Complications in Biologics

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Complications Following Biologic Therapeutic Injections: A Multicenter Case Series

Claire D Eliasberg [1], Daniel A Nemirov [2], Bert R Mandelbaum [3], Andrew D Pearle [4], John M Tokish [5], Michael R Baria [6], Peter J Millett [7], Shane A Shapiro [8], Scott A Rodeo [4]

- ***"biologic injection":*** a therapeutic injection using products obtained from a human source, including cellular therapies, platelet-rich plasma, bone marrow aspirate concentrate, adipose-derived products or any placental, umbilical cord or amniotic products

BACKGROUND

- Various allogeneic tissues are being developed and used in the area of “orthobiologics”
  - Allogeneic bone marrow
  - Amniotic fluids, placental tissues, umbilical cord blood, Wharton’s jelly
- Indiscriminate use by numerous types of practitioners presents risks for complications
- There is currently lack of regulation, transparency, and standardization
- Products that bypass FDA oversight through exemptions and off-label use

METHODS

- Physician members of the Biologic Association were asked if they had any patients meeting the inclusion criteria:
  - ❑ Received a biologic injection
  - ❑ Sustained an adverse reaction
  - ❑ Had a minimum of 1-year follow-up

Table 1. List of Data Collected: Patient Information, Biologic Administered, Details, and Treatment of Adverse Event

Patient information
Patient age
Patient BMI
Underlying diagnosis
Existing joint pathology
History of diabetes (HgbA1c)
Comorbidities
Current medications
Smoking history
Prior treatments
Biologic administered
Description of biologic administered
Volume of dose administered
Anatomic location where biologic administered
Manufacturer of biologic
Route of administration
Details of adverse event
Patient's symptoms at presentation
Time between treatment and presentation of adverse response
CBC
ESR
CRP
Lactate
Culture results
Imaging studies
Pathology reports
Treatment of adverse event
Antibiotics administered
Surgical procedures performed
Outcome of treatment

CBC, complete blood count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HgbA1c, hemoglobin A1c.

RESULTS

- Collected data on 14 total patients from 6 institutions across the U.S:
  - ❑ 11 male, 4 female patients
  - ❑ Mean age 63 years (range, 35-83 years)
  - ❑ Mean BMI 27.3 (range, 19.7-38.9)
  - ❑ Few medical co-morbidities in the cohort:
    - ➢ No patients had diabetes mellitus
    - ➢ No patients with h/o chronic steroid use or immunosuppressive disorders
    - ➢ Only 3 patients had a remote history of smoking (all had quit at least 30 years prior to presentation)

RESULTS

Table 2. Patient Diagnoses, Previous Treatments, Complications, and Pathogens From Infections

	Number of Patients	Percentage of Patients
Underlying diagnosis		
Osteoarthritis	11	78.5%
Myofascial pain	1	7.1%
Achilles tendinopathy	1	7.1%
Low back pain	1	7.1%
Previous treatments		
No previous treatment	8	57.1%
Previous nonbiologic injection (i.e., HA, CSI)	3	21.4%
Previous surgical intervention	2	14.3%
Previous biologic injection (i.e., adipose-derived "stem cell" injection)	1	7.1%
Injection Site		
Knee (intra-articular)	7	50.0%
Shoulder (intra-articular)	3	21.4%
Knee and shoulder (intra-articular)	1	7.1%
Hip (intra-articular)	1	7.1%
Muscle/tendon	2	14.3%
Complications		
Infection	7	50.0%
Suspected inflammatory response	6	42.9%
Infection and inflammatory response	1	7.1%
Pathogens from isolated infections*		
Escherichia coli	4	57.1%
Staphylococcus epidermidis	1	14.3%
Methicillin-sensitive *Staphylococcus aureus*	1	14.3%
Citrobacter	1	14.3%

CSI, corticosteroid injection; HA, hyaluronic acid.

*All patients with isolated infections (n = 7) underwent treatment with at least one subsequent surgical intervention and intravenous (IV) antibiotic treatment.

