Seminars in Diagnostic Pathology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Diagnostic Pathology

journal homepage: www.elsevier.com/locate/semdp

Review article

Iatrogenic lesions of soft tissue and bone

SM. O'Connor[a], SE. Wobker[a], DM. Cardona[b], W. Eward[c], RJ. Esther[d], LG. Dodd[a,*]

[a] Department of Pathology and Laboratory Medicine, University of North Carolina Chapel Hill, United States
[b] Department of Pathology, Duke University, Durham, NC, United States
[c] Division of Oncology, Department of Orthopaedic Surgery, Duke University, Durham, NC, United States
[d] Department of Orthopaedic Surgery, University of North Carolina Chapel Hill, United States

Introduction

Iatrogenically induced lesions of bone and soft tissue range from exuberant benign reactive or proliferative lesions (often termed "pseudo tumors") to aggressive, life-threatening malignancies. Inadvertent harms are often a result of a number of well-meaning interventions. These would include implantation of foreign materials, medical interventions, administration of drugs or other agents and therapeutic radiation or chemotherapy.

The following review will illustrate some of the more common iatrogenically induced proliferations of mesenchymal tissues. For purposes of organization and clarification they are described and illustrated in association with their presumed causes. The major causes of injury discussed in the following include: medical device or implant associated proliferations, diagnostic and therapeutic interventions, and the adverse outcomes of selected drugs and radiation.

Medical device/implant-associated lesions

Aseptic lymphocytic vasculitis-associated lesion (ALVAL)

It is estimated that primary total hip arthroplasties (THA) will increase to well over 500,000 procedures and almost 100,000 revisions annually within the next twenty years.[1] Early metal-on-metal (MOM) prosthetic devices were abandoned in favor of articulations with polyethelene and ceramic components. Improved second generation of MOM implants subsequently became more desirable for younger and more active patients, given the anticipated greater longevity and functionality.[2–5] It is estimated that currently approximately 35% of THA utilize MOM bearings in the United States.[6] Unfortunately, a rare complication has been associated with these MOM bearings- "aseptic lymphocyte-dominated vasculitis-associated lesion" (ALVAL).[7–10] Other potential synonyms include "metal hypersensitivity reaction" and "pseudotumor".[11–17] The current incidence of ALVAL is calculated at 1% of patients with MOM bearings; however, this figure is expected to increase over time.[16]

ALVAL is thought to occur as a local type IV hypersensitivity response to the metal alloys (composed of Cobalt, Chromium, Molybdenum or Nickel) and is hypothesized to cause early prosthetic failure in a small subset of patients with MOM THA.[9,17,18] Chromium and cobalt, two metals commonly used in medical grade alloys, appear to be particularly immunogenic.[19] Metal ions are slowly released into the surrounding peri-prosthetic soft tissue, and potentially blood stream, as a by-product of normal wear of the prosthetic bearing surfaces. Lymphocytes, histiocytes and in some instances, multinucleate giant cells are recruited into the affected tissue and chemotactic factors and cytokines, such as IFN and IL-6, are released leading to a delayed type, cell mediated hypersensitivity response.[9,19,20] The cytotoxic T cells and activated macrophages instigate tissue damage that can be extensive, leading to pain, osteolysis, loosening of the prosthetic components and pseudotumor formation.[21–23]

The clinical diagnosis of ALVAL is difficult and currently not possible to confirm without histologic examination of the peri-prosthetic soft tissue. Imaging features are non-specific.[11,16,24] And although measurement of metal alloy components, specifically chromium and cobalt, in the blood and urine may be helpful since elevated quantities can be seen in patients with loose prostheses, these laboratory findings do not appear to predict the development of ALVAL.[25–27] Cultures of the peri-prosthetic tissue and serum markers of inflammation (C reactive protein or erythrocyte sedimentation rate) are almost always within normal limits, unlike septic causes of prosthetic failure.

