Aseptic Lymphocyte-Dominated Vasculitis-Associated Lesion

A Clinicopathologic Review of an Underrecognized Cause of Prosthetic Failure

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Key Words: Aseptic lymphocyte-dominated vasculitis-associated lesion; ALVAL; Metal hypersensitivity; Pseudotumor; Revision arthroplasty

Abstract

It is estimated that 35% of total hip arthroplasties (THAs) involve a second-generation metal-on-metal (MOM) prosthesis. A novel complication has appeared in a subset of patients with MOM THAs that is described as an aseptic, lymphocyte-dominated vasculitis-associated lesion (ALVAL). The clinical features of ALVAL are nonspecific, but patients complain of pain and may develop “pseudotumors.” It is hypothesized that metal ions are released from the prosthesis and form haptens with native proteins that elicit a type IV hypersensitivity response in the local soft tissues. Histopathologic descriptions of ALVAL are similar to those of failed arthroplasty in general, with the addition of a dense perivascular inflammatory infiltrate that is the hallmark of ALVAL. We report 3 cases of ALVAL with clinical, radiographic, and histologic findings. Accurate assessment is crucial because an intraoperative diagnosis of chronic inflammation suggestive of ALVAL will necessitate a replacement of the prosthetic component surfaces.

Hip arthroplasty is a common procedure used to alleviate pain and dysfunction associated with a variety of joint problems, the most common being degenerative joint disease. It is estimated that the number of people undergoing hip replacement more than doubled in the interval between 1990 and 2002.1 As the incidence of primary hip arthroplasty has increased dramatically during the last several years, so too has the need for revision of older prostheses. It is estimated that the number of procedures will increase to substantially more than 500,000 primary hip arthroplasty procedures and almost 100,000 revisions annually within the next 20 years.2

The earliest joint replacement procedures were performed with components using metal-on-metal (MOM) articulations.3 These first-generation MOM prostheses were ultimately deemed unsatisfactory because of a high failure rate. Mechanisms of MOM failure included frictional torque complications resulting in locking and seizing with subsequent corrosion of the bearing surfaces.3–7 Early MOM prostheses were abandoned in favor of bearing surfaces that included polyethylene and ceramic components on the acetabular side. More recently, improvements in bearing surface manufacturing and composition have resulted in a second generation of MOM implants that have improved wear properties.5,8 It has been proposed by some that a modern MOM bearing is desirable for a younger and more active patient population, in whom the prosthetics are anticipated to have greater longevity. Preliminary reports on their performance have been favorable.8–11 Current estimates indicate that about 35% of total hip arthroplasties (THAs) performed in the United States involve the use of improved MOM bearings.12
Despite their potential advantages, a rare and novel complication has been described in association with these MOM bearings. It has been proposed that a local hypersensitivity response to the metal component alloys (composed of cobalt, chromium, molybdenum, or nickel) leads to an early prosthetic failure in a small subset of patients with MOM hip arthroplasties. The clinical, radiologic, and histologic features of what has been described as a delayed-type hypersensitivity reaction have been documented in the clinical literature but, to date, have yet to be well described in the pathology literature.

A consensus for the nomenclature of this entity has yet to be reached. It has been referred to in the literature as “metal hypersensitivity reaction,” “pseudotumor,” and “aseptic lymphocyte-dominated vasculitis-associated lesion” (ALVAL). The latter term is the most descriptive and seems to be the most widely recognized. The term ALVAL will be used in the following clinicopathologic, histologic, and radiographic descriptions of 3 cases of this newly recognized entity.

**Report of Cases**

**Case 1**

In April 2009, a 75-year-old man was admitted to our institution with progressive left-sided groin pain and lower extremity edema during the preceding 5 months. He had undergone successful left THA 17 months earlier for osteoarthritis, in which a large-diameter, femoral head MOM prosthesis was used. Before admission, the patient had undergone Doppler ultrasound at an outside institution that demonstrated extraluminal compression of the femoral vein by a soft-tissue thigh mass. Magnetic resonance imaging (MRI) revealed fascial edema and signal abnormality in the medial and posterior compartments of the thigh surrounding the prosthesis with significant fluid collections. Given the manifestations, a diagnosis of inflammatory pseudotumor secondary to delayed hypersensitivity reaction was considered, and the patient was scheduled for open biopsy and revision to an alternative prosthetic articulation. During the revision procedure, extensive thickening of the hip capsule was noted, with destruction of the abductors and short external rotators. The femoral and acetabular components were noted to be grossly loose. Tissue specimens and evacuated fluid were sent for pathologic evaluation and culture.

