Date of submission: 31 December 2020

Date of acceptance: 26 April 2021

Date of online publication: 11 June 2021

~ Case Report ~

Post-Operative Wound Infection in the Context of Immunosuppression.

Sarah Noonan

Doctor of Medicine
4th year of 4 year degree
University of Wollongong
Student

Electronic submission

I aspired to a career in medicine because it is the highest pursuit for someone who loves problem solving and continual learning. I have a strong commitment to rural communities and I look forward to a long career in rural medicine. I am from a rural background and chose to undertake my studies at UOW for their strong rural connection. I further undertook many clinical placements in rural and remote communities and consider myself a rural health advocate. I would eventually like to further my career into rural paediatric medicine. I have always held an interest in this field as seen by my previous research in paediatric immobilisation in medical imaging as well as rural induction of labour.

Keywords: Post-operative, Infection, Immunosuppression, Surgical, DMARDs.

Word Count: 1498
Abstract word count: 129

Tables: 1

Abstract

Introduction: Surgical site infections remain one of the most common complications associated with surgery in Australia and the world. Many factors contribute to infection risk, however, immunosuppressive and immunomodulatory drugs such as DMARDs, biological DMARDs and glucocorticoids pose a unique risk.
Case Overview: A 70-year-old female developed a surgical site infection post-repair of a ruptured achilles tendon. She had a background of psoriatic arthritis treated with immunosuppressive agents which were not ceased prior to the surgical treatment.
Discussion Overview: The current literature suggests that biologic DMARDs and glucocorticoids increase the risk of surgical site infections in patients undergoing a procedure. It is therefore imperative to emphasize the importance of careful medication histories and recognition of medication side effects with a risk versus benefit balance.

Introduction

Surgical site infections are healthcare-associated infections that occur after a surgical incision. They are one of the most common complications associated with surgery and in Australia, occurring in approximately 3% of surgical patients [1]. Surgical site infections contribute significantly to adverse clinical outcomes, increased morbidity and mortality as well as increased healthcare costs [1].

Many factors contribute to infection risk, including perioperative antibiotic use, surgical experience and technique, post-operative care and patient characteristics [2]. The single most important risk factor for surgical site infections remains a history of prior surgical site infection or skin infection. However, immunosuppressive and immunomodulatory drugs used in the treatment of inflammatory conditions pose a unique risk for some patients [2].

Immunosuppressive and immunomodulatory drugs such as conventional disease-modifying antirheumatic drugs (DMARDs), biologic DMARDs including tumour necrosis factor (TNF) alpha antagonists and glucocorticoids are indicated for the treatment of inflammatory arthritic conditions and inflammatory bowel disease to name a few [3]. Commonly used conventional DMARDs include methotrexate and leflunomide. Biologic DMARDs are usually only prescribed after the failure of treatment with a conventional DMARD therapy [3].

The theory that immunosuppressant medications may predispose to postoperative complications and surgical site infections is rooted in their role in inhibiting the inflammatory cascade, a key component of the wound healing process. Via this mechanism of action, it is important to understand that stopping these medications before surgery can lead to a higher chance of flares of the inflammatory condition. A higher dose of glucocorticoid may be required post-surgery to control the inflammation and it may take up to three months for DMARDs and biological DMARDs to become fully effective again. Medication management requires a risk-benefit discussion between patients, surgeons, and physicians [4].

Case

JM, a 70-year-old female, presented to a rural hospital with a one-week history of worsening pain and swelling in the right ankle with general malaise. JM described isolated 7/10 deep, throbbing pain to the achilles tendon. This was on a background of achilles tendonitis after an injury 19 months earlier for which she received physiotherapy. JM then suffered an achilles tendon rupture 11 months ago and surgical repair two months ago receiving five days roxithromycin 150mg orally for infection prophylaxis. The wound was healing well immediately post-operatively.

Past medical history was significant for right total knee replacement nine months prior to achilles tendon rupture which required significant immobilisation and precipitated a right groin DVT. This was being treated with rivaroxaban 20mg daily as treatment. There was a medical history of obesity, hypothyroidism, hypertension, and hypercholesterolaemia for which she was taking levothyroxine 125mcg daily, candesartan/hydrochlorothiazide 32/25mg daily and rosuvastatin 20mg daily. There was an important history of moderate psoriatic arthritis diagnosed at 36 years of age. JM has been taking prednisone 3mg daily, adalimumab 40mg subcutaneously fortnightly and leflunomide 20mg orally daily for many years, although the time-course was unknown. Family history was significant for rheumatoid arthritis in JM's mother and sister. She lived at home with her husband in a rural town three hours from the nearest regional centre. JM was completely independent with activities of daily living and mobilised unaided.

JM was admitted to the rural hospital and treated with intravenous 2g cephazolin. The following day, the wound spontaneously erupted with purulent and bloody discharge from a one centimetre opening over the old excision site. JM experienced continual pain despite analgesia and progressive wound discharge, oedema, and erythema despite intravenous cephazolin and was transferred to a larger referral hospital the following day. She was then taken to theatre for a surgical washout of the achilles wound.

Investigations undertaken on admission to the referral hospital included full blood count demonstrating lymphocytosis with neutrophilia, C-reactive protein raised to 331, and erythrocyte sedimentation rate 99 which were down-trending. A wound swab demonstrated methicillin sensitive Staphylococcus aