



Case Report

Total Knee Periprosthetic Joint Infection in the Setting of Hematologic Malignancy: Considerations for Management

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ABSTRACT

Patients with malignancy are often profoundly immunocompromised due to chemotherapy, placing them at potential increased risk for periprosthetic joint infection (PJI). However, there is little information regarding PJI management in these patients. We describe 4 patients with a history of primary total knee arthroplasty followed by diagnosis of multiple myeloma or Waldenström macroglobulinemia who received chemotherapy within 4 months prior to PJI. The Musculoskeletal Infection Society major and minor criteria and either debridement, antibiotics, and implant retention or a 2-stage approach appear to be effective for acute or chronic PJI, respectively. We recommend an anticoagulant be administered concomitantly with antineoplastics that significantly increase deep vein thrombosis risk, and we recommend long-term oral suppressive antibiotics postoperatively, especially if chemotherapy will be resumed. Additional studies are needed to investigate risks and benefits of PJI prophylaxis during chemotherapy and long-term suppressive antibiotics after PJI treatment.

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Introduction

Periprosthetic joint infection (PJI) is a growing cause of knee and hip arthroplasty failure and is difficult and expensive to treat. There are 2 main type of PJIs based on the timing and duration of symptoms: acute and chronic. Chronic infections are found when the hip or knee has symptoms for a duration greater than 4 weeks. Oftentimes, the clinical presentation is unremarkable other than pain and swelling. In cases of acute infection, the patient's joint often becomes painful, red, and/or swollen. This can be accompanied by systemic symptoms such as fever, malaise, or even sepsis. Acute joint infections usually stem from inoculation of newly implanted hardware or, in later spontaneous cases, hematogenous spread of bacteria with seeding to the foreign implant material. The diagnosis of PJI remains imprecise, but the Musculoskeletal Infection Society (MSIS) major and minor criteria have helped increase the sensitivity and specificity of diagnosing a PJI event. If acute

infections are diagnosed within 3–4 weeks of symptom onset, it is possible to retain the fixed components and only replace the modular bearing after performing a thorough debridement. Similar to a 2-stage approach, patients are treated postoperatively with a 6-week course of intravenous (IV) antibiotics tailored to the infectious organism. This protocol, known as debridement, antibiotics, and implant retention (DAIR), has shown promising results when treating infections that are truly acute. The 2-stage procedure involves initial removal of prosthesis and placement of an articulating antibiotic spacer followed by delayed reconstruction [1–10].

Immunocompromised patients are thought to be at higher risk for hematogenous spread of infections. Patients who are undergoing acute cancer treatment fall into this category [11]. The presentation of PJI when a patient has pancytopenia due to malignancy or chemotherapy presents the surgeon and oncologist with challenges. In some cases, patients may not be able to undergo surgery until they improve from the side effects of their cancer treatment. In addition, patients receiving certain chemotherapies may be at higher risk of deep vein thrombosis (DVT) in the perioperative and postoperative periods. The rates of hematologic malignancies are increasing as the general population ages, and newer chemotherapy agents with immunosuppressive side effects are now

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available for use by oncologists. With an increasing number of joint replacements being performed and increasing numbers of patients undergoing treatment for multiple myeloma (MM) and other hematologic cancers, PJI after chemotherapy is likely to become more prevalent in the future [11].

Kao et al [12] recently reported data for a cohort of patients with and without a history of cancer who then underwent total knee arthroplasty (TKA), showing similar 1-year PJI rates between the 2 groups; however, the management of postoperative PJI was not discussed. Although much has been studied regarding PJI treatment strategies, there is a paucity of information regarding PJI management and outcomes in patients being treated for concomitant cancer. Arguments could be made for or against treatment with either debridement with component retention or 2-stage implant removal in this patient population. We describe 4 cases in which patients with previously well-functioning TKA developed PJI within 4 months of receiving chemotherapy for a hematologic malignancy. We hypothesize that acute or chronic PJI in immunocompromised patients can be successfully treated with either DAIR or a 2-stage approach, respectively.

Case histories

Case 1

Case 1 involves a 74-year-old woman who underwent primary right TKA 12 years before developing PJI. She was diagnosed with IgA kappa MM 4 years before presentation and had begun a chemotherapy regimen of bortezomib (Velcade [Takeda Oncology; Cambridge, MA, USA]) 1 mg/m² subcutaneously (subQ) weekly, lenalidomide (Revlimid [Celgene; Summit, NJ, USA]) 10 mg by mouth (PO) daily (days 1–21, every 28 days), and dexamethasone 12 mg PO weekly (VRd protocol) 2 months before presentation.

She presented with pancytopenia secondary to chemotherapy, acute kidney injury, pneumonia of the left lower lung, sepsis, gram-positive bacteremia, and a 3-day history of right knee pain. Her blood work showed an erythrocyte sedimentation rate (ESR) of 90 mm/hr (0–30 normal), C-reactive protein (CRP) of 372 mg/L (0–10 normal), red blood cell (RBC) count of 2,340,000/μL (4,000,000–5,200,000 normal), platelet count of 63,000/μL (150,000–450,000 normal), white blood cell (WBC) count of 1710/μL (3600–9500 normal), and neutrophil count of 920/μL (1400–6000 normal) [53.7%]. She was admitted and started on empiric vancomycin 750 mg IV daily, ceftazidime 500 mg IV twice daily (bid), and acyclovir 200 mg PO daily. Ceftazidime was switched to meropenem 500 mg IV bid the next day for aspiration pneumonia coverage.

