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Case Report

When prosthetic joint infection may lead to premalignant colorectal lesion detection

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ABSTRACT

Osteoarthritis (OA) is a common musculoskeletal disorder that affects millions of people worldwide, and total knee arthroplasty (TKA) is a common treatment for advanced OA. However, joint replacement surgeries may lead to complications such as deep vein thrombosis (DVT), surgical site infection, and prosthetic joint infection (PJI). Our objective is to discuss a *Streptococcus bovis* group (SBG) PJI case after TKA and its possible consequences in clinical practice. We describe a 67-year-old female who underwent TKA and developed initial complications including wound hematoma, symptomatic anemia, and acute DVT. Further investigations because of knee pain persistence and inflammatory signs post TKA revealed the presence of *Staphylococcus aureus* in the synovial and scar tissues from the knee and SBG in the periprosthetic membrane from the revision surgery, as well as mitral infective endocarditis and a large stenosing villous polypoid lesion in the ascending colon. SBG osteoarticular infection post TKA is a rare condition, but it may be associated with severe diseases. This article highlights the link between SBG and colorectal cancer (CRC) and emphasizes the importance of an echocardiogram and a colonoscopy for early detection and prompt treatment of infective endocarditis and CRC. This diagnostic workup should be performed even in the absence of symptoms, for early diagnosis and increased chance of cure. A multidisciplinary approach, involving orthopedists, infectious disease specialists, cardiologists, and gastroenterologists, among others, is advised to effectively manage SBG infections and improve patient outcomes.

Keywords: Knee OA, TKA, Prosthesis-related infections, Infective endocarditis, CRC

INTRODUCTION

Osteoarthritis (OA) is a prevalent musculoskeletal disorder with a substantial biopsychosocial effect on individuals' daily functioning, resulting in notable pain and disability and engendering significant individual, societal, and economic consequences.[1,2] According to the Global burden of disease 2019, OA ranks as the 15th leading contributor to years lived with disability (YLD) and the knee joint is the most frequently affected site of OA.[3] OA is influenced by a range of risk factors, such as obesity, advanced age, female gender, past joint injury, joint malalignment, genetic predisposition, and reduced muscle mass.[4] In addition, due to the aging populations and increasing obesity rates in countries, the incidence of OA is projected to continue rising.[5,6]

Zhuo et al nominated metabolic OA as the fifth component of metabolic syndrome (MetS) and warned that proper treatment of MetS is essential for arthritic knee pain

management.[7] For patients with advanced knee OA, TKA is usually regarded as a safe and successful treatment option. Complications could occur both during and after TKA, though. These include hazards associated with anesthesia, comorbidities' decompensation, adverse drug responses, and problems specifically associated with the surgery. Related risks include DVT, surgical site infection, and perioperative blood loss.[8,9]

Periprosthetic joint infection (PJI) after TKA occurs in 1-3% of cases worldwide, and invariably requires lengthy and costly treatment.[10] The bacteria can reach the joint space through direct inoculation during surgery, from a nearby infection in the soft tissue around the knee or by the migration of bacteria from a distant site in the body through the bloodstream into the joint space surrounding the knee prosthesis. This is known as hematogenous spread of infection. Once the bacteria settle around the prosthesis, they form a biofilm, which makes it difficult for the body's immune system and antibiotics to eliminate the infection. The pathophysiology of periprosthetic joint infection involves a complex interplay between host factors, bacteria, and the implant. Host factors such as diabetes, obesity, immunosuppression, and poor nutrition can increase the risk of infection by impairing the immune response and reducing the body's ability to fight infection. Bacterial factors such as virulence and antibiotic resistance also play a role in the development of infection. The type of prosthesis used can also affect the risk of infection. For example, there is some evidence that metal-to-metal hinged-knee prostheses are more frequently infected than metal-to-plastic prostheses. Factors related to the surgical procedure, like lack of appropriate antibiotic surgical prophylaxis, prolonged surgical duration, hematoma formation and wound dehiscence are also known risk factors for PJI.[11]

The SBG constitutes a group of bacteria that have been associated with infections in animals and humans. It has been linked to septicemia, infective endocarditis (IE), meningitis, biliary infections, urinary tract infections in people.[12-16] These latter infections have been linked to septic arthritis, both native and prosthetic, spondylodiscitis, and osteomyelitis.[17-20]

SBG species underwent major taxonomic changes in the late 1990s and early 2000s, which led to the renaming of *S. bovis* biotype I as *Streptococcus gallolyticus subsp. gallolyticus;* biotype II/1 as *S. lutetiensis* (i.e. *S. infantarius subsp. infantarius*); and biotype II/2 as *S. gallolyticus subsp. pasteurianus*.[21,22] *Streptococcus gallolyticus* subgroups are also linked to colonic cancer, according to numerous studies; however, they are less common than *Streptococcus gallolyticus subsp. gallolyticus*.[23,24] Numerous clinicians are still ignorant of the new speciation years later, in part because conventional methods frequently cannot ensure accurate and complete classification of SBG species, as well as of other members of the *viridans* group *Streptoccocci*.[25,26] So, even though we recognize the importance of drawing attention to this nomenclature actualization, throughout the text we will use the acronym SBG, unless the new classification is specified.

This article objective is to discuss a SBG PJI case after TKA and its possible consequences in clinical practice.

CASE REPORT

Female patient, 67 years old, with hypertension, dyslipidemia, overweight (body mass index 26), and hypothyroidism, presented with pain, edema, and functional limitation in both knees, worse on the right, due to OA. She underwent a right posterior stabilized TKA without patellar resurfacing at the Brazilian national institute of traumatology and orthopedics on September 19th, 2016**.** In the immediate postoperative period, she developed a wound hematoma (conservative treatment) and symptomatic anemia requiring a blood transfusion on September 23rd, 2016, with no complications. In addition, she presented with acute DVT of the soleal veins on the 7th postoperative day (September 26th, 2016), which was treated with full-dose enoxaparin (for a total of 3 months). She was discharged from the hospital 10 days after surgery.

As she still presented significant right knee anterior pain and patellar crepitus months after the arthroplasty, with elevated inflammatory blood markers, we performed the patellar resurfacing with right knee joint aspiration to investigate periprosthetic infection 7 months after the primary TKA. Culture's results were negative at that time.

Twenty months after the primary TKA (May 22nd, 2018), due to persistent pain, limited range of motion, and swelling, we performed an arthrotomy for releases of arthrofibrosis on the right knee, with open biopsy and collection of synovial and scar tissues, both of which were positive for *Staphylococcus aureus*.

The patient was readmitted for a thorough surgical debridement, and prosthesis removal surgery, with the placement of an articulated prefabricated antibiotic knee spacer (Subiton®, Buenos Aires, Argentina), combined with gentamycin impregnated cement-coated intramedullary Kirschner wires, both in tibia and femur, and intravenous antibiotic therapy. The culture of the periprosthetic membrane from this revision surgery showed growth of a streptococci identified as *Streptococcus bovis* (Automated microbial identification and antimicrobial susceptibility testing system: MicroScan WalkAway 96 Plus - Beckman Coulter, Brea, CA, USA).

To investigate associated infective endocarditis, a transthoracic echocardiogram was performed, which showed a mitral valve with slight regurgitation and a tiny filamentary image adhered to the atrial surface, without valve dysfunction. Given the association of the SBG with intestinal neoplasms, colonoscopy was performed and revealed a large stenosing villous polypoid lesion in the

ascending colon, whose biopsy was compatible with a high-grade dysplastic villous adenoma, later treated with partial colectomy and ileocolonic anastomosis.

The antibiotic treatment initially consisted of amikacin plus linezolid (empiric treatment) for 13 days. After culture results, the treatment was changed to sulfametoxazol-trimetoprim plus levofloxacin for 6 days. After the echocardiogram image suggestive of infective endocarditis, treatment was changed to oxacillin, ampicillin, gentamicin and rifampin. Gentamycin was discontinued after 14 days. On October 17th 2018, oxacillin was replaced for daptomycin due to diarrhea. The patient was discharged on November 8, 2018, with home antibiotic therapy for 6 months with levofloxacin 750mg once a day associated with rifampicin 300mg every 12 hours, with operative wound healing in less than 1 month after the first stage revision surgery of the TKA. On November 12th, 2020, the second stage TKA revision was performed with rotating-hinge knee implants (Zimmer Biomet®, Warsaw, IN, USA), with negative cultures, and a control transthoracic echocardiogram showed no more signs of bacterial endocarditis. In 2023 a new colonoscopy showed erosion lesions around the ileocolonic anastomosis and transverse colon. The histopathologic study of the biopsy of these lesions showed no malignancy, parasites, or granulomas. On July 05th 2023 the patient walks without assistance, with a favorable functional evolution, with a stable knee, range of motion from 0 to 100 degrees, without signs of inflammation, and occasional pain in the knee with more vigorous movements.

DISCUSSION

The reported case describes a 67-year-old woman who presented positive knee cultures for *Staphylococcus aureus* and *Streptococcus bovis* two years after primary TKA. Investigations revealed associated endocarditis and a partially obstructive premalignant bowel lesion.

There are few studies on the epidemiology and pathophysiology of infective endocarditis due to SBG. Massaroni et al concluded that there is a higher prevalence of gastrointestinal tract diseases in patients with SBG infective endocarditis.[27] In addition, they reported the death rate due to SBG infective endocarditis was 7.7%, due to cardiac complications, and the evolution was unfavorable in younger male patients (mean age 52 years±5.35), and with left native valvular endocarditis. The sensitivity of transthoracic and transesophageal echocardiography in detecting endocarditis proved to be a good test for diagnosing endocarditis due to SBG.[27]

The link between *S. gallolyticus* subsp. *gallolyticus* and CRCs appears to be causal, but the function of *S. gallolyticus* subsp. *gallolyticus* in cancer is not entirely understood. A review article by Boleij et al iscusses the association between *S. gallolyticus* subsp. *gallolyticus* and CRC, suggesting that bacterial factors such as adhesion molecules and biofilm formation may contribute to the development of CRC in these patients.[23] Abdulamir et al describes various pro-carcinogenic properties of *S. gallolyticus* subsp. *gallolyticus*, including its proinflammatory potential, leucocytic recruitment, selective adhesion and colonization in tumor cells, proliferation in tumor microenvironments, disruption of tumor tissues and capillaries allowing entry into blood circulation, and induction of cytokines and transcriptional factors such as IL-1, IFN-g, IL-8, and NFkB.[28] These findings collectively suggest that *S. gallolyticus* subsp. *gallolyticus* is most likely responsible for the slow progression of colorectal mucosal tissue carcinogenesis. Furthermore, *S. gallolyticus* subsp. *gallolyticus*-induced carcinogenesis appears to occur through the transformation process from normal tissue to premalignant lesions, adenomas, and finally malignant cancerous tissues.[28] It is unknown why this should apply to *S. gallolyticus* subsp. *gallolyticus* but not to other organisms. Some scientists have hypothesized that S. *gallolyticus* subsp. *gallolyticus* may create a toxin that causes intestinal cancer.[29,30]

CRC is the third most common malignancy, and it is the second deadliest cancer worldwide. Some risk factors include smoking, overweight or obese body weight, diabetes, lack of regular physical activity, and poor diet.[31] Emerging studies have analyzed the role of the intestinal microbiota-the "forgotten organ"- in colorectal carcinogenesis and the microbiome alterations even in colorectal adenoma, the early stage of CRC.[32,33] Karpinski et al reviewed the bacteria linked to the development of CRC and the carcinogenic mechanisms of action mediated by them.[30] The associated organisms were *Bacteroides fragilis*, *Clostridium* spp., *Enterococcus faecalis*, *Escherichia coli*, *Fusobacterium nucleatum*, *Helicobacter pylori*, *Peptostreptococcus anaerobius*, *Streptococcus gallolyticus* group and sulfate-reducing bacteria. Besides, bacteremia from CRC-associated species may warrant colorectal workup to look for neoplasic lesions.[34]

Few reports in literature points out the link between osteoarticular infections (septic arthritis of native joints) caused by SBG and colon cance.[35,36] As far as we know this is the first case of SBG PJI leading to a colorectal premalignant lesion diagnosis described in literature.

CONCLUSION

SBG osteoarticular infection post TKA is a rare condition, but it may be associated with severe diseases, such as infective endocarditis and CRC. A diagnostic workup including an echocardiogram and a colonoscopy should be performed, even in the absence of symptoms, for early detection and prompt treatment, to increase the chance of cure. A multidisciplinary approach, involving orthopedists, infectious disease specialists, cardiologists, and gastroenterologists, among others, is advised to effectively manage SBG infections and improve patient outcomes.

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