Histologic examination of the periprosthetic tissue revealed a pseudocapsule composed of indistinct layers. The superficial layer was characterized by a necrotic surface exudate and the deeper layer by fibrous tissue. Within the fibrous layer were very focal collections of chronic inflammatory cells. On closer inspection, the inflammatory infiltrate, composed of lymphocytes and histiocytes, appeared centered on small vessels. In some instances, the inflammation formed a “cuff” around patent vessels. Patent vessels usually displayed some degree of endothelial hyperplasia. In rare instances, the inflammatory process resulted in a complete destruction of the vessel with obliteration of the lumen.

Because ALVAL was suspected clinically, immunohistochemical staining for B- and T-cell antigens was performed. These stains revealed a predominance of T cells with obliteration of small vessels secondary to vasculitis.

**Case 2**

In September 2009, a 62-year-old woman was admitted to our institution with complaints of right-sided medial thigh and hip discomfort with a palpable fullness in her groin. She had undergone successful right THA 28 months earlier for osteoarthritis in which a large-diameter femoral head MOM prosthesis was used, and she had been without complaints before the complaints that led to admission. An MRI demonstrated a small soft tissue mass and fluid collection surrounding the implant in the medial part of the thigh, which was biopsied under ultrasound guidance. The biopsy specimen demonstrated fibrous tissue with perivascular chronic inflammation with a lymphocyte predominance, thought to be consistent with a metal hypersensitivity reaction. During the revision procedure, the patient’s acetabular and femoral components were noted to be well fixed. The abductors, short external rotators, and hip capsule were preserved. The fluid collection was evacuated,
Chronic inflammatory infiltrate within the fibrous layer of the peri-implant tissue (H&E, ×40). Immunohistochemical staining for pan-B-cell (B) and pan-T-cell (C) markers reveals an obliterated vessel with a predominance of T cells (immunoperoxidase, ×200).

(Case 2) Axial T1-weighted (A) and fast spin echo T2-weighted (B) images demonstrate a mass (arrows) in the soft tissues anterior to the right hip between the iliopsoas and pectineus muscles.
and the abnormal mass-like tissue was excised and sent for complete pathologic evaluation. The revision was to a ceramic-on-polyethylene articulation with a highly cross-linked polyethylene acetabular liner and a ceramic femoral head.

Histologic exam revealed a pseudocapsule composed of a synovial-like layer and a deeper, dense fibrous tissue with prominent vessels Image 4A. The synovial-like tissue had a villous architecture with hyperplasia and hypertrophy of the synovial lining and proliferation of the subsynovial tissue. Within the latter were modest infiltrates of chronic inflammatory cells and histiocytes. Deep within the fibrous layer of the capsule were focal aggregates of chronic inflammatory cells. On close inspection, the inflammatory infiltrate appeared to be centered on small vessels Image 4B. Notably absent were giant cells, debris or metal particles, and other histologic evidence of foreign body reaction.

Case 3

In September 2009, a 57-year-old man was admitted to our institution with complaints of progressive left-sided hip pain during the preceding 6 months. He had undergone successful left hip resurfacing arthroplasty 20 months earlier for osteoarthritis, in which a MOM hip-resurfacing prosthesis was used. Plain films demonstrated moderate resorption of the femoral neck, and the MRI revealed a significant fluid collection surrounding the prosthesis Image 5. Laboratory
markers were not suggestive of periprosthetic infection. Given the patient’s symptoms and radiographic findings, possible implant loosening and metal hypersensitivity were considered, and he was scheduled for a revision procedure with conversion to THA. During the revision procedure, the patient’s acetabular component was noted to be stable, although the femoral component was loose. The tissue lining the joint capsule was noted to be grossly abnormal and was sent for pathologic evaluation along with the evacuated fluid surrounding the implant. The revision was subsequently converted to a THA using a ceramic-on-polyethylene–bearing surface.

