Acute Host Reaction After Anterior Cruciate Ligament Reconstruction

Caroline Park, BA, Samuel Klatman, MS, Hollis G. Potter, MD, and Anil S. Ranawat, MD

Abstract

Anterior cruciate ligament (ACL) rupture is a common condition often treated with an allograft reconstruction. In this case, a patient presented 2 months post-ACL allograft reconstruction with acute knee synovitis. Initially, it was assumed to be septic arthritis; however, based on magnetic resonance imaging, pathology, serology, and cultures, his acute synovitis was believed to be due to a host mediated immune response.

Allograft tissue is a well-established graft choice for anterior cruciate ligament (ACL) reconstruction. There are many benefits to using allograft tissue including low donor site morbidity, greater availability of tissue, shorter operative time, less pain, and minimal antigen burden.[1] Since musculoskeletal tissue is typically considered immunopriviledged,[2] immunosuppression and tissue typing are not performed with well established results.[3] However, there is evidence that significant immunogenic reactions can occur in tendon allografts.[2,4] Consequently, techniques have been designed, such as freeze drying, ethylene oxide sterilization, and gamma irradiation, to both sterilize and decrease the antigenicity of the allograft implant while increasing the success of graft transplantation.[5] Unfortunately, freeze-dried ethylene oxide-sterilized allografts can elicit an immune response resulting in graft dissolution.[6,7] The observed failure rates of allograft implants sterilized with ethylene oxide led to an increase in the use of gamma irradiation,[5] but the current trend is now moving towards non-irradiated ACL allografts. There are limited reports of acute reactions after ACL allograft reconstruction.[2,4,8] Thus, we present a unique case of a patient who presented with acute synovitis following ACL allograft reconstruction. Based on magnetic resonance imaging (MRI), cytology, serology, and cultures, it was determined that the observed inflammatory response was due to a host mediated immune response.

The patient provided written informed consent for print and electronic publication of this case report.

Case Report

A 40-year-old man presented to clinic suffering from a rotational injury of his left knee acquired while skiing. He had no past medical history and no known drug allergies. On clinical examination, he walked with a non-antalgic gait with no utilization of an assistive device. He had full range-of-motion (ROM), no facet tenderness, no apprehension, and no crepitation. He presented with a 2+ Lachman, 2+ pivot, and negative posterior drawer. Evaluation of the collateral ligaments showed them to be stable. Routine radiographs showed no evidence of fracture or osteoarthritis of the femorotibial or patellofemoral compartments. MRI showed a complete tear of the proximal ACL and a tear of the posterior horn of the lateral meniscus.

Considering his age, lifestyle, sports activity level, and absence of comorbidities, an ACL reconstruction was recommended. Under spinal anesthetic and sedation, a tourniquet was placed on the left upper thigh, and an arthroscopic partial lateral meniscectomy, an ACL reconstruction, was performed using a freeze-dried, irradiated, anterior tibialis allograft. The anterior tibialis tendon allograft was obtained from Tissue Bank International. According to their protocol, tissues are harvested and sterilized via gamma irradiation between 17 and 23 kGy with a target of 18 kGy, followed by a saline wash. The extra-cortical button was used to fix the allograft to the femur, and a biocomposite interference screw and a metal post screw were used for tibial fixation. The patient was placed in a brace and mobilized within the second postoperative day. Over the next several days, the patient progressed from partial to full weight bearing on crutches with no pain or effusion by 6 weeks. At 6 weeks on physical examination, he had full ROM, and good ligament stability including a negative Lachman and no pivot.

Eight weeks after ACL reconstruction, the patient returned to the office due to a slight fever (99°F), and new onset of swelling and pain that lasted for several days. Clinical examination revealed normal gait, healed incisions, good ROM, and good stability, but a mild effusion was noted. An aspiration was performed yielding 20 cc of cloudy, musky fluid, which was sent for analysis. The cell count revealed 200/mm^3 red blood cells (RBC) and 47,000/mm^3 white blood cells (WBC), of which 38% were polymorphs, 41% were lymphocytes, and 21% were monocytes. No crystals were noted. Serum blood tests were also performed and revealed the values of RBC count (Hgb 12.4

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gm/dL; Hct 37.3%), WBC Count (6.72 /nL with 57% neutrophils, 31.8% lymphocytes, 3.4% monocytes, 5.6% eosinophils, 0.8% basophils), C-Reactive Protein (CRP = 2.6 mg/dL), and the erythocyte sedimentation rate (ESR) value (11 mm/hr).