The histopathology of both conventional and MOM failed THA is characterized by peri-prosthetic soft tissues with a fibrinous exudate, variable chronic inflammatory infiltrate and accumulation of foamy macrophages (Fig. 1). Non-metallic debris, polymethylmethacrylate cement and polyethylene, often leave empty spaces within the tissue since these elements are extracted during processing. Collection of metallic debris within macrophages (metallosis) may or may not be visible by conventional light microscopy.[15,28–35] The one exceptional histologic feature associated with ALVAL is the presence of a dense, multifocal perivascular chronic inflammatory infiltrate composed predominantly of small T cells (Fig. 2a, b).[9] The vessels are typically small and patent; however, focal obliteration of vascular lumens and/or endothelial hyperplasia can be seen. The importance of this key

* Correspondence to: Department of Surgical Pathology, Women's and Children's Hospital, Room, 3rd Floor, 101 Manning Drive, Chapel Hill, NC, United States.
E-mail address: Leslie.dodd@unchealth.unc.edu (L. Dodd).

http://dx.doi.org/10.1053/j.semdp.2017.09.003

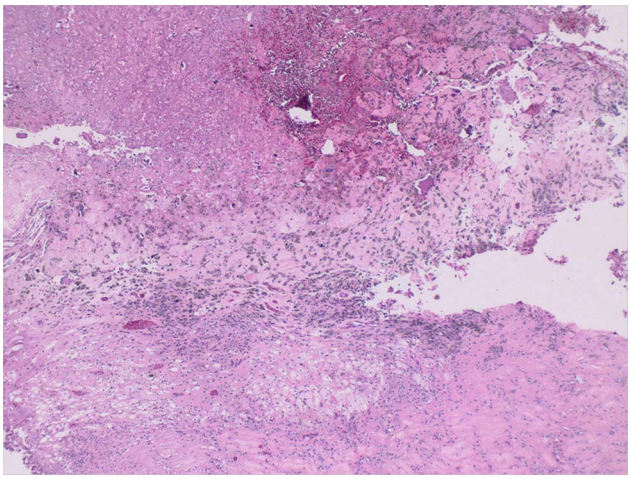

Fig. 1. Low power photomicrograph of peri-prosthetic soft tissue reaction associated with metal on metal implants. The pseudo-tumorous soft tissue reaction is comprised of fibrin, sparse chronic inflammation and histiocytes containing metallic debris.

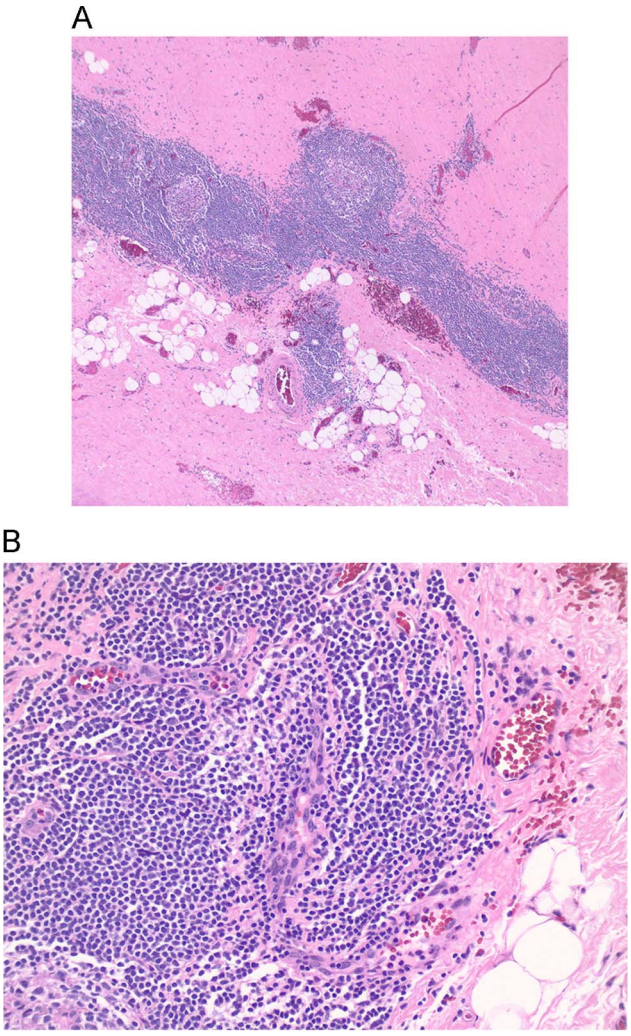

Fig. 2. Lymphocytic vasculitis: A. Low power showing dense lymphoid aggregates in a perivascular distribution. B. High power showing lymphocytic vasculitis with obliteration of a small vessel lumen.

