- Toll-like receptor 4
WBC- white blood cell

death as the most common. Immunologically based inflammation was not on the list.

Yet the inflammation associated with sensitization to 1 or more joint components can plausibly cause a number of these mechanical complications, such as aseptic loosening, instability, stiffness, arthrofibrosis, swelling, warmth, and pain.[11,12] This suggests that implant sensitization may underlie a number of implant failure findings that, to date, have not been specifically identified as the cause. This is where the allergist/immunologist can have the most impact—in making the diagnosis of sensitization to implant components as an increasingly recognized and important cause of joint failure that can be treated once the allergens are identified.

Clinical presentation

Part of the difficulty in determining the reason for joint failure is that the clinical presentation is common to a number of causes, which broadly include allergy, infection, and mechanical mismatch and scarring. Symptoms common to all 3 typically consist of joint pain, joint swelling, and warmth.[13] Other nonspecific presentations of joint failure may include implant loosening, instability, and osteolysis.[14] For example, adverse local tissue reactions to metal-on-metal hip replacements have been reported to arise from corrosion,[15] infection,[16] and allergy,[17] and the clinical symptoms alone are insufficient to determine the cause.[12] Metal debris from metal-on-metal hips may cause metallosis and pseudotumor formation from the toxic and necrotic effects of local metal ions,[18-20] loosening and instability from local inflammation, and, importantly, metal sensitization. Several articles have attempted to differentiate between joint failure due to infection versus joint failure due to metal sensitization, admitting that the clinical presentation does not serve to distinguish the cause.[21,22]

Evaluation of synovial fluid may help to establish the reason for the joint failure. A synovial fluid WBC count of more than 12,800 cells/μL, more than 89% polymorphonuclear lymphocytes, elevated C-reactive protein level of more than 93 mg/L, and elevated erythrocyte sedimentation rate have been shown to sensitively and specifically diagnose hip arthroplasty failure from infection[23] compared with other causes. A meta-analysis of 15 such studies supported the conclusion that the number of WBCs in synovial fluid coupled with a predominant percentage of polymorphonuclear lymphocytes was sensitive and specific for joint infection, although the thresholds varied from 1100 to 6200 WBC/μL and from 60% to 89% polymorphonuclear lymphocytes.[24] In contrast, a different study of 54 patients with knee failure suggested that elevated monocyte and lymphocyte cell counts were possible indicators of wear rates of the tibial polyethylene insert and could differentiate that cause from infection.[25] Fluorescence-activated cell sorting analysis of joint fluid from 72 total knee arthroplasties from 64 patients with postoperative joint effusions differentiated metal-sensitized patients by a preponderance of $CD3^+CD45RO^+$ T cells compared with an increase in $CD14^+$ macrophages in patients with particle-induced synovitis and increased $CD16^+$ neutrophils in those with deep infection.[26]

Taken together, most patients with joint replacement failure (of any cause) present with common symptoms of joint pain, swelling, and decreased range of motion. An eczematous dermatitis over the implant site is rare, but more likely to be caused by sensitization to implant components as patients with implant-localized dermatitis have a 47% to 67% incidence of positive patch test results.[13] Such patients are more likely to be reported in the dermatological and allergic literature than in orthopedic reports. The lack of cross-talk between these and orthopedic specialties may be the reason that allergy to implant components is, as yet, not commonly considered in the differential diagnosis of joint failure in the orthopedic literature.

Sensitizing components of medical implants

Medical implants are made of a number of allergenic materials that have been separately reported to cause sensitization and contact dermatitis.

Metals used in surgical implants. Patients may be previously exposed to metal through personal products such as jewelry, piercings, braces, watchbands, belt buckles, or jean snaps (Table I[27]). The timing and route of personal exposure appears to help determine the response. Patch testing of 1501 eighth-grade students in Denmark demonstrated that the lowest prevalence (1.7%) of nickel sensitization occurred in those who had dental braces before ear piercing and the highest (20.4%) in those who first had pierced ears and then braces.[28] Other exposures causing metal sensitization can occur in the workplace, such as primarily in industrial settings of metal smelting, refining, pouring, machining, electroplating, or direct handling of metals and metal items. Work with metals in the laboratory and research setting can also cause metal sensitization.

Bone cement. Bone cement, a polymethyl methacrylate (PMMA), is used in a number of orthopedic procedures in which it serves as a kind of grout that is squirted under pressure to fill the space between the implant and the bone. Bone cement is almost always used with knee replacements, infrequently with hip replacements in the United States, occasionally with hip revisions, in reverse shoulder operations, and in some spinal surgery. PMMA is also the material used in kyphoplasty (Kyphon KyphX HV-R Bone Cement), and PMMA suspended in bovine collagen (Artecoll) or a chemical colloid (MetaCrill) is used as an injectable dermal filler in cosmetics.[29] Multiple components of bone cement have been reported separately to cause contact dermatitis and joint failure in exposed patients, as listed in Table II.

Methyl methacrylate (MMA) is primarily used in the manufacture of plastics, resins, and Plexiglas, which are subsequently used to make building panels, siding, molding, signs, skylights, and lighting fixtures. It is also used to impregnate concrete to render it water-repellent. Early nail porcelains (artificial nails) were composed of MMA, until the Food and Drug Administration recommended against its use in the early 1970s because of multiple reports of nail damage, contact dermatitis, and asthma in customers and nail technicians. Thirty-two states and 3 state