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Chromium-Induced Diffuse Dermatitis and Lymph Node Involvement by Langerhans Cell Histiocytosis After Metal-on-Metal Hip Resurfacing

Running Head: Chromium-Induced Dermatitis and Langerhans Cell Histiocytosis of Lymph Nodes

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What's already known about this topic?

- Metal-on-metal (MOM) hip resurfacing (HR) is frequently associated with metallic corrosion, release of wear debris, and high levels of metal ions in blood.
- Systemic and local signs of prolonged exposure to metal ions include hypersensitivity, possible carcinogenicity, and pseudotumor formation.
- Metal-related dermatitis and lymphadenopathy after orthopedic joint prostheses are well-known.

What does this study add?

- To date, and to the best of our knowledge, combined diffuse dermatitis and lymph node involvement by Langerhans cell histiocytosis induced by chromium after MOM-HR have not been described.
- The prolonged release of metal ions and the consequent high serum level may cause sensitization and type IV hypersensitivity reaction to chromium. Clinical signs - redness, pruritus, and dermatitis - may be related to delayed type IV hypersensitivity reaction.

- Lymphadenopathy with diagnosis of special Langerhans cell histiocytosis may be due to prolonged activation of the type IV immune response.
- Only replacement of the prosthesis using alternative coupling surfaces may definitely solve the symptoms.

Summary

Total Hip Arthroplasty (THA) is a highly effective surgical treatment for severe joint involvement. However, due to the release of metal ions in the blood, the patients undergoing hip replacement with metal-on-metal (MOM) bearings may develop signs of allergic skin disease. We report a case of a 60-year-old man who had received MOM hip resurfacing (HR) five years earlier for osteoarthritis and presented with a 3-year history of diffuse dermatitis not responding to antihistamines and corticosteroids and elevated serum levels of chromium and cobalt. A patch test revealed chromium-sulfate hypersensitivity. Skin biopsy showed nonspecific perivascular lymphocytic infiltrate associated with histiocytes. Biopsy of an inguinal lymph node demonstrated large aggregates of Langerhans cells, suggesting type IV delayed-type hypersensitivity. Three months following replacement of the prosthesis using ceramic-on-ceramic bearings the dermatitis resolved. Lymph nodes decreased in volume and serum chromium normalized 24 months after revision surgery. The high levels of serum ions associated with the metal debris from MOM-THAs may induce sensitization and type IV hypersensitivity reactions. Only replacement of the prosthesis using alternative coupling surfaces may definitely solve the symptoms. Physicians who are not familiar with this issue may misdiagnose systemic symptoms and lack adequate treatment.

Total hip arthroplasty (THA) is a standard successful treatment for symptomatic osteoarthritis of the hip joint.¹ Metal-on-metal (MOM) hip resurfacing (HR) has been developed as an alternative to conventional THA in younger and active patients, with comparable long-term

outcomes.² However, all MOM bearings implants corrode and cause a release of metal ions in the blood. The prevalence of metal sensitivity among the general population is approximately 10% to 15%, with sensitivity to cobalt and chromium of 3%.³ Many concerns still remain regarding the effects of prolonged exposure to increased metal ion levels: hypersensitivity, carcinogenicity, aseptic lymphocyte-dominated vasculitis-associated lesion and pseudotumor formation.³ Allergic dermatitis and reactive histiocytosis caused by orthopedic implants are well-known.⁴ To date, and to the best of our knowledge, diffuse dermatitis and associated lymph node involvement by Langerhans cell histiocytosis after MOM-HR have not been described.

Case report

In January 2012, a 60-year-old man was referred to Orthopedic Department with a 3-year history of unresponsive diffuse dermatitis (Fig. 1) associated with high serum levels of chromium and cobalt. In December 2006, he had undergone right MOM-HR (ASR™ Hip Resurfacing System, DePuyOrthopaedics, Warsaw, IN, USA) for primary osteoarthritis. Both acetabular and femoral components are made of a cobalt-chrome-molybdenum alloy.

After surgery, the patient had been working full time and enjoyed excellent general health, without pain or symptoms from the right hip. In May 2009, general pruritus and psoriatic-like dermatitis with general skin redness and desquamation developed, and progressed over time. Although skin symptoms were compatible with systemic contact allergy, no past history of atopy or metal-contact dermatitis was elicited. Dermatitis was distributed symmetrically along the body axis, on the neck, wrist, hand, ankle, and buttock. The patient had a prolonged generalized pruritus unresponsive to antihistamines and corticosteroids. Dermatological treatments were performed without success and a clear diagnosis was not identified, although

a pyiriasis rubra was supposed. In May 2010 a diffuse lymphadenopathy, especially in the inguinal region, occurred bilaterally, and a skin biopsy revealed perivascular lymphocytic infiltrate in the upper dermis associated with varying number of histiocytes, which could suggest type IV delayed-type hypersensitivity (DTH). Further treatments with steroids and methotrexate started without success. In January 2012, a patch test showed chromium-sulfate hypersensitivity (++/-), and higher chromium and cobalt levels were found: 10.32 µg/L (nv<1) and 9.10 µg/L (nv<1), respectively. Ion levels were determined in serum using an atomic absorption spectrometer. Whole body CT scan documented no signs of bony lesions and diffuse large lymph nodes especially in the inguinal region bilaterally.

In February 2012, we performed a biopsy of the skin and the right inguinal lymph node, which appeared enlarged in size with metal-like color. Histological examination of the lymph node revealed large aggregates of Langerhans cells (Fig. 2a). The inflammatory infiltrate included plasma cells, lymphocytes, neutrophils, and eosinophils. The identity of the Langerhans cells was proved by strongly positive immunohistochemical staining for S100 and CD1a (Fig. 2b). Skin biopsy demonstrated nonspecific perivascular lymphocytic infiltrate in the upper dermis associated with varying number of histiocytes (Fig. 3). Therefore, diagnosis of special Langerhans cell histiocytosis suggesting type IV DTH was definitely confirmed.

All symptoms were supposed to be correlated with the chromium and cobalt particles, and although the THA was stable and well-functioning, surgical removal was planned and performed in March 2012 under general anesthesia. Intraoperatively, metallosis around the implant and the joint was observed, and black-stained granulation tissue was found all around the rim and on the hypertrophic synovia, with no signs of infection. Prosthesis was removed

and debridement of metal stained tissue was undertaken. Finally, a new cementless THA with ceramic bearings was implanted.

Energy-dispersive X-ray analysis of inguinal lymph nodes and articular synovia was performed with XL30 ESEM (FEI-Philips, Hamburg, Germany), permitting the identification of histiocytes with metallic particles, compatible with cobalt and chromium particles. No further investigation of the retrieved components was performed.

Three days after revision surgery pruritus healed. At 3-month follow-up dermatitis resolved spontaneously. Ten months postoperatively serum chromium and cobalt levels reduced to 1.48 µg/L and 1.12 µg/L, respectively. The patient was completely free from symptoms only after 24 months (Fig. 4): lymph nodes decreased in volume and serum chromium and cobalt levels normalized (0.64 µg/L and 0.52 µg/L, respectively).

Discussion

Implant materials in humans may induce an immunological response, depending on the type of the material and the sensitivity of the patient.⁵ Local and regional reactive histiocytosis following orthopedic prosthesis placement is an unusual, but well-recognized phenomenon.⁶

MOM-HRs are known to be particularly prone to corrosion, releasing a variety of metal ions into local tissues and circulation.⁷ With regards to systemic and cutaneous manifestations, there is no a clear line that distinguishes metal allergic reactions and metal hypersensitivity. There is actually a strong evidence for the type IV DTH involvement in the pathogenesis of metal hypersensitivity.^{8,9} Consequently, the patient is exposed to elevated

and prolonged serum levels of ions,⁷ with resultant sensitization of tissue dendritic cells in lymph nodes and skin; the dendritic cells process and present metal allergens, leading to remote T cell sensitivity.¹⁰ Cutaneous manifestations (pruritus and dermatitis), which can occur in these patients even after years, are primarily T cell-mediated type IV delayed-type reactions.⁵ In lymph nodes, the prolonged type IV DTH, due to the presence of microparticles of cobalt-chromium, results in constant stimulation and activation of histiocytes.¹¹ Migration of microparticles of cobalt-chromium, titanium and polyethylene from articular prostheses may elicit lymphadenopathy with histiocytosis.^{6,11} However, Langerhans cell histiocytosis involving lymph nodes after MOM-HR has not been previously described. In our patient, immunohistochemistry revealed histiocytes with S100 + and CD1a +. This pattern has been identified as a Langerhans-type histiocytosis.

Pathologists should be aware of this characteristic foreign-body tissue response to avoid confusion with other types of sinus histiocytosis. Clinical manifestations of toxicity may occur many years after implantation of the prosthesis, and persist over extended periods of time.^{12,13}

The patch test on the skin is mainly used to evaluate cutaneous reactions, as dermatitis, and resulting manifestation on the back is probably a direct recreation of the type IV reaction.¹⁴ Patch test evaluation is the gold standard for metal hypersensitivity, although the results may be subjective. Moreover, the positive test alone does not warrant changes in management of an asymptomatic patient. Only clinically relevant manifestations in symptomatic patients should be treated. Despite serum chromium and cobalt levels that were slightly higher than those considered critical,¹⁵ revision surgery was carried out because of the evidence of clinically relevant skin allergic reaction.

In conclusion, in our patient, the prolonged release of ions and the consequent high serum level induced sensitization and type IV hypersensitivity reaction to chromium. Redness, pruritus, and dermatitis were related to the DTH reaction. Lymphadenopathy with diagnosis of special Langerhans histiocytosis was likely to be due to prolonged activation of the type IV immune response. We are concerned that chromium and cobalt toxicity may be under-recognized, especially if patients consult physicians who may not be familiar with the possible release of metal ions from specific models of hip arthroplasty. Therefore, the occurrence of diffuse dermatitis which is unresponsive to conventional treatments in patients who underwent MOM bearings THA should recommend revision surgery, as only replacement of the prosthesis using alternative coupling surfaces may definitely solve the symptoms.

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Figure legends

Fig. 1. Neck (a) and legs (b) dermatitis presented two years following metal-on-metal hip resurfacing arthroplasty, and was unresponsive to antihistamines and corticosteroids.

Fig. 2. An inguinal lymph node biopsy revealed large aggregates of Langerhans cells (a), confirmed by strongly positive CD1a + staining (b). Special Langerhans cell histiocytosis suggesting type IV hypersensitivity reaction to chromium was diagnosed.

Fig. 3. A skin biopsy showed nonspecific perivascular lymphocytic infiltrate in the upper dermis (a) associated with varying number of histiocytes (b).

Fig. 4. Twenty-four months following replacement of the MOM hip resurfacing arthroplasty with conventional THA using ceramic bearing surfaces the diffuse dermatitis resolved completely: see neck (a) and legs (b).