Orthopaedic surgery was consulted the day after admission, and examination of the right knee showed an effusion and limited active and passive range of motion (ROM) because of pain. Right knee aspiration revealed a synovial fluid WBC count of 365,200/μL and a neutrophil percentage of 98%, consistent with an acute PJI diagnosis. Synovial fluid culture grew pansensitive *Streptococcus pneumoniae*.

Several surgical options, including DAIR and removal of implants with placement of an antibiotic spacer, were considered. Given the acuity of presentation, she chose to pursue DAIR and was taken to the operating room (OR) 3 days after presentation and 6 days after the onset of knee symptoms. Perioperative findings included gross purulence in the joint capsule and well-fixed tibial and femoral components. Postoperatively, she was switched to vancomycin and ceftriaxone 2 g IV daily and began aspirin 81 mg PO daily for DVT prophylaxis for 6 weeks. She was immediately mobilized, and her sepsis and pneumonia improved. She was discharged on postoperative day (POD) 5 with plans for 6 weeks of ceftriaxone 2 g IV daily. Her blood work at this time showed a CRP

of 86.60 mg/L and improvement of her pancytopenia with a hemoglobin level of 8.0 g/dL (12.0–15.0 g/dL normal), platelet count of 75,000/μL, WBC count of 7270/μL, and neutrophil count of 5570/μL (76.6%).

She began antibiotic suppression with penicillin V potassium 500 mg PO bid after completing 6 weeks of ceftriaxone as recommended by the infectious disease specialist. She experienced no surgical complications within 90 days of PJI treatment. Four months after DAIR, she began a new chemotherapy regimen of daratumumab 900 mg IV weekly. At 14-month follow-up, she reported intermittent pain in her right knee but denied drainage or redness. Examination of the right knee showed a stable joint without edema or erythema and ROM 0°–100°. She remained on long-term suppressive antibiotics after the most recent follow-up.

Case 2

Case 2 involves a 73-year-old man with a past medical history of unilateral renal agenesis, chronic kidney disease, DVT, hypertension, cytomegalovirus infection, prostatectomy, and peripheral neuropathy at presentation. He underwent primary left TKA 5 years before presentation and was diagnosed with IgG lambda MM 2 years before presentation. He was treated for MM and achieved complete remission 13 months prior to presentation. He then began a maintenance chemotherapy protocol of Velcade 1 mg/m² subQ weekly and dexamethasone 12 mg PO weekly (Vd protocol). Four months before presentation, he was diagnosed with pancytopenia with severe thrombocytopenia, L4–L5/L5–S1 discitis, and *Streptococcus infantarius* osteomyelitis of the spine and received 6 weeks of ceftriaxone 2 g IV daily, followed by 6 weeks of levofloxacin 750 mg PO every other day. He discontinued his maintenance chemotherapy protocol at the onset of infection. At follow-up, blood cultures were negative, and magnetic resonance imaging showed continuous improvement of his osteomyelitis and discitis.

He presented with improving back pain, pancytopenia of unknown etiology, several weeks of intermittent left knee swelling, and a 2-week history of a painful left knee. His most recent bone marrow biopsy showed normocellular marrow with trilineage maturation and was morphologically negative for plasma cell myeloma. His blood work showed an ESR of 44 mm/hr, CRP of 87.1 mg/L, platelet count of 101,000/μL, WBC count of 2710/μL, and neutrophil count of 1440/μL (53.2%). Antibiotics were held on admission. His peripheral blood culture result was negative.

Orthopaedic surgery was consulted the day after admission, and examination showed a visible and palpable effusion about the left knee. Left knee aspiration revealed turbid synovial fluid with a WBC count of 23,870/μL and a neutrophil percentage of 86%. The synovial fluid culture result was negative; however, alpha-defensin testing was positive.

Owing to concerns for chronic knee infection based on symptom recurrence and aspirate findings, the patient opted to pursue resection and placement of an articulating antibiotic spacer with plans for 2-stage reconstruction. Perioperative findings included gross purulence, a thick rind of inflamed synovial tissue surrounding the joint, good remaining bone stock, and intact medial and lateral collateral ligaments. Postoperatively, he began ceftriaxone 2 g IV daily and vancomycin 1 g IV daily. Enoxaparin 40 mg subQ daily and aspirin 81 mg PO bid were given for DVT prophylaxis. While soft-tissue culture results were negative, blood cultures grew *Enterobacter*. As a result, he was switched to meropenem 1gIV bid. Before discharge, he developed left proximal femoral DVT, which was treated with enoxaparin 30 mg subQ daily for 2 days followed by 70 mg (1 mg/kg) subQ bid. He was discharged on

ertapenem 1 g IV daily, with plans for discontinuation of the antibiotic after 6 weeks.

On POD 23, he was admitted to our facility with acute altered mental status, acute kidney injury, acute swelling and hemarthrosis of the left knee, and an acute retroperitoneal hematoma after an unwitnessed fall that required multiple blood transfusions. The cause of the fall was unclear because of his altered mental status at the time of the fall, and it was thought that the acute left knee swelling was secondary to trauma with the fall. Enoxaparin was decreased to 30 mg subQ daily because of the hematoma, and he underwent inferior vena cava filter placement for his chronic left lower extremity DVT. He then received enoxaparin 40 mg subQ daily after his hemoglobin and hematocrit levels stabilized, and his dose was later increased to 110 mg subQ daily for therapeutic treatment. The infectious disease team changed his antibiotic regimen to daptomycin 450 mg (6 mg/kg) and ertapenem 1 g IV daily for an additional 6 weeks.

