



Questioning the Clinical Relevance of Positive Post-implantation Allergy Testing for Metal Hypersensitivity in Total Knee Arthroplasty: A Didactic Case Report

Michael-Alexander Malahias, MD, PhD · Thomas W. Bauer, MD · Alex Gu, MS · Allina A. Nocon, PhD, MPH · Ivan De Martino, MD · Peter K. Sculco, MD

Received: 19 March 2019/Accepted: 2 July 2019
© Hospital for Special Surgery 2019

Introduction

Evaluation of the painful total knee arthroplasty (TKA) includes physical examination, radiographic evaluation, and laboratory testing. Metal allergy testing, including skin patch testing (SPT), lymphocyte transformation testing (LTT), and leukocyte migration inhibition testing (LMIT), has gained increased interest in the evaluation of possible metal hypersensitivity to implanted components [2]. According to Guenther et al. [5], allergy to components used in arthroplasty is common in the general population, with 13% having an allergy to nickel, 3% to cobalt, and 1% to chromium.

However, metal allergy as a reason for failure after TKA is still quite controversial, and some have argued against its existence [4]. Post-TKA testing is also controversial, and positive LTT or SPT to confirm a diagnosis of metal allergy continues to be debated [13]. In a literature review, Middleton et al. [8] concluded that metal hypersensitivity as an allergic process cannot justify a revision arthroplasty, since there is no evidence that allergy exists in TKA. Furthermore, Wawrzynski et al. [15] concluded that testing patients with functional implants is not clinically useful, as the rate of hypersensitivity is higher in implant recipients than in the general population, regardless of the status of the implant. Whether sensitization is a cause of implant failure or a benign

response to implant exposure continues to be a matter of debate on this highly controversial topic [15].

In this report, we present a patient who was referred to a tertiary care orthopedic hospital to undergo revision for presumed nickel allergy based on persistent knee pain and positive allergy testing. The purpose of this case report is to highlight the current limitations of systemic and cutaneous allergy testing to reflect the peri-prosthetic tissue response on the cellular level.

Case Report

A 70-year-old woman (a former smoker; body mass index, 27.3 kg/m²) underwent primary total knee arthroplasty with Gender Solutions Natural-Knee Flex System with patella replacement (Zimmer, Warsaw, IN, USA) for osteoarthritis in October 2010. Her medical history included depression, thyroid disease, esophageal reflux, cardiac murmur, squamous cell cancer of the skin of her hand, uterine cancer, and obstructive sleep apnea. Her surgical history was noncontributory (Table 1). She reported to be allergic to pine pollen, milk products, barbiturates, various antibiotics, ephedrine, epinephrine, codeine, gabapentin, tramadol, acetaminophen, omeprazole, hydromorphone, propoxyphene, and zolpidem.

She had persistent knee pain and stiffness; however, 1 year after her first TKA, she underwent revision surgery. The revision prosthesis was a Triathlon Total Stabilizer with polymethylmethacrylate fully cemented femoral component with an offset stem and tibial component with hybrid fixation (cemented baseplate and metaphysis with uncemented stem) (Stryker, Kalamazoo, MI, USA). The Triathlon femoral component contains a cobalt-chromium alloy containing less than 0.5% nickel [1]. Post-operative pain after the second surgery continued or even worsened within the next year, and she complained of arthralgias and myalgias in both the upper and lower limbs, as well as increased fatigue, dysphagia, epigastric discomfort, and bloated abdomen.