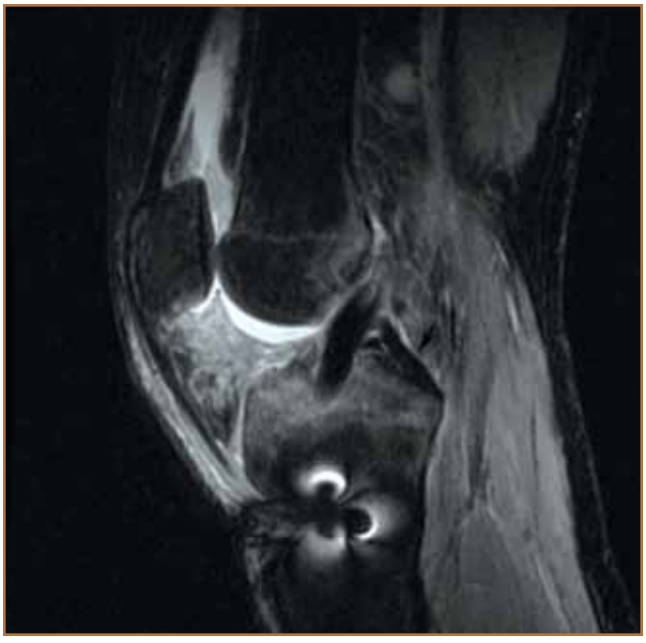

Figure 1. Sagittal fat suppressed fast spin echo MRI of the patient's left knee demonstrates diffuse bone marrow edema pattern in the proximal tibia and the presence of an inflammatory synovitis, with edema in the fat pad.

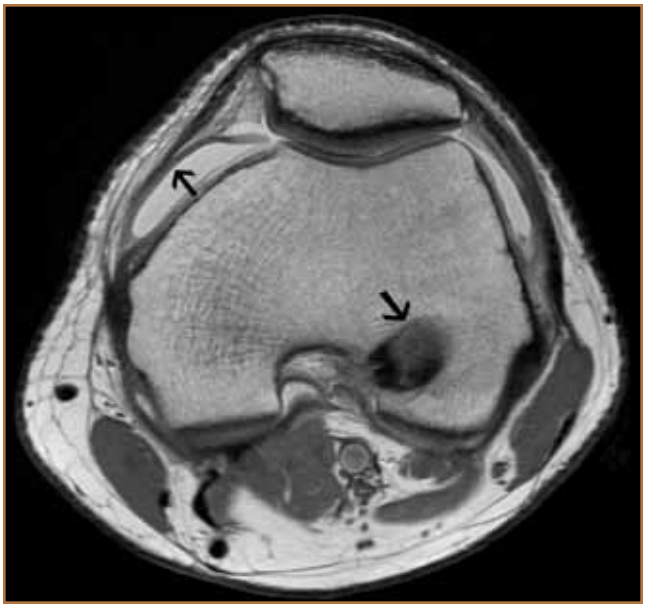

Figure 2. Axial fast spin echo MRI demonstrates diffuse nonspecific thickening of the synovial lining (arrow) and a fine proliferative inflammatory synovial response. There is mild resorption of bone along the femoral tunnel (arrow).

Due to the elevated WBC count in the synovial fluid, elevated CRP, effusion, and fever, an emergent arthroscopic irrigation and debridement were performed. Arthroscopy showed mild reactive synovitis, a viable graft, and no evidence of purulence. Small amounts of scar tissue, hematoma, and inflamed synovial tissue were debrided. Nine liters of antibiotics were used to perform the irrigation. The patient was kept overnight and received intravenous Cefazolin for 24 hours and was discharged on oral Cephalexin 500 mg every 6 hours.

On postoperative day 3, peripheral blood analysis revealed normal RBC (4.44/pl; Hgb 12.8 gm/dL; Hct 38.2%) and WBC levels (5.61/nL with 58.4% neutrophils and 31% lymphocytes), a normal ESR (7 mm/hr) and cultures showed no growth to date. The patient was evaluated by an infectious disease doctor who decided to continue with oral Cephalexin treatment and to add Metronidazole 500 mg 3 times a day to cover anaerobic infection. A 1.5 Tesla MRI using sagittal fast short tao inversion recovery (STIR) and sagittal, coronal, and axial fast spin echo techniques was then ordered the same day. MRI revealed a small to moderate sized effusion with diffuse thickening of the synovial lining, a non-specific mild fine proliferative inflammatory response, minimal bone resorption in the femoral and tibial tunnels, and marrow edema within the femur and proximal tibia (**Figures 1, 2**). Based on MRI findings, the patient was started on Naproxen 500 mg 2 times a day to treat the inflammatory response.