Four months after knee resection, inflammatory markers had normalized. The articulating knee spacer was painful, and he wished to undergo stage 2 reimplantation. Revision knee replacement was performed with a constrained polycomponent and short-cemented stems. All intraoperative culture results were negative. He was discharged on rivaroxaban 10 mg PO daily for 6 weeks for DVT prophylaxis and doxycycline 100 mg PO bid for 10 days as per our infectious disease colleagues. Six months after stage 2 reimplantation, he presented to the orthopaedic clinic for his most recent follow-up. Examination of the left knee showed a well-healed incision with no signs of infection and ROM 0°–70°. He resumed chemotherapy 10 months after reimplantation.

Case 3

Case 3 involves a 75-year-old woman with a history of anemia, kidney disease, chronic femoral and popliteal DVT, congestive heart failure, myocardial infarction, pacemaker implantation, chronic obstructive pulmonary disease, and type 2 diabetes mellitus at presentation. She underwent primary right TKA 5 years before presentation and was diagnosed with IgG kappa MM 3 years before presentation. She was initially treated with Revlimid IV and dexamethasone PO (Rd protocol). Six months before presentation she began lenalidomide 25 mg IV weekly, and her last dose was administered at an outside facility 3 months before presentation.

When she transferred care for her MM to our institution, a right posterior iliac crest bone marrow biopsy was performed for staging. Her blood work that day showed an ESR of 36 mm/hr, CRP of <5.0 mg/L, platelet count of 100,000/ μ L, WBC count of 4700/ μ L, and neutrophil count of 3130/ μ L (66.6%). Two days later she presented with complaints of a painful, hot, and swollen right knee that began immediately after her bone marrow biopsy. Her blood work showed a CRP of 155.3 mg/L and WBC count of 10,150/ μ L. Arthrocentesis of the right knee revealed turbid synovial fluid with a WBC count of 172,760/ μ L and 95% neutrophils, and cultures grew oxacillin-resistant *Staphylococcus aureus*.

Orthopaedic surgery was consulted, and examination in the emergency department showed a warm, swollen, and erythematous right knee that was very painful with any ROM. She was diagnosed with acute PJI and admitted for further treatment. The patient chose to pursue a DAIR approach and underwent surgery 1 day after presentation and 3 days after the onset of symptoms. Perioperative findings included gross purulence but no evidence of loosening. Vancomycin 1250 mg IV daily and rifampin 300 mg IV bid were administered postoperatively for 6 weeks. She began aspirin 81 mg PO bid on POD 1 for DVT prophylaxis for 6 weeks and was discharged on POD 3. After completion of 6 weeks of IV

antibiotics, she began long-term suppressive doxycycline 100 mg PO bid.

Two months after DAIR, she was diagnosed with right ankle cellulitis, right femoral and popliteal DVT, and left distal popliteal DVT. This was treated acutely with a course of IV antibiotics and therapeutic enoxaparin. Owing to worsening of her MM, she began a combination chemotherapy regimen of Velcade 2.1 mg (1 mg/m²) subQ weekly, Revlimid 15 mg PO daily (days 1–21, every 28 days), and dexamethasone 20 mg IV weekly (VRd protocol). She had several further admissions for leg swelling and cellulitis.

Eight months after her DAIR procedure, she presented to our institution with a 7-day history of worsening right knee pain and swelling. Her blood work at this time showed a CRP of 59.8 mg/L, WBC count of 5650/ μ L, and neutrophil count of 4200/ μ L (74.3%). On examination, the right knee was edematous with significant effusion and warmth; active and passive ROM was limited owing to pain. Her radiographs showed a well-fixed, well-aligned cemented right TKA with significant soft-tissue fullness in the prepatellar and suprapatellar regions. Right knee aspiration revealed purulent synovial fluid with a WBC count of 190,300/ μ L and 83% neutrophils. Synovial fluid and peripheral blood culture results were negative. She was diagnosed with chronic PJI and started on empiric vancomycin 1250 mg IV daily and ceftriaxone 2 g IV daily. She elected for removal of right TKA and placement of an articulating antibiotic spacer 3 days after the onset of symptoms. Perioperative findings included signs of chronic PJI and lateral distal femoral bone loss. OR cultures again grew oxacillin-resistant *S. aureus*. Postoperatively, she was treated with vancomycin 1250 mg IV daily for 6 weeks and enoxaparin 40 mg subQ daily for DVT prophylaxis. She was discharged 3 weeks after surgery after resolution of a postoperative partial bowel obstruction.

She began Bactrim (Hoffmann-La Roche Inc.; Litte Falls, NJ, USA) 800–160 mg PO bid for 6 months after her IV antibiotic regimen. Sixteen months after DAIR and 8 months after stage 1 resection and spacer placement, she presented to the orthopaedic clinic for her most recent follow-up. She was ambulating with a walker and reported minor pain in her right knee at full flexion. The Knee Injury and Osteoarthritis Outcome Score was 65.99, and she had ROM 0–90°. Due to her satisfaction with the function of her articulating spacer, the necessity for ongoing chemotherapy treatment, and her chronic medical conditions, she opted to keep the spacer and not pursue stage 2 reimplantation.