M.-. Malahias, MD, PhD (✉) · A. Gu, MS ·
A. A. Nocon, PhD, MPH · I. De Martino, MD · P. K. Sculco, MD
Stavros Niarchos Foundation Complex Joint Reconstruction Center,
Hospital for Special Surgery,
535 E 70th St,
New York, NY 10021, USA
e-mail: malachiasm@hss.edu

T. W. Bauer, MD
Department of Pathology and Laboratory Medicine, Hospital for
Special Surgery,
535 East 70th St,
New York, NY 10021, USA

Table 1 Surgical history of the patient

Previous surgeries
Breast surgery
Skin cancer excision
Diverticulum resection
Cataract surgery
Hysterectomy
Tonsillectomy
Shoulder surgery
Ankle surgery
Biopsy of lymph node

She underwent various gastroenterological examinations in 2013 and 2014, including abdominal ultrasound, barium computed tomography (CT) scan, endoscopy, hepatobiliary scan, esophageal flow test, and blood tests, which were interpreted as normal. The patient was treated with various proton pump inhibitors and histamine 2 inhibitors, none of which reduced pain or bloating.

In January 2014, she was hospitalized with severe hives and was examined by dermatologists, rheumatologists, and allergists. She was diagnosed with severe idiopathic chronic urticaria disorder and was started on monthly subcutaneous injections of omalizumab 300 mg, a recombinant DNA-derived humanized immunoglobulin G (IgG)1 κ monoclonal antibody, which improved but did not resolve her symptoms. In autumn 2015, she underwent skin patch testing (thin-layer rapid use epicutaneous), primarily for metals. Tests indicated an immediate and significantly positive initial reaction to nickel, which increased in intensity as each day passed. In

addition, a metal lymphocyte transformation test (metal-LTT) was performed, which reported a marked reaction to nickel (highly reactive) and a mild reaction to cobalt, aluminum, molybdenum, and zirconium ions. On the contrary, the values of bone cement monomer and particles, as well as cobalt alloy particles, titanium alloy particles, chromium, iron, and vanadium, were normal.

Her treating orthopedic surgeon recommended revision TKA due to metal allergy and she was referred to our department for evaluation for revision surgery. At that point, the patient reported a variety of chronic symptoms, such as abdominal pain, nausea, hot flashes, bloated abdomen, shortness of breath, arthralgias and myalgias in her whole body, and weakness, which were thought to have all followed the revision TKA surgery. Imaging control with X-rays, CT, and magnetic resonance imaging of her left knee showed well-implanted components with anatomic alignment and no signs of loosening, active infection, or periprosthetic fracture (Fig. 1). On physical examination, there was minimal effusion and no active rash or erythema around the knee joint (prior images demonstrated diffuse rash around both lower extremities and upper extremities), demonstrating an unrestricted painless range of motion.

Although SPT and LTT were highly positive, the clinical presentation did not clearly indicate an implant-related metal allergy. This fact in combination with the morbidity associated with removal of a fully cemented offset femoral component led to the decision to collect peri-prosthetic synovial tissue for additional diagnostic confirmation. In order to perform a complete synovectomy and most comprehensive soft tissue biopsy, a left knee arthrotomy was performed. Several synovial