morphologic feature is captured in the entity's name ("vasculitis associated lesion").[9,17,18,34] Some additional findings that can be observed in these cases include pseudotumor formation and although non-specific, heterotopic ossification and/or cartilage production.[36]

Despite its rather non-descript histology and nascent pathophysiology, ALVAL is becoming increasingly recognized as a clinical syndrome associated with prosthetic failure by orthopaedic surgeons. Historically, 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.[37,38] In the near future, pathologists may also be called upon to assess for the presence of significant perivascular chronic inflammation as well. Therefore recognition of the appropriate clinical setting and accurate histologic assessment is essential since a diagnosis of ALVAL will likely necessitate the replacement of the prosthetic component bearing surfaces with non-metal materials.[7]

Pseudo-Kaposi Sarcoma

Pseudo-Kaposi sarcoma (PKS) is a benign reactive vascular proliferation associated with a number of conditions involving chronic venous stasis. Initially described by Mali in 1996, this lesion is also known as acro-angiodermatitis or acro-angiodermatitis of Mali.[39] PKS is a benign and uncommon pseudotumor that occurs in many common settings including: chronic venous insufficiency, stasis dermatitis, arteriovenous fistula, paralyzed limbs and amputation stumps. In addition, PKS has been described in association with amputees outfitted with poorly fitting prostheses and as a rare complication of vascular access grafts for hemodialysis patients.[40–43] Clinically, PKS appears strikingly similar to true Kaposi Sarcoma (KS) with common features including localized swelling or lymphedema of soft tissue, hyperpigmentation, ill-defined areas of raised vascular blebs or plaques, and ulceration.

Histologically PKS shows some similarities to Kaposi sarcoma: a proliferation of small, blood filled vascular channels lined by low flat to cuboidal endothelium and a sparse chronic inflammatory infiltrate.[41] PKS may also show extravasation of red blood cells and deposition of hemosiderin pigment. Unlike KS, the endothelial cells of PKS form regular channels, not slit-like spaces. In addition, PKS lacks cytologic atypia or an increased mitotic rate. Also unlike classic KS, viral infection with Human Herpes Virus 8 (HHV-8) is not linked to pathogenesis. Immunohistochemical staining for HHV8 latent nuclear antigen may be utilized to distinguish early stage KS from PKS. PKS will often resolve once the offending agent (vascular access graft or prosthetic) is revised or removed. Non-iatrogenic forms of PKS can be treated with a number of conservative therapies including application of pressure to the affected region or debridement.

Synovial metaplasia associated with breast prostheses

Synovial metaplasia is a proliferative response occurring in the fibrous capsule surrounding synthetic breast implants. Its reported incidence ranges from 28% to 47%.[44,45] It consists of a proliferation of synovia-like cells located in the interface between capsule and implant. The cells are arranged perpendicular to the surface and have round to oval nuclei and abundant eosinophilic cytoplasm (Fig. 3). Multinucleated cells and villous hyperplasia may also be present. The cells comprising the lesion are CD68 positive and negative for cytokeratins, consistent with histiocytic/macrophage derivation.[45–47] Evidence suggests that synovial metaplasia is a relatively early change, and several studies have correlated the response with the age of the implant.[48–51] Synovial metaplasia has been found surrounding silicone and polyurethane implants and in both textured and smooth types.[50–52]

Capsular contracture is the most common complication of implants. Some authors have suggested that synovial metaplasia may provide a protective effect against capsular contracture, but others have not seen a correlation.[49,51,53] It is important to recognize synovial metaplasia as a relatively common benign response to breast prostheses, and not mistake it as a malignant process.