Case 4

Case 4 involves a 64-year-old man with a history of depression, seizures, vertigo, and right bundle branch block at presentation. He underwent primary right TKA 19 years before presentation and was also diagnosed with stable MYD88-positive Waldenström macroglobulinemia 19 years before presentation. He developed fatigue, low-grade fever, and unintentional weight loss and subsequently began a chemotherapy protocol of ibrutinib (Imbruvica [Pharmaceuticals LLC; Sunnyvale, CA, USA]) 560 mg PO daily 3 months before presentation.

He initially presented with a 12-day history of a traumatic right knee pain and swelling. His blood work revealed an ESR of 86 mm/hr, CRP of 95.7 mg/L, platelet count of 176,000/ μ L, WBC count of 3180/ μ L, and neutrophil count of 1530/ μ L (48.2%). Imbruvica was discontinued at this time. Orthopaedic surgery was consulted later that day. Right knee aspiration revealed purulent synovial fluid with a WBC count of 20,220/ μ L and a neutrophil percentage of 45%. Synovial fluid and peripheral blood culture results were negative. Acute PJI was diagnosed, and aztreonam 2 g IV 3 times daily and vancomycin 1500 mg IV bid were started. He elected for a DAIR approach and underwent surgery 2 days after presentation and

14 days after onset of symptoms. Perioperative findings included gross purulence, a mobile, noninflamed synovium, and well-fixed tibial and femoral components. The OR culture results were negative, and ceftriaxone 2 g IV daily and vancomycin 1750 mg IV bid were started postoperatively. On POD 6, the infectious disease team discontinued vancomycin and replaced it with daptomycin 6 mg/kg IV daily. He spiked a fever on POD 8, and ceftriaxone was switched to cefepime 2 g IV bid. He was discharged on POD 10 with plans for 6 weeks of IV antibiotic treatment.

He was started on long-term suppressive doxycycline 100 mg PO bid after completing IV antibiotics. Three months after DAIR, he began an 8-week chemotherapy protocol of rituximab 900 mg weekly. Six months after DAIR, he switched to a protocol of venetoclax 400 mg PO daily. His Knee Injury and Osteoarthritis Outcome Score Jr. 6 months after DAIR was 100. One year after DAIR, he had a well-healed incision, no effusion or joint line tenderness, and active and passive ROM 0°–110°.

Discussion

We presented a series of patients who were undergoing hematologic cancer treatment and developed TKA PJI (Table 1). While each patient's surgical management was dictated by the timing of his or her PJI diagnosis (acute vs chronic), all 4 patients completed 6 weeks of intravenous antibiotics, and 3 were placed on long-term suppressive antibiotics. No recurrence of infection was noted at the

most recent follow-up. We believe it is important for orthopaedic surgeons to be aware of certain immunosuppressive medications used in hematologic malignancies that may place a patient at higher risk for PJI.

Chemotherapy agents used before PJI

The patients in this study were treated with chemotherapy agents that may be unfamiliar to the orthopaedic surgeon. Three patients with MM received varying combinations of antineoplastic agents before development of PJI, and 1 patient with Waldenström macroglobulinemia received ibrutinib immediately before development of PJI (Table 2).

Bortezomib (Velcade) is a proteasome inhibitor that has been known to inhibit osteoclasts and induces osteoblast differentiation [13]. Adverse effects of bortezomib include peripheral neuropathy, infection (urinary tract, bacteremia, listeriosis, toxoplasmosis, pneumonia, and sepsis), and less commonly neutropenia and thrombocytopenia [14–17]. Lenalidomide (Revlimid) is an immunomodulatory drug derived from thalidomide that induces B cell ubiquitination leading to cell death [18]. Lenalidomide administration poses a significant risk for neutropenia, thrombocytopenia, anemia, infection (urinary tract, upper respiratory tract, sepsis, bacteremia, fungal, and renal), and DVT (especially with coadministration of dexamethasone) [16,19–22]. It is recommended that standard-risk patients receive prophylactic low-dose aspirin, and

Table 1

Summary.

	Case 1	Case 2	Case 3	Case 4
Past medical history				
Primary TKA				
Laterality	Right	Left	Right	Right
Year	2004	2011	2011	1998
Malignancy				
Type	Multiple myeloma	Multiple myeloma	Multiple myeloma	Waldenström macroglobulinemia
Diagnosis year	2012	2014	2014	1998
Chemotherapy drugs	VRd, ixazomib, IRd, VRd ^a , daratumumab	Vd ^a	Rd, R ^a , VRd	Ibrutinib ^a , rituximab, venetoclax
Prophylaxis given	Antiviral, none, none, none, none	None	Unknown, unknown, ASA	Antiviral, antiviral, antiviral
DVT	No	Yes	Yes	No
Recent separate-site infection	Yes	Yes	Yes	No
PJI				
Index TJA to diagnosis, y	12	5	5	19
Last chemotherapy to diagnosis, d	56	73	99	1
WBC count at diagnosis, #/μL	1710	2710	4700	2440
Joint fluid cell count	365,000 WBC	23,870 WBC	172,760 WBC	22,220 WBC
Culture results	<i>Streptococcus pneumoniae</i>	Culture negative	Methicillin-resistant <i>Staphylococcus aureus</i>	Culture negative
MSIS major or minor criteria met	Yes	Yes	Yes	Yes
Surgical treatment	DAIR	Two-stage Revision	DAIR (failed); Stage 1 only	DAIR
Onset of symptoms to treatment interval	6 d	3 mo	3 d	14 d
Postoperative period				
Initial postoperative antibiotic treatment	Ceftriaxone	Ertapenem; daptomycin + ertapenem	DAIR: vancomycin, rifampin; stage 1: vancomycin	Ceftriaxone + daptomycin
Suppressive antibiotic treatment	Penicillin V	-	DAIR: doxycycline, Bactrim; stage 1: Bactrim	Doxycycline
DVT	No	Yes	Yes	No
Reinfection	No	No	Yes; no	No
PJI surgery to resuming chemo, mo	4	10	2.5; 3.5	4
PJI diagnosis to most recent follow-up, mo	13.5	11.6	16.6	12.6