At postoperative day 14, the patient had a trace effusion, a negative Lachman's test, and a ROM of 0° to 120°. Cytologic examination showed a mixture of inflammatory cells consisting of lymphocytes, few neutrophils, and occasional macrophages in a density not typical of an infectious exudate (**Figure 3**). In addition, fairly numerous small and minute particles of metallic debris were present (**Figure 4**). Final cultures from the arthrocentesis and arthroscopic debridement were negative.

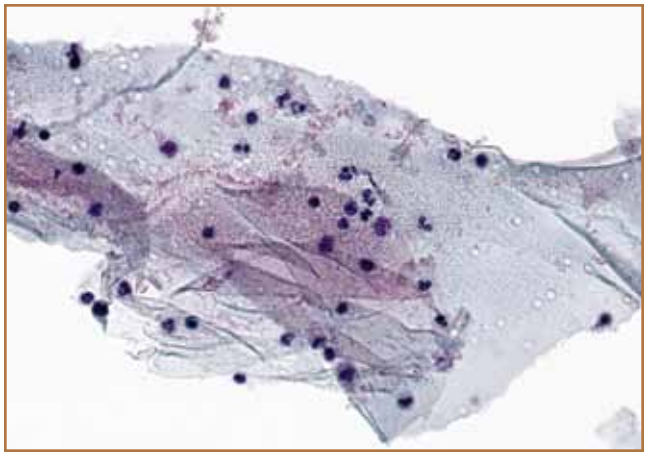

Figure 3. Photomicrograph of a ThinPrep® cytology specimen that shows scattered cells within a film of proteinaceous material. The mixture and density of cells, which include polymorphonuclear neutrophils, small round lymphocytes and large, bilobed and clefted macrophages, are not consistent with infection (X40, Pap).

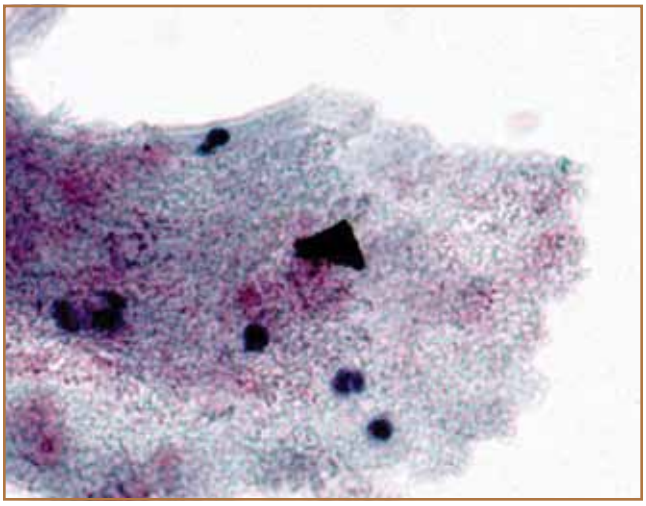

Figure 4. Another photomicrograph of a ThinPrep® cytology specimen that shows a multi-angular fragment of metallic, opaque (black) debris within the proteinaceous material (X80, Pap).