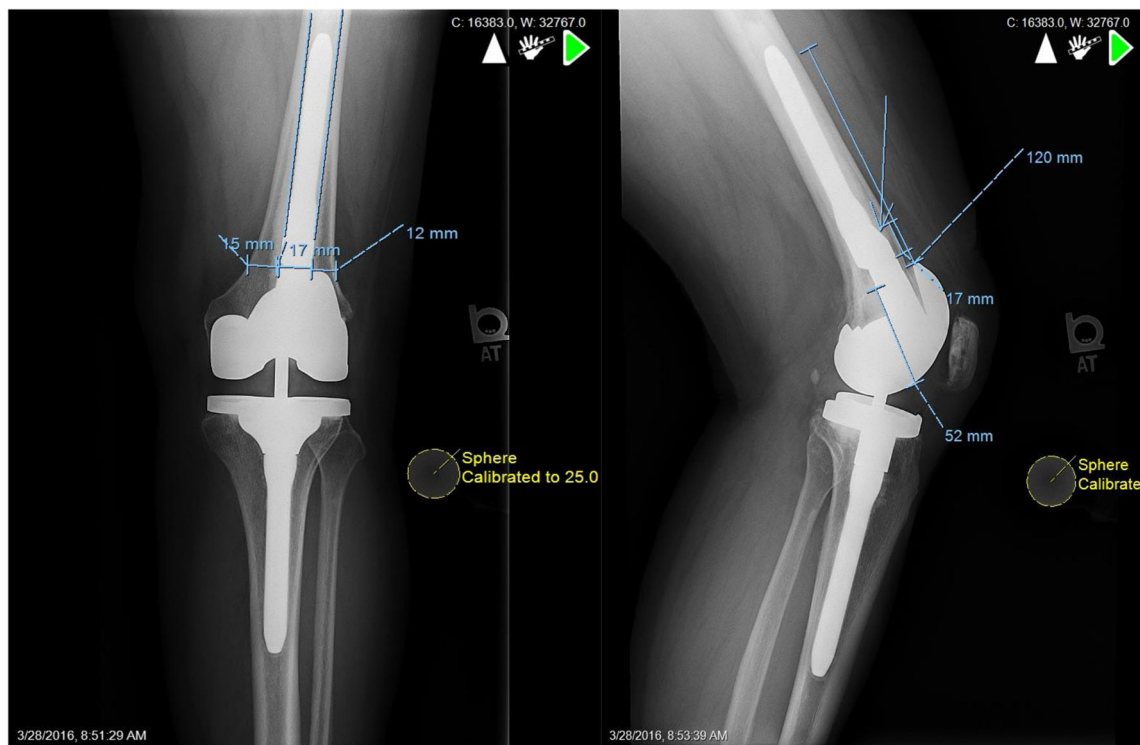


Fig. 1. Anteroposterior (left image) and lateral (right image) X-rays illustrating the normal position of the TKA components.

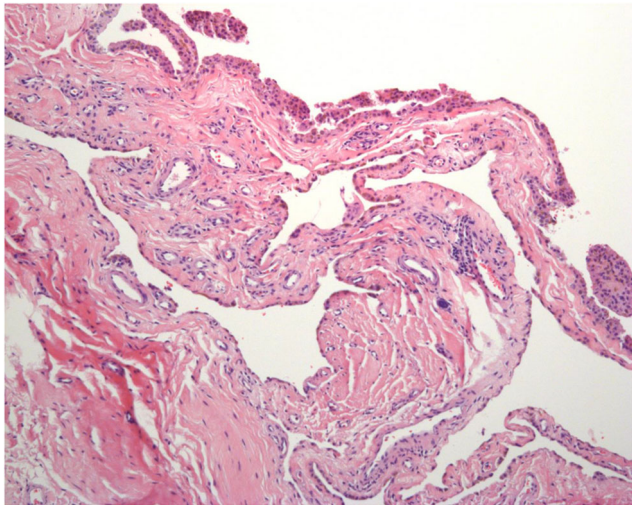


Fig. 2. Low magnification of the synovial biopsy shows non-specific reactive papillary synovial hyperplasia. There are mild vascular ectasia and focal hemosiderin deposition, but there is no significant inflammation (hematoxylin and eosin [H&E] staining, $\times 100$)

specimens were obtained. The implant was intra-operatively evaluated and it was found well-fixed and ligamentously stable without any signs of polyethylene wear, scratching, or infection. In addition, there were no gross signs of inflammation, and the macroscopic condition of the peri-prosthetic soft tissue envelope was not suspicious for allergic reaction. A complete synovectomy was performed, and all tissue was sent to pathology for histological analysis.