Frozen section examination of the peri-implant tissue was performed to assess for acute inflammation and evidence of ALVAL. On histologic examination, the articular surface of the pseudocapsule was composed of a fibrinous, necrotic layer of debris. Deep to the surface layer was a dense fibrous layer of capsular tissue containing small and medium-sized vessels. Several of the former were surrounded by a dense chronic inflammatory infiltrate (Image 6). Again, histologic examination was negative for evidence of methylmethacrylate cement, metallic wear debris, or a foreign body granulomatous-type of response. In addition, the presence of acute inflammation was excluded by the absence of neutrophils.

Discussion

There are numerous anecdotal reports of allergic-like reactions, including urticaria, eczema, and pruritus, to implanted metallic hardware.26-32 In almost all cases reported, the symptoms resolve shortly after removal of the metal. The mechanism involved is thought to be a type IV delayed hypersensitivity reaction. The delayed-type hypersensitivity response is cell mediated and characterized histologically by the presence of lymphocytes, histiocytes, and, in some cases, multinucleate giant cells. Recruitment of inflammatory cells into affected tissue involves a release of chemotactic factors and cytokines. Tissue damage, which can be extensive, is a result of the combined effects of cytotoxic T cells and activated monocyte/macrophages.

In ALVAL, it is hypothesized that metal ions are slowly released from the prosthetic bearing surfaces as a by-product of normal wear. Wear products from metal prosthetics are demonstrable in adjacent periprosthetic soft tissue and in distant sites such as lymph nodes, liver, and spleen. These wear particles, in conjunction with native proteins, form haptenes that elicit a type IV response in the local tissue. Chromium and cobalt, 2 metals commonly used in medical-grade alloys, seem to be particularly immunogenic. Lymphocyte transformation testing, an indirect measure of allergen sensitization, has demonstrated increased metal-specific lymphocytic reactivity in patients with metal THAs. Polymerase chain reaction, fluorescent in situ hybridization, and immunohistochemical studies of periprosthetic tissues have demonstrated the presence of oligoclonal T cells in addition to strong expression of interferon and interleukins, mediators associated with delayed-type allergic response.40,42
The histopathologic features of failed THA have been well described and are fairly commonplace.\textsuperscript{43-47} In brief, characteristic features of periprosthetic soft tissues include a fibrous exudative capsule surface, a variable chronic or granulomatous inflammatory infiltrate, and an accumulation of foamy macrophages. Nonmetallic components of arthroplasty, namely polymethylmethacrylate cement and polyethylene component debris, are often embedded in the periprosthetic soft tissue. Metallic debris may or may not be visible by conventional light microscopy. Extensive collection of metal-stained macrophages in periprosthetic soft tissues is a phenomenon known as metallosis.\textsuperscript{44,48} This complication may be associated with prosthetic failure and has been documented in conventional and MOM metal systems.\textsuperscript{18,37,48}

Histopathologic descriptions of ALVAL are similar to those of failed arthroplasty soft tissues in general.\textsuperscript{13-15,46} Common findings include a fibroinous or necrotic exudate and an accumulation of macrophages. Our study of ALVAL demonstrated these findings and some often associated with inflammatory arthritis such as synovial inflammation and hyperplasia. The single unique histologic feature associated with ALVAL is the presence of a dense perivascular infiltrate.\textsuperscript{15} This unique perivascular inflammatory infiltrate, in fact, is specifically referred to in the name of the syndrome (“vasculitis-associated lesion”).