RESULTS

Table 3. Details of Patient Injections, Adverse Events, and Pathogens

Patient	Age	Sex	Injection Description	Manufacturer	Injection Site	Adverse Event	Pathogen
1	78	M	Placental stem cells	Biogenix/ GenCure	Bilateral knees	Septic arthritis	*E. coli*
2	83	M	Umbilical cord blood	Genetech, Inc.	Bilateral shoulders	Septic arthritis	*E. coli*
3	57	M	Umbilical cord blood	Genetech, Inc.	Unilateral shoulder	Septic arthritis	*E. coli*
4	65	F	Microfragmented adipose tissue	Lipogems	Bilateral knees	Inflammatory response	N/A
5	51	F	Amniotic fluid	Unknown	Unilateral knee	Septic arthritis	*Citrobacter*
6	69	M	Stem cell	Genetech, Inc.	Bilateral shoulders, unilateral knee	GVHD, sepsis	*E. coli*
7	65	M	Lipoaspirate	Unknown	Unilateral knee	Septic arthritis	*Staphylococcus epidermidis*
8	44	F	PRP	Unknown	Bilateral shoulders	Septic arthritis	MSSA
9	73	M	BMAC	Arthrex Angel System	Bilateral knees	Inflammatory response	N/A
10	67	M	Umbilical cord blood	Unknown	Bilateral knees	Inflammatory response	N/A
11	65	M	Amnion membrane	Amniofix	Achilles tendon	Inflammatory response	N/A
12	62	M	Umbilical cord blood	Genetech, Inc.	Unilateral hip	Septic arthritis	*E. coli*
13	70	M	Placental tissue + PRP	Unknown	Unilateral knee	Inflammatory response	N/A
14	36	M	Wharton's jelly + PRP	Invitrx	Paraspinal musculature (multiple sites)	Inflammatory response	N/A

BMAC, bone marrow aspirate concentrate; F, female; GVHD, graft-versus-host disease; M, male; PRP, platelet-rich plasma; MSSA, methicillin-sensitive *Staphylococcus aureus*; N/A, not applicable.

RESULTS

- All patients who developed infections (n=8) received injections at outside facilities

- Time to presentation:
  - ❑ Mean time from injection to time of presentation was 8.9 days (range, 3 hours to 30 days)
  - ❑ No significant difference in time from injection to presentation between those diagnosed with infection vs. inflammatory response

- All patients with isolated infections underwent treatment with at least 1 surgical intervention and IV antibiotic therapy (mean: 3.6 surgeries, range, 1-12)