Four formalin-fixed tissue specimens were examined and consisted of synovial and capsular tissue. The synovium showed moderate hyperplasia of the lining layer with scattered multinucleate giant cells and focally dense deposits of hemosiderin, likely reflecting previous hemarthrosis. A sparse and patchy macrophage and giant cell reaction to

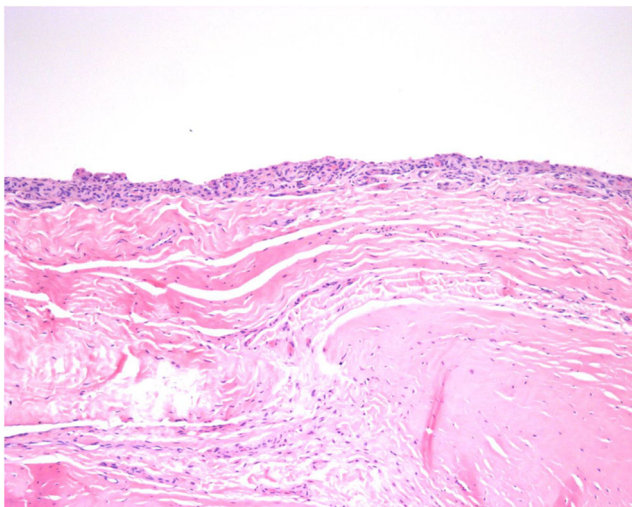


Fig. 3. Low magnification of another portion of the biopsy shows slight hyperplasia of synovial surface lining cells, but no inflammation, no necrosis, and no granulomas (hematoxylin and eosin [H&E] staining, $\times 100$)

small particles of polyethylene and cement debris was present focally. These findings illustrate a mild reaction to particles of debris, with no significant acute or chronic inflammation. There were no peri-vascular lymphocytes, no necrosis, no lymphoid aggregates, and no significant increase in eosinophils or plasma cells. That is, the histologic findings did not show any cellular signs of the morphologic features thought to reflect an adaptive immune system response (Figs. 2, 3, and 4).

Post-operative Follow-up

The patient had an uneventful recovery. The patient was post-operatively diagnosed with fibromyalgia, for which she was successfully being treated with oral pregabalin in combination with tranylcypromine and clonazepam. During the 30-month follow-up period since the open biopsy, no topical signs of effusion, rash, or erythema around the knee were reported, but the patient also continues to take monthly subcutaneous injections of omalizumab. The non-specific, general symptoms such as weakness, arthralgias, and myalgias were improved after the treatment applied for fibromyalgia, while mild pain, mostly localized to the anterolateral portion of the knee, was still present.

Discussion

The purpose of this case report is to further awareness of the difficulty of diagnosing or excluding clinically significant metal allergy after TKA with current diagnostic tools. As this report demonstrates, neither positive skin patch testing nor LTT testing reliably correlates with the histologic tissue response around a TKA and should be interpreted with caution. Patients suffering from fibromyalgia or psychiatric disorders such as depression who post-operatively report generalized but not regional symptoms around the operated

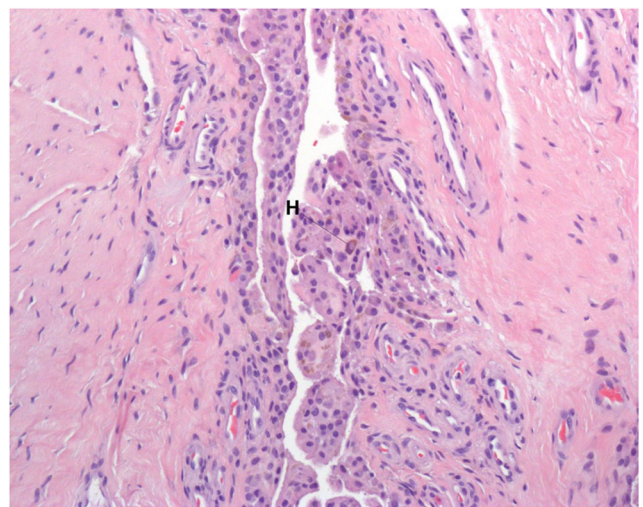


Fig. 4. Slightly higher magnification of the biopsy shows mild synovial hyperplasia with focal hemosiderin deposition (H) but no inflammation. The hemosiderin likely reflects prior hemarthrosis. There is no histologic evidence of an adaptive immune response (hematoxylin and eosin [H&E] staining, $\times 200$)