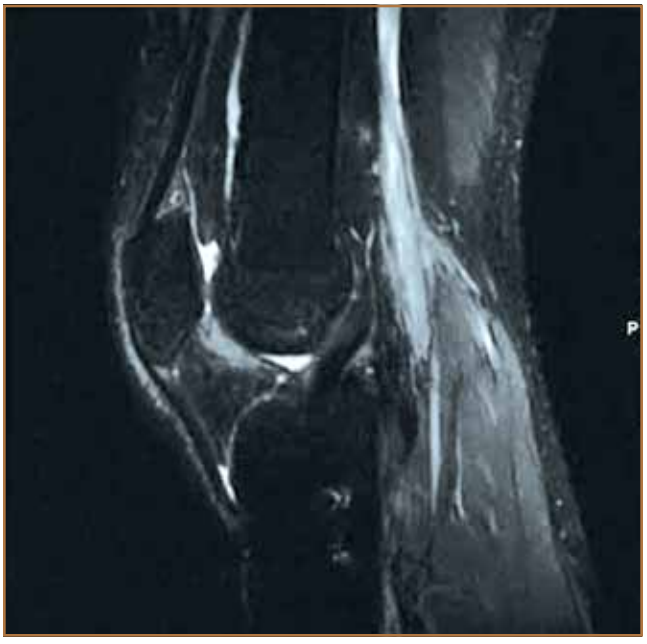

Figure 5. Sagittal fat suppressed fast spin echo MRI of the patient's left knee at 1-year follow-up. MRI demonstrates intact graft and complete interval resolution of marrow edema, synovitis and soft-tissue edema.

Based on the culture report, a decision was made to discontinue the antibiotics while continuing the anti-inflammatories. At follow-up, 16 weeks after the washout, the patient presented with a benign physical exam. The patient was encouraged to return to normal athletic activities. At 1-year postoperative, the physical examination was unremarkable. A new MRI was ordered and it showed an intact graft and complete interval resolution of previously visualized inflammatory synovitis with associated marrow and soft-tissue edema (**Figure 5**). Patient was advised to resume normal activities. The postoperative work up is outlined in **Figure 6**.

Discussion

Failure rates after ACL reconstruction remain as high as 14% due to poor surgical technique, recurrent trauma, infection, errors in rehabilitation, and failed biologic incorporation.[9,10] Despite advances in sterilization, rates of septic arthritis vary between 0.1% to 0.9% and while uncommon, will yield poor clinical outcomes and graft failure.[11] Furthermore, a culture-negative result has been documented in 10% to 20% of cases.[12] Inflammation may be induced by reasons other than infection, such as antigenic determinants. Allergic reactions to the degradation byproducts of the implant materials have been reported.[13-15] In this case, cytology revealed metal fragments in the synovial fluid most likely left be-

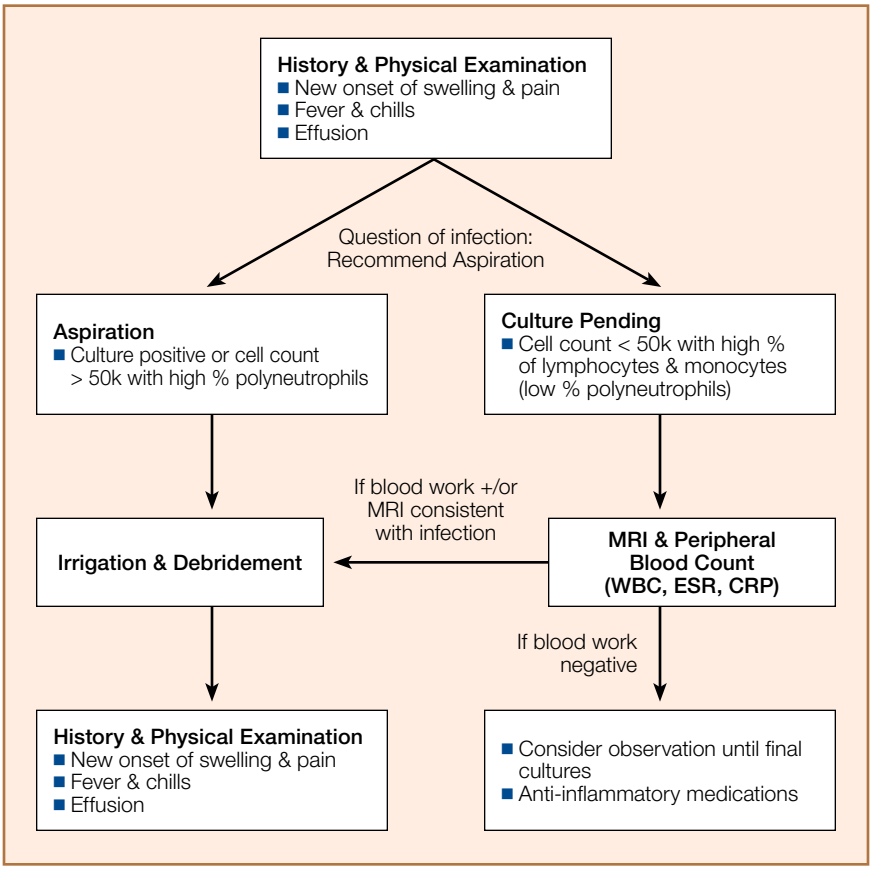

Figure 6. Flow chart outlining the work up for synovitis and infection of an allograft ACL reconstruction.