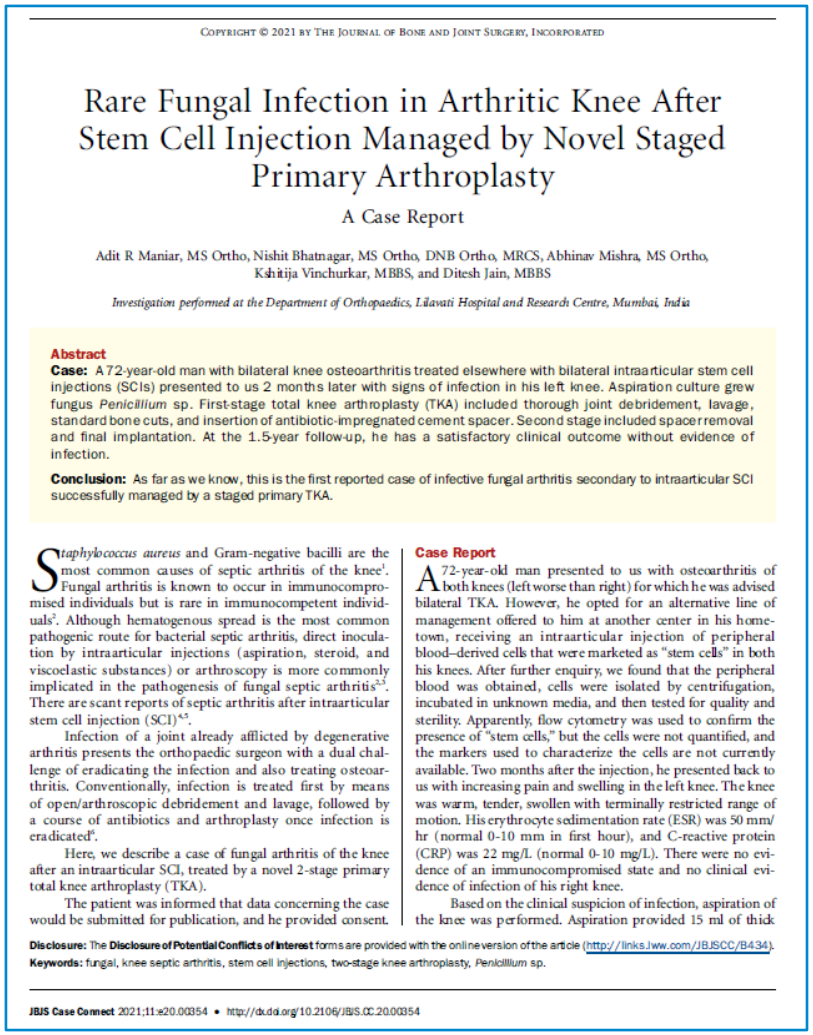
DISCUSSION

- **Limitations:**
  - This constitutes a large series of complications, but this series is by no means comprehensive
    - Complications collected were limited to the physicians queried and their regional networks
    - We cannot estimate the overall incidence of complications because we do not know the overall number of injections administered
  - Do not have all data about injection administration details or manufacturers

DISCUSSION

- **Conclusions:**
  - While the overall incidence is unknown, serious complications can occur following treatment with biologic injections
  - Of this small series of 14 patients with known complications, 50% had infection, 42.9% had sterile inflammatory reactions, and one patient (7.1%) had a combination of both
  - Some infections in this series required multiple surgical procedures and long-term antibiotic use
  - More research is necessary to determine the overall incidence of complications and to better identify the risk factors for these complications
  - The field will be aided by more rigorous oversight and standardization

Rare Fungal Infection in Arthritic Knee After Stem Cell Injection Managed by Novel Staged Primary Arthroplasty A Case Report



Rare Fungal Infection in Arthritic Knee After Stem Cell Injection Managed by Novel Staged Primary Arthroplasty

A Case Report

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Abstract

Case: A 72-year-old man with bilateral knee osteoarthritis treated elsewhere with bilateral intraarticular stem cell injections (SCIs) presented to us 2 months later with signs of infection in his left knee. Aspiration culture grew fungus *Penicillium* sp. First-stage total knee arthroplasty (TKA) included thorough joint debridement, lavage, standard bone cuts, and insertion of antibiotic-impregnated cement spacer. Second stage included spacer removal and final implantation. At the 1.5-year follow-up, he has a satisfactory clinical outcome without evidence of infection.

Conclusion: As far as we know, this is the first reported case of infective fungal arthritis secondary to intraarticular SCI successfully managed by a staged primary TKA.

Staphylococcus aureus and Gram-negative bacilli are the most common causes of septic arthritis of the knee[1]. Fungal arthritis is known to occur in immunocompromised individuals but is rare in immunocompetent individuals[2]. Although hematogenous spread is the most common pathogenic route for bacterial septic arthritis, direct inoculation by intraarticular injections (aspiration, steroid, and viscoelastic substances) or arthroscopy is more commonly implicated in the pathogenesis of fungal septic arthritis[2,3]. There are scant reports of septic arthritis after intraarticular stem cell injection (SCI)[4,5].

Infection of a joint already afflicted by degenerative arthritis presents the orthopaedic surgeon with a dual challenge of eradicating the infection and also treating osteoarthritis. Conventionally, infection is treated first by means of open/arthroscopic debridement and lavage, followed by a course of antibiotics and arthroplasty once infection is eradicated[6].