joint should be carefully assessed before their symptoms are attributed to an implant-related metal allergy. In such cases, even positive post-operative patch testing and/or metal-LTT could be misleading and are of questionable value for diagnosing implant-related metal allergy. We support a step-by-step diagnostic and therapeutic procedure after a positive metal skin patch test and/or positive metal-LTT. In our practice, a comprehensive clinical evaluation and consideration to obtain intra-articular synovial biopsies to identify cellular evidence of peri-prosthetic hypersensitivity reaction is used to guide evidence-based diagnosis and decision-making. For patients with general clinical signs and symptoms that are not specific for implant-related metal allergy, and only when intra-articular biopsy is positive for metal allergy, is a revision arthroplasty using an alternative prosthesis performed. The presence of polyethylene particles and macrophages without lymphocytes and plasma cells in peri-prosthetic tissues supports a reaction to wear debris instead of an allergic reaction.

Evidence is not conclusive as to whether metal joint implants increase metal sensitivity or whether metal sensitivity leads to prosthesis failure [11]. Rare cases of patients with clinically real implant-related allergic reactions have been reported [6, 7]. Those reactions most dramatically influence the skin over the arthroplasty site (or elsewhere) and do not seem to be associated with implant loosening.

Physicians should bear in mind that discussion of metal hypersensitivity in metal-on-metal total hip arthroplasty (THA) differs from that of metal hypersensitivity after TKA or non-metal-on-metal THA. A retrospective registry-based crosslink study showed that detected metal allergy was not associated with revision surgery and furthermore that cases with metal allergy prior to implantation did not appear to have a higher prevalence of complications or revision surgery [10]. These results support the hypothesis that metal allergy is not a general risk factor for TKA failure [10]. Current methods for evaluating metal hypersensitivity after TKA include skin patch testing and serologic testing, including LTT [12]. For skin patch testing, a number of potential allergens are applied to patches which are then placed on the skin. Subsequent contact dermatitis at the site is interpreted as a positive test result, thought to represent a delayed allergic reaction to an allergen. Pre-operative testing for metal allergy is becoming increasingly commonplace, but evidence supporting it is minimal, and the physician must set realistic expectations with the patient as to what information patch testing might elicit that would influence clinical practice [9]. According to Munch et al. [10], revision arthroplasty in a patient with a positive patch test might be reasonable to address associated dermatitis. However, there was a lack of evidence in that study that the patch test correlated with implant fixation, since all patients with metal allergy had excellent bone growth into the implant, and were revised due to dermatitis rather than implant loosening [10].

This patient described a wide variety of symptoms and at one point was hospitalized for “hives.” This led to an initial diagnosis of idiopathic chronic urticarial disorder. The skin reaction commonly called “hives,” some types of food allergies, anaphylaxis after a bee sting, and some drug reactions represent

manifestations of immunoglobulin E (IgE)-mediated, type I hypersensitivity. Biopsies of tissue involved in a type I reaction should contain numerous eosinophils, mast cells, and CD4+ T lymphocytes. Our patient was treated with antihistamines and steroids, commonly used to treat type I hypersensitivity, but those drugs only temporarily resolved her symptoms. Treatment with recombinant DNA-derived humanized IgG1 κ monoclonal antibody, an immunomodulator that binds to the crystallizable fragment (Fc) of IgE (IgE-Fc) that inhibits inflammatory reactions, has successfully prevented recurrence. She then underwent additional skin patch testing that demonstrated a reaction to nickel. Contact antigens that can induce a cell-mediated, type IV hypersensitivity reaction include various fungi and viruses, poison ivy, hair dyes, and nickel. Biopsies of a type IV reaction in the skin demonstrate an infiltrate of T lymphocytes, often in a peri-vascular distribution. Vascular injury can lead to edema, endothelial hypertrophy, and the aggregation of epithelioid macrophages into granulomas. Besides contact sensitivity in the skin, cell-mediated, type IV hypersensitivity is also responsible for chronic rejection of transplanted allograft organs. Biopsies of organs undergoing type IV, cell-mediated rejection also show interstitial and peri-vascular lymphocytes, often associated with evidence of tissue damage and swollen endothelial cells, vascular intimal fibrosis leading to ischemia, fibrosis, and atrophy of the involved organ.