ASA, low-dose aspirin; Bactrim, sulfamethoxazole + trimethoprim; DAIR, debridement, antibiotics, and implant retention; IRd, ixazomib + Revlimid + dexamethasone; PJI, periprosthetic joint infection; R, Revlimid; Rd, Revlimid + dexamethasone; Vd, Velcade + dexamethasone; VRd, Velcade + Revlimid + dexamethasone; TKA, total knee arthroplasty; WBC, white blood cell.

^a Denotes chemotherapy regimen received immediately before PJI.

Table 2

Chemotherapy agents used for hemotologic malignancies before PJI.

	Bortezomib (Velcade)	Lenalidomide (Revlimid)	Ibrutinib (Imbruvica)
Pharmacologic category	Antineoplastic, proteasome inhibitor	Antineoplastic, angiogenesis inhibitor; immunomodulator	Antineoplastic agent; Bruton's tyrosine kinase inhibitor
Mechanism(s) of action	Reversibly inhibits chymotrypsin-like activity at the 26S proteasome, leading to activation of signaling cascades, cell cycle arrest, and apoptosis	Selectively inhibits secretion of proinflammatory cytokines; enhances cell-mediated immunity by stimulating proliferation of anti-CD3 stimulated T cells; inhibits trophic signals to angiogenic factors in cells; inhibits the growth of myeloma, myelodysplastic, and lymphoma tumor cells by inducing cell cycle arrest and cell death	Potent and irreversible inhibitor of Bruton's tyrosine kinase resulting in decreased malignant B cell proliferation and survival.
Antineoplastic uses	Labeled: mantle cell lymphoma, multiple myeloma; off-label: cutaneous T-cell lymphomas, follicular lymphoma, peripheral T-cell lymphoma, Waldenström macroglobulinemia	Labeled: follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, multiple myeloma, myelodysplastic syndromes; off-label: chronic lymphocytic leukemia, diffuse large B-cell lymphoma, multiple myeloma (newly diagnosed), myelodysplastic syndrome without deletion 5q	Labeled: chronic lymphocytic leukemia/small lymphocytic lymphoma, mantle cell lymphoma, marginal zone lymphoma, Waldenström macroglobulinemia
Relevant adverse reactions	Peripheral neuropathy, neuralgia, paresthesia, dizziness, infection (herpes zoster reactivation, urinary tract, bacteremia, listeriosis, toxoplasmosis, pneumonia, and sepsis), thrombocytopenia, neutropenia, anemia, leukopenia, asthenia, dyspnea, fever	Thrombocytopenia [US boxed warning], neutropenia [US boxed warning], thromboembolic events (thromboprophylaxis recommended) [US boxed warning], teratogenic [US boxed warning], infection (urinary tract, upper respiratory tract, sepsis, bacteremia, fungal, influenza, and renal), leukopenia, anemia, muscle spasm, asthenia, arthralgia, back pain, muscle cramps, limb pain	Neutropenia, thrombocytopenia, anemia, serious infection (fungal, pneumonia, sepsis, upper respiratory tract, pleural, skin, cellulitis, sinusitis, <i>Streptococcal</i> endocarditis, subcutaneous abscess, and urinary tract), peripheral edema, decreased hemoglobin, petechiae, second primary malignant neoplasm, tendinitis, tenosynovitis, arthralgia, musculoskeletal pain, muscle spasm, asthenia, arthropathy, falls, fever, atrial fibrillation, atrial flutter, ventricular tachycardia, postprocedural hemorrhage, abnormal platelet aggregation, peripheral neuropathy, reactivation of HBV, renal failure syndrome, Stevens-Johnson syndrome, tumor lysis syndrome
Monitoring parameters	Obtain CBC with differential and platelets, liver function tests (dosage adjustments may be needed), and blood glucose levels. Monitor tumor response to therapy. Watch for signs of tumor lysis syndrome (elevated uric acid, potassium, phosphate, hypocalcemia, or acute renal failure) or worsening cardiac function, particularly heart failure. Monitor for peripheral neuropathy, postural hypotension, dehydration, and infections. Monitor for visual or neurologic symptoms and consider MRI if they develop. Be alert to the potential for reactivation of herpes.	Obtain CBC with differential, serum creatinine, liver function test, and thyroid function tests. Dosage adjustment may be needed in patients with renal impairment. Obtain ECG when clinically needed. Screen patients for lactose intolerance before therapy. Assess other drugs the patient may be taking; alternate therapy or dosage adjustments may be needed. Assess for signs and symptoms of adverse effects.	Obtain CBC (monthly), renal function tests, liver function tests, and uric acid. Obtain ECG before initiation in patients with cardiac risk factors. Assess other medicines the patient may be taking; alternate therapy or dosage adjustments may be needed. Assess for signs and symptoms of bleeding, infections, progressive multifocal encephalopathy, tumor lysis syndrome, atrial fibrillation, and secondary malignancies.