hind from the arthroscopic shaver. However, we felt infection and allergic reaction were unlikely, as they were ruled out by negative culture, negative differential count, time of presentation, MRI, and pathology. This led us to hypothesize that the failure mechanism was a host-mediated immune response, which typically results in delayed graft healing and worse outcomes in comparison to patients that present with no immune response.[16]

Host-mediated immune responses present a spectrum of disease from delayed graft healing to synovitis to complete biologic failure.[3,4,16-19] Based on published literature, this is an under-reported and under-recognized phenomenon. Immune responses are typically precipitated by host-graft mismatch and have been documented in cases of ACL allograft reconstruction, despite the notion that musculoskeletal grafts are immunologically privileged tissue.[2,20] Rodrigo and colleagues[20] reported an antibody response against donor HLA antigens in synovial fluid after ACL reconstruction using allograft tissue. Furthermore, immune responses to hardware and byproducts of implant degradation have been seen in humans and may yield complications such as acute synovitis or pre-tibial cysts.[21,22] Although it has been shown that human leukocyte antigen (HLA) matching and immunosuppression can increase graft survival, the belief that allograft tissue is immunologically privileged results in the lack of matching histocompatibility antigens.[3] The clinical consequence of an immune response is not completely understood, but it is suspected that host-graft mismatch may affect graft incorporation, prolonging the time to regain full strength.[19] This may represent an underappreciated source of failure and may be the underlying mechanism of failed biological incorporation.[19,20]

While specific procurement and sterilization procedures can reduce the antigenicity, it does not eliminate the possibility of a host-mediated immune response.[23] Cryopreservation dramatically reduces the antigenicity by reportedly denaturing the MHC antigens on the cell surface.[24] This raises the question of whether irradiation has a similar effect on the antigenicity of the tendon graft. Gamma irradiation is used primarily because it decreases the chances of viral or bacterial transmission and the development of infection.[25] However, gamma irradiation also alters the biomechanical properties of ACL tendon allografts, reducing the strength of the graft at high doses of radiation.[25] Moreover, irradiation reportedly preserves the MHC antigens. Thus, it has been suggested that while the tissue may be less antigenic, a host mediated immune response, similar to the one seen in this case, remains a possibility in irradiated tendon allografts.[16]

Imaging studies should also be considered in examining the viability and success of allograft transplantation. MRI can be used as an indirect measure of graft viability.[18] Typical MRI findings related to infection include synovitis, bone erosion, peri-articular edema, marrow edema, sinus tracts, and soft-tissue abscesses.[9] On MRI, graft changes due to immune mediated responses will be manifested to a greater extent as the postoperative time increases.[18] Specifically, abnormalities on MRI may initially represent non-specific inflammation associated with the surgical procedure whereas MRI abnormalities that persist or worsen may represent a host-mediated immune response.[18] The MRI findings in this case report were not consistent with infection, given the lack of intense surrounding soft-tissue edema and presence of a fine, inflammatory synovitis without bulky debris. Consequently, infection was ruled out and the acute synovitis was thought to be a result of a host-mediated immune response.

Infection and allergic reaction were unlikely, as they were ruled out by negative culture, negative differential count, time of presentation, MRI, and pathology. This led us to hypothesize that the failure mechanism was a host-mediated immune response, which typically results in delayed graft healing and worse outcomes in comparison to patients that present with no immune response.

Traditionally, return to sport after autograft ACL reconstruction is approximately 6 months;[23] however, there is literature to support that return to sport after allograft reconstruction should be longer.[24] In this particular case, the patient returned to normal athletic activities 1 year postoperatively. The physician wanted to err on the conservative side to give the allograft a longer time to mature from the host immune response. The patient was cleared only after there was no effusion, full ROM, negative physical examination, and the repeat MRI showed low signal on the graft.

To the best of our knowledge, there are few reported cases of a host-mediated immune response to freeze-dried irradiated anterior tibial tendon allografts. In the future, one may want to consider this diagnosis and the role of anti-inflammatory therapy to treat acute synovitis secondary to host mediated immune responses.

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