Here, we describe a case of fungal arthritis of the knee after an intraarticular SCI, treated by a novel 2-stage primary total knee arthroplasty (TKA).

The patient was informed that data concerning the case would be submitted for publication, and he provided consent.

Case Report

A 72-year-old man presented to us with osteoarthritis of both knees (left worse than right) for which he was advised bilateral TKA. However, he opted for an alternative line of management offered to him at another center in his hometown, receiving an intraarticular injection of peripheral blood–derived cells that were marketed as "stem cells" in both his knees. After further enquiry, we found that the peripheral blood was obtained, cells were isolated by centrifugation, incubated in unknown media, and then tested for quality and sterility. Apparently, flow cytometry was used to confirm the presence of "stem cells," but the cells were not quantified, and the markers used to characterize the cells are not currently available. Two months after the injection, he presented back to us with increasing pain and swelling in the left knee. The knee was warm, tender, swollen with terminally restricted range of motion. His erythrocyte sedimentation rate (ESR) was 50 mm/hr (normal 0-10 mm in first hour), and C-reactive protein (CRP) was 22 mg/L (normal 0-10 mg/L). There were no evidence of an immunocompromised state and no clinical evidence of infection of his right knee.

Based on the clinical suspicion of infection, aspiration of the knee was performed. Aspiration provided 15 ml of thick

Disclosure: The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJSCC/B434).

Keywords: fungal, knee septic arthritis, stem cell injections, two-stage knee arthroplasty, *Penicillium* sp.

- A 72-year-old man with bilateral knee OA treated
- Bilateral intraarticular "stem cell" injections
- Peripheral blood cells were isolated by centrifugation, incubated in unknown media, and then tested for quality and sterility
- Cells were not quantified, and the markers used to characterize the cells were not available
- Presented 2 months later with *Penicillium* sp.fungus infection
- Amphotericin B therapy followed by 2-stage I and D, insertion of antibiotic-impregnated cement spacer → TKR
- Freported case of infective fungal arthritis secondary to intraarticular cell therapy injections

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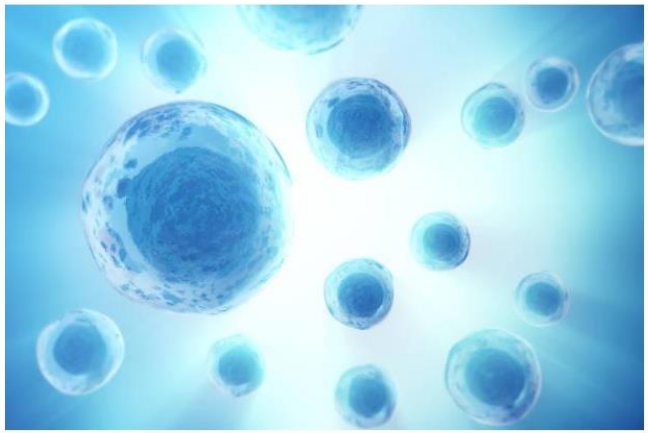

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The US Food and Drug Administration (FDA) regulates regenerative medicine products. There continues to be broad marketing of unapproved products considered regenerative medicine therapies that are intended for the treatment or cure of a wide range of diseases

These regenerative medicine products have risks but are often illegally marketed by clinics as being safe and effective for the treatment of a wide range of diseases or conditions, even though they haven't been adequately studied under an IND to demonstrate the claims of safety and effectiveness. Safety concerns with any product that is illegally marketed as a regenerative medicine therapy include the following:

- Blindness;
- Tumor formation
- Neurological events;
- Bacterial infections including life-threatening blood infections;
- Reactions at the site of collection and administration;
- Unwanted inflammatory or immune response to the cell or therapy;
- Cells moving to another part of the body and turning into an unintended type of tissue or excessively growing in the body (i.e., forming a tumor);
- Failure of the therapy to work as anticipated when approved treatments are available;
- Cross-contamination with bacteria, viruses or mold related to processing (preparation of the product) or the therapy not being tested for infectious diseases such as hepatitis and HIV.

HSS

THANK YOU