CBC, complete blood count; MRI, magnetic resonance imaging; ECG, echocardiogram.

high-risk patients receive low-molecular-weight heparin or vitamin K antagonists during lenalidomide treatment [16]. Dexamethasone is used in combination with bortezomib and/or lenalidomide in the treatment of refractory MM (Vd, Rd, or VRd protocols). It is thought that in this role, dexamethasone aids in the apoptosis of MM cells. However, high-dose dexamethasone when administered with lenalidomide has shown to lead to an increase in incidence of DVT, pulmonary embolus, infection, pneumonia, and mortality when compared with low-dose dexamethasone [23].

Ibrutinib is an orally administered chemotherapeutic agent that leads to apoptosis of Waldenström macroglobulinemia cells that have high expressivity of the MYD88^{L265P} cell surface protein. Adverse effects include neutropenia, thrombocytopenia, anemia, serious infection (fungal, pneumonia, sepsis, pleural, skin, cellulitis, sinusitis, *Streptococcal* endocarditis, subcutaneous abscess, and urinary tract), tenosynovitis, and arthralgias. Owing to the increased risk of bleeding, it is recommended that patients with a

history of bleeding diathesis be tested for von Willebrand activity before initiation, and ibrutinib should be held 3–7 days before and after surgery. Ibrutinib should not be administered to patients already receiving anticoagulation therapy for comorbidity. Antimicrobial prophylaxis should be considered in patients receiving ibrutinib who are at risk for opportunistic infection [24–29].

Knowledge of the increased risks of pancytopenia, DVT, and infection is important to both the treating cancer physician and the consulting orthopaedic surgeon. Given the propensity of these drugs to cause neutropenia or pancytopenia, the suspicion for infection must remain high during and after chemotherapy treatment.

Diagnosis, treatment, and postoperative complications

Obtaining a thorough history of prior total joint arthroplasty will give clues to clinical oncologists to potential at-risk sites for

infection. It is critical for patients and clinicians to act quickly if the knee or hip suddenly becomes swollen and/or painful. All 4 patients presented with at least 1 of the well-established signs and symptoms of PJI. All 4 had elevated synovial WBC counts and met either the MSIS major or minor criteria for PJI diagnosis. Two patients had pancytopenia and 3 patients had low or low-to-normal serum neutrophil levels at the time of PJI diagnosis. The cases of neutropenia and pancytopenia were thought to be secondary to chemotherapy, but it is difficult to know whether the cause was a result of the chemotherapy, the hematologic malignancy, or a side effect of the PJI. Although neutropenia and pancytopenia may pose potential challenges to the orthopaedic surgeon when diagnosing PJI, the standard MSIS criteria appears to be an effective diagnostic tool in this patient population based on our small sample size.

In these cases, we used an operative treatment algorithm for PJI similar to that for patients who have not recently received chemotherapy. The 1 patient who initially presented with signs and symptoms of chronic PJI was successfully treated with a 2-stage approach. Of the 3 patients diagnosed with acute PJI, 2 were successfully treated with DAIR. The patient who failed DAIR (case 3) subsequently underwent removal of implants and placement of a well-functioning articulating spacer. Owing to being considered a class C host, the decision was made to forgo stage 2 reimplantation. The articulating spacer has so far survived and functions well for this patient. Patients with sudden onset of symptoms and acute infection are thought to be candidates for implant retention, and this seemed to be a reasonable approach in our population despite perioperative immunosuppression and the necessity for additional chemotherapy after surgery. However, the exact DAIR methodology that provides the greatest success for immunosuppressed patients remains unclear. Irrigation with Betadine (Avrio Health L.P.; Stamford, CT, USA) and chlorhexidine seems to be the most effective approach in preventing infection recurrence [30,31]. A 2-stage DAIR approach with the use of antibiotic-eluting beads may help improve results in this patient population [32]. DAIR should remain contraindicated in the setting of chronic PJI in patients with malignancy.

None of the patients in this study developed surgical complications such as hematoma or delayed wound healing because of pancytopenia. However, postoperative DVT occurred in 2 (50%) of our cases. The patient in case 2 had a history of DVT and had a recent history of infection at a separate site. He did not develop DVT during chemotherapy but developed DVT after PJI treatment. The patient in case 3 had a history of DVT, had a recent history of infection at a separate site, and had taken lenalidomide before PJI development. She also did not develop DVT during chemotherapy but developed DVT after PJI treatment. More aggressive postoperative anti-DVT agents may be warranted in patients who have recently received chemotherapy for hematologic malignancies and subsequently develop PJI—especially in those who also have a recent history of or active infection at a separate site, a history of DVT, and/or have recently received lenalidomide.

Based on the results of these cases, DAIR and 2-stage revision TKA are indeed viable surgical treatment options for immunosuppressed patients with hematologic malignancies. Early detection, early referral, and timely treatment of acute PJI with DAIR can potentially alleviate the need for 2-stage revision, reduce cost, and decrease comorbidity in this patient population.

PJI prophylaxis

The American Society of Clinical Oncology and the Infectious Diseases Society of America currently recommend antifungal and antibiotic prophylaxis with a fluoroquinolone for patients who are at high risk for febrile neutropenia or profound, protracted

neutropenia (<100 neutrophils/ μ L for >7 days), which includes most patients with myelodysplastic syndromes [33]. Long-term suppressive antibiotic therapy has been used in cases of vascular graft and cardiovascular implantable electronic device infections; however, data on treatment success and long-term survival are limited [34].

All 4 patients received at least 6 weeks of empiric or organism-specific antibiotics after surgical treatment for PJI. Three patients then received subsequent long-term suppressive antibiotics; however, 1 of the 3 patients (case 3) discontinued antibiotics (owing to adverse effects) for approximately 4 months after definitive surgical treatment. All 4 of our patients remained free of recurrent PJI at the most recent follow-up.

The role of long-term suppressive antibiotics after PJI treatment in patients who require further chemotherapy is undefined. In addition, given the propensity for certain chemotherapy agents discussed to cause neutropenia and infection, the current practice of recommending antimicrobial prophylaxis concomitantly during chemotherapy treatment for some blood cancers but not others is intriguing. Large multicenter studies are needed to further investigate the risks and benefits of long-term suppressive antibiotics after PJI treatment. Studies on the incidence and risk of PJI after chemotherapy treatment for hematologic malignancies would also be useful to determine if and when antimicrobial prophylaxis is warranted to prevent PJI during certain periods of a chemotherapy cycle or with particular combination of chemotherapeutic agents.

Summary

This study reviews 4 patients treated with chemotherapy for a hematologic malignancy who subsequently developed TKA PJI. Chemotherapy agents taken before PJI development included bortezomib and/or lenalidomide with or without dexamethasone, and ibrutinib. Routine clinical and laboratory evaluation for evidence of joint infection appears to be effective in diagnosing acute PJI, even in patients with pancytopenia secondary to chemotherapy. Patients with previous TKA who subsequently require chemotherapy for hematologic malignancies can benefit from either DAIR for acute PJI or a 2-stage approach for chronic PJI. Rates of failure in this small study did not seem to vary significantly from the literature. Patients who receive chemotherapy agents that increase the risk of DVT, including lenalidomide, should receive appropriate thrombolytic prophylaxis for the duration of their chemotherapy treatment. We recommend that all patients treated for PJI after receiving chemotherapy for a hematologic malignancy receive long-term suppressive antibiotics targeted against the culprit organism if identified, especially if chemotherapy will be resumed postoperatively.

Conflict of interest

G. Bloom: None; S. Mears: Delta Ortho LLC: Stock or stock Options, Fragility Fracture Network: Board or committee member, International Geriatric Fracture Society: Board or committee member, Journal of the American Geriatrics Society: Editorial or governing board, SAGE: Editorial or governing board; P. Edwards: DJ Orthopaedics: IP royalties and Paid consultant; C. Barnes: American Association of Hip and Knee Surgeons: Board or committee member, ConforMIS: Research support, DJO: IP royalties, HealthTrust: Paid consultant, HipKnee Arkansas Foundation: Board or committee member, Journal of Arthroplasty: Editorial or governing board, JSOA: Editorial or governing board, Medtronic: IP royalties and Paid consultant, Mid American Orthopaedic Association: Board or committee member, Responsive Risk Solutions: Paid consultant and Stock or stock Options, Southern Orthopaedic Association: Board or committee member, Zimmer: IP royalties; J.

Stambough: American Association of Hip and Knee Surgeons: Board or committee member.

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References

- [1] Ottesen CS, Troelsen A, Sandholdt H, Jacobsen S, Husted H, Gromov K. Acceptable success rate in patients with periprosthetic knee joint infection treated with debridement, antibiotics, and implant retention. *J Arthroplasty* 2019;34(2):365.
- [2] Zhu Y, Zhang F, Chen W, Liu S, Zhang Q, Zhang Y. Risk factors for periprosthetic joint infection after total joint arthroplasty: a systematic review and meta-analysis. *J Hosp Infect* 2015;89(2):82.
- [3] Kuiper JW, Willink RT, Moojen DJF, van den Bekerom MP, Colen S. Treatment of acute periprosthetic infections with prosthesis retention: review of current concepts. *World J Orthop* 2014;5(5):667.
- [4] Lidgren L. Chronic inflammation, joint replacement and malignant lymphoma. *J Bone Joint Surg Br* 2008;90-B(1):7.
- [5] Morrison TA, Figgie M, Miller AO, Goodman SM. Periprosthetic joint infection in patients with inflammatory joint disease: a review of risk factors and current approaches to diagnosis and management. *HSS J* 2013;9(2):183.
- [6] Ji B, Zhang X, Xu B, et al. The fate of immunocompromised patients in the treatment of chronic periprosthetic joint infection: a single-centre experience. *Int Orthop* 2018;42(3):487.
- [7] George MD, Baker JF, Hsu JY, et al. Perioperative timing of infliximab and the risk of serious infection after elective hip and knee arthroplasty. *Arthritis Care Res (Hoboken)* 2017;69(12):1845.
- [8] Berbari EF, Osmon DR, Lahr B, et al. The Mayo prosthetic joint infection risk Score: implication for surgical site infection reporting and risk stratification. *Infect Control Hosp Epidemiol* 2012;33(8):774.
- [9] Diaz-Ledezma C, Baker J, Parvizi J. "Warning signs" of primary immunodeficiency among patients with periprosthetic joint infection. *J Appl Biomater Funct Mater* 2014;12(2):65.
- [10] Parvizi J, Zmistowski B, Berbari EF, et al. New definition for periprosthetic joint infection: from the workgroup of the musculoskeletal infection society. *Clin Orthop Relat Res* 2011;469(11):2992.
- [11] Safdar A, Armstrong D. Infections in patients with hematologic neoplasms and hematopoietic stem cell transplantation: neutropenia, humoral, and splenic defects. *Clin Infect Dis* 2011;53(8):798.
- [12] Kao FC, Hsu YC, Lai PY, Wang CB, Tu YK, Chen WK. One-year mortality and Periprosthetic infection rates after Total knee Arthroplasty in Cancer patients: a population-based cohort study. *BMC Cancer* 2018;18(1):1.
- [13] Accardi F, Toscani D, Bolzoni M, Dalla Palma B, Aversa F, Giuliani N. Mechanism of action of bortezomib and the new proteasome inhibitors on myeloma cells and the bone microenvironment: impact on myeloma-induced alterations of bone remodeling. *Biomed Res Int* 2015;2015:172458.
- [14] Lonial S, Waller EK, Richardson PG, et al. Risk factors and kinetics of thrombocytopenia associated with bortezomib for relapsed, refractory multiple myeloma. *Blood* 2005;106:3777.
- [15] Wu KL, Heule F, Lam K, Sonneveld P. Pleomorphic presentation of cutaneous lesions associated with the proteasome inhibitor bortezomib in patients with multiple myeloma. *J Am Acad Dermatol* 2006;55(5):897.
- [16] Bringhen S, De Wit E, Dimopoulos MA. New agents in multiple myeloma: an examination of safety profiles. *Clin Lymphoma Myeloma Leuk* 2017;17(7):391.e5.
- [17] Bortezomib. In: Lexi-drugs online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2019. <http://online.lexi.com>. [Accessed 1 May 2020]. Subscription required to view.
- [18] Fink EC, Ebert BL. The novel mechanism of lenalidomide activity. *Blood* 2015;126(21):2366.
- [19] Dimopoulos MA, Richardson PG, Brandenburg N, et al. A review of second primary malignancy in patients with relapsed or refractory multiple myeloma treated with lenalidomide. *Blood* 2012;119(12):2764.
- [20] Qiao SK, Guo XN, Ren JH, Ren HY. Efficacy and safety of lenalidomide in the treatment of multiple myeloma: a systematic review and meta-analysis of randomized controlled trials. *Chin Med J (Engl)* 2015;128(9):1215.
- [21] Ying L, YinHui T, Yunliang Z, Sun H. Lenalidomide and the risk of serious infection in patients with multiple myeloma: a systematic review and meta-analysis. *Oncotarget* 2017;8(28):46593.
- [22] Lenalidomide. In: Lexi-drugs online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2019. <http://online.lexi.com>. [Accessed 1 May 2020]. Subscription required to view.
- [23] Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial [published correction appears in *Lancet Oncol*. 2010 Jan;11(1):14]. *Lancet Oncol* 2010;11(1):29.
- [24] Treon SP, Gustine J, Meid K, et al. Ibrutinib monotherapy in symptomatic, treatment-naïve patients with Waldenström macroglobulinemia. *J Clin Oncol* 2018;36(27):2755.
- [25] Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenström's macroglobulinemia. *N Engl J Med* 2015;372(15):1430.
- [26] Abeykoon JP, Zanzwar S, Ansell SM, et al. Ibrutinib monotherapy outside of clinical trial setting in Waldenström macroglobulinemia: practice patterns, toxicities and outcomes. *Br J Haematol* 2020;188(3):394–403.
- [27] Papanota AM, Ntanasis-Stathopoulos I, Kastritis E, Dimopoulos MA, Gavriatopoulou M. Evaluating ibrutinib in the treatment of symptomatic Waldenström's macroglobulinemia. *J Blood Med* 2019;10:291.
- [28] Varughese T, Taur Y, Cohen N, et al. Serious infections in patients receiving ibrutinib for treatment of lymphoid cancer. *Clin Infect Dis* 2018;67(5):687.
- [29] Ibrutinib. In: Lexi-drugs online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2019. <http://online.lexi.com>. [Accessed 1 May 2020]. Subscription required to view.
- [30] Kavolus JJ, Schwarzkopf R, Rajae SS, Chen AF. Irrigation fluids used for the prevention and treatment of orthopaedic infections. *J Bone Joint Surg Am* 2020;102(1):76.
- [31] Blom A, Cho J, Fleischman A, et al. General assembly, prevention, antiseptic irrigation solution: proceedings of international consensus on orthopedic infections [published correction appears in *J Arthroplasty*. 2019 Jun;34(6):1299]. *J Arthroplasty* 2019;34(2S):S131.
- [32] Chung AS, Niesen MC, Graber TJ, et al. Two-stage debridement with prosthesis retention for acute periprosthetic joint infections. *J Arthroplasty* 2019;34(6):1207.
- [33] Taplitz RA, Kennedy EB, Bow EJ, et al. Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression: ASCO and IDSA clinical practice guideline update. *J Clin Oncol* 2018;36(30):3043.
- [34] Lau JSY, Korman TM, Woolley I. Life-long antimicrobial therapy: where is the evidence? *J Antimicrob Chemother* 2018;73(10):2601.