Despite the abundance of circumstantial evidence supporting a delayed-type hypersensitivity reaction as the proximate cause of ALVAL, it is not a universally accepted conclusion.\textsuperscript{8,16,48,49} For one, the issue of cause and effect has not been clearly defined. Does sensitization to metal have a direct role in the failure of the prosthesis, or alternatively, does loosening of the prosthesis allow release of metal ions that induce a metal allergy? The actual proof of a sensitivity reaction leading to prosthetic failure is lacking.\textsuperscript{17,50,51} Likewise, histologic examination of so-called ALVAL periprosthetic tissue offers relatively little to support an allergic process. The inflammatory cellular infiltrate associated with ALVAL, namely the presence of lymphocytes and plasma cells, is completely nonspecific. And with the exception of the perivascular lymphocytic infiltrate, all other histologic features described in association with ALVAL can be seen to some degree in other types of prosthetic failure.\textsuperscript{43,45} Nevertheless, many orthopedic investigators believe the arrangement (perivascular) and extent of chronic inflammation are “specific” features of ALVAL.\textsuperscript{10,13,15} Despite the controversy, it is important that surgical pathologists become familiar with the features of ALVAL described to date because this represents a clinically well-recognized cause of MOM joint replacement failure.\textsuperscript{13,17,19,25}

The clinical diagnosis of ALVAL is difficult and probably not possible to confirm without benefit of the histologic examination of the periprosthetic soft tissue. Imaging features are nonspecific and include descriptions of solid and cystic peri-implant masses.\textsuperscript{21,24,52} Potentially helpful laboratory tests include serum measurements of the metal alloy components. Chromium and cobalt, in particular, have been demonstrated in elevated quantities in the blood and urine of patients with loose prostheses,\textsuperscript{53-56} but this finding does not appear to correlate with the development of ALVAL. As mentioned previously, skin patch testing for allergy to metals has demonstrated a greater frequency of positivity in patients with metallic implants,\textsuperscript{40} but recommendations for routine testing are still controversial.\textsuperscript{16,19,39,50} Unlike septic causes of prosthetic failure, cultures of the periprosthetic tissue are almost always negative, and serum markers of inflammation (C-reactive protein or erythrocyte sedimentation rate) are usually not elevated. For the present, a preoperative diagnosis of ALVAL is difficult to corroborate.

To date, the surgical pathologist’s role in the evaluation of hip revision tissues has largely consisted of intraoperative assessment of tissue for the presence or absence of acute inflammation by frozen section. The finding of rare neutrophils, 1 or more per high-power field, in a sample of periprosthetic soft tissue has been shown to be a reliable marker for infection in revision arthroplasty.\textsuperscript{57-62} We anticipate that in the near future, surgical pathologists may be called on to give an intraoperative assessment of chronic inflammation as well. The differential diagnosis in this setting is limited to few entities. There is some histologic overlap between ALVAL and the inflammatory arthritides, particularly rheumatoid arthritis. However, this diagnosis should be easily eliminated based on a combination of clinical history and serologic findings. Perhaps the most difficult problem pathologists will face at frozen section is attempting to distinguish ALVAL from the more common mechanical causes of failure by histopathologic examination. Both entities result in similar reactive changes in the periprosthetic tissue: various degrees of inflammation, fibrosis, and repair. Failure due to mechanical loosening, however, should show more evidence of trauma in the form of foreign debris, chiefly metal particles and cement (if used), than that noted in ALVAL. Likewise, a foreign body reaction with an abundance of histiocytes and/or giant cells is usually associated with aseptic loosening, even with prostheses of relatively short duration.\textsuperscript{15,18,44,45}

Regardless of its poorly understood pathophysiology and its rather nondescript histologic features, ALVAL is becoming increasingly recognized as a clinical syndrome by orthopedic surgeons treating patients with joint replacements. Although the current incidence of ALVAL is calculated at only 1% of patients with MOM bearings, this figure is expected to increase over time.\textsuperscript{24} As more people undergo hip arthroplasty and an increasingly younger population receives these MOM components, one can anticipate an increased number of revisions for prosthetics failure. While not all failures will be
due to ALVAL, the intraoperative evaluation of this type of prosthetic revision is likely to include a request for the evaluation for histologic evidence of ALVAL in addition to septic causes of failure. Accurate assessment is crucial because an intraoperative diagnosis of chronic inflammation suggestive of ALVAL will necessitate a replacement of the prosthetic component bearing surfaces with conventional polyethylene or other nonmetal (ceramic) materials.

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Dr Bolognesi receives educational and research support from the following manufacturers of orthopedic devices and implants: DePuy (Johnson and Johnson), Zimmer, Biomet, and Wright Medical.

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