As far as we know, there are no well-established descriptions of the histology of peri-prosthetic tissue associated with arthroplasty failure involving a local type IV hypersensitivity reaction shown to be due to nickel. Most of our understanding of an adaptive immune reaction in peri-prosthetic tissues has been related to metal-on-metal hip arthroplasty constructs or implants with corrosion products produced at modular interfaces in which at least one component is a chromium-cobalt alloy. In those cases, the histology is thought to reflect an adaptive immune response and is characterized by necrosis, a thick hyalinized membrane with diffuse and peri-vascular lymphocytes and plasma cells [3, 16]. As described above, biopsies of peri-prosthetic tissue from this patient showed none of the features thought to reflect either a type I (IgE-mediated) or type IV (cell-mediated) hypersensitivity reaction. More specifically, the histology showed essentially no lymphocytes or plasma cells, no lymphoid aggregates, no eosinophils, no endothelial cell hypertrophy, no vascular intimal hyperplasia, and no necrosis. Therefore, while we cannot comment on the pathogenesis of the patient's reported urticaria, we have no evidence to suggest that a hypersensitivity reaction to metal was responsible for her urticaria or intermittent pain associated with knee implants.

Some authors recommend performing arthroscopic inspection to obtain biopsies for histopathology before revision surgery and exchange of the implant [14]. Instead, we performed an open arthrotomy in which a comprehensive synovectomy was performed to provide the highest yield for histopathological analysis. Whether the methods of open arthrotomy-obtained biopsies is more accurate in diagnosing implant-related metal allergy or arthroscopically retained biopsies lead to the same results is a matter that has yet to be investigated. We chose this therapeutic strategy in order to

macroscopically evaluate the peri-prosthetic soft tissue condition, the rotation, and the stability of the arthroplasty and to get the most comprehensive soft tissue sampling possible. We understand that this is not a traditional strategy, but the morbidity associated with removal of a long fully cemented offset femoral stem necessitated the most comprehensive assessment possible prior to component revision.

In conclusion, our case report questions the clinical relevance of positive metal allergy diagnostic tests in patients who have undergone joint replacement. Our experience demonstrates that the final diagnosis of implant-related metal allergy and the necessity of arthroplasty revision to an alternative prosthesis should not be exclusively based on skin patch testing and metal-LTT. In-depth critical assessment of the clinical condition by the treating physician in combination with the results of intra-articular synovial biopsies should be the definitive guides for an accurate evidence-based diagnosis and the consequent decision-making. Further research on the topic of metal hypersensitivity after TKA is warranted, as current diagnostic algorithms lack the accuracy to produce reliable clinical results after revision TKA.

Compliance with Ethical Standards

Conflict of Interest: Michael-Alexander Malahias, MD, PhD, Alex Gu, MS, Allina A. Nocon, PhD, MPH, and Ivan De Martino, MD, declare that they have no conflicts of interest. Thomas W. Bauer, MD, reports being a paid consultant for Stryker Orthopaedics, Leica Biosystems, Acumed, and Regeneron, and an unpaid consultant for Bio2 Technologies and Premia Spine, outside the submitted work. Peter K. Sculco, MD, reports grants from Intellijoint, outside the submitted work.

Human/Animal Rights: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki declaration of 1975, as revised in 2013.

Informed Consent: Informed consent was obtained from the patient included in this study.

Required Author Forms: Disclosure forms provided by the authors are available with the online version of this article.

References

1. ARCAM. ASTM F75 CoCr Alloy. Available at <https://web.archive.org/web/20110707155747/http://www.arcam.com/CommonResources/Files/www.arcam.com/Documents/EBM%20Materials/Arcam-ASTM-F75-Cobalt-Chrome.pdf>. Accessed May 9, 2019.
2. Caicedo MS, Solver E, Coleman L, Hallab NJ. Metal sensitivities among TJA patients with post-operative pain: indications for multi-metal LTT testing. *J Long-Term Eff Med Implants*. 2014;24(1):37–44.
3. Davies, AP, Willert HG, Campbell PA, Learmonth ID, Case CP. An unusual lymphocytic perivascular infiltration in tissues around contemporary metal-on-metal joint replacements. *J Bone Joint Surg Am*. 2005;87(1):18–27.
4. Faschingbauer M, Renner L, Boettner F. Allergy in total knee replacement. Does it exist? *HSS J*. 2017;13(1):12–19. <https://doi.org/10.1007/s11420-016-9514-8>.
5. Guenther D, Thomas P, Kendoff D, Omar M, Gehrke T, Haasper C. Allergic reactions in arthroplasty: myth or serious problem? *Int Orthop*. 2016;40(2):239–244. <https://doi.org/10.1007/s00264-015-3001-6>.
6. Kruckeberg BM, Ridley TJ, Reichel LM. Severe metal hypersensitivity following internal fixation of an ankle fracture: a case report. *JBJS Case Connect*. 2017;7(2):e38. <https://doi.org/10.2106/JBJS.CC.16.00202>.
7. Kulichová D, Gehrke T, Kendoff D, Summer B, Parvizi J, Thomas P. Metal hypersensitivity mimicking periprosthetic erysipelas-like infection: a case report. *JBJS Case Connect*. 2014;4(3):e65–e5. <https://doi.org/10.2106/JBJS.CC.M.00154>.
8. Middleton S, Toms A. Allergy in total knee arthroplasty: a review of the facts. *Bone Joint J*. 2016;98-B(4):437–441. <https://doi.org/10.1302/0301-620X.98B4.36767>.
9. Mowad CM. Practice gap: the role of patch testing in the selection and management of metal device implants. *Arch Dermatol*. 2012;148(6):693–694.
10. Münch HJ, Jacobsen SS, Olesen JT, et al. The association between metal allergy, total knee arthroplasty, and revision: study based on the Danish Knee Arthroplasty Register. *Acta Orthop*. 2015;86(3):378–83. <https://doi.org/10.3109/17453674.2014.999614>.
11. Pinson ML, Coop CA, Webb CN. Metal hypersensitivity in total joint arthroplasty. *Ann Allergy Asthma Immunol*. 2014;113(2):131–136. <https://doi.org/10.1016/j.janai.2014.05.012>.
12. Schalock PC, Menné T, Johansen JD, et al. Hypersensitivity reactions to metallic implants—diagnostic algorithm and suggested patch test series for clinical use. *Contact Dermatitis*. 2012;66(1):4–19. <https://doi.org/10.1111/j.1600-0536.2011.01971.x>.
13. Teo WZW, Schalock PC. Metal hypersensitivity reactions to orthopedic implants. *Dermatol Ther (Heidelb)*. 2017;7(1):53–64. <https://doi.org/10.1007/s13555-016-0162-1>.
14. Thomsen M, Krenn V, Thomas P. Adverse reactions to metal orthopedic implants after knee arthroplasty. *Hautarzt*. 2016;67(5):347–351. <https://doi.org/10.1007/s00105-016-3793-3>.
15. Wawrzynski J, Gil JA, Goodman AD, Waryasz GR. Hypersensitivity to orthopedic implants: a review of the literature. *Rheumatol Ther*. 2017;4(1):45–56. <https://doi.org/10.1007/s40744-017-0062-6>.
16. Willert, HG, Buchhorn GH, Fayyazi A, et al. Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study *J Bone Joint Surg Am*. 2005;87(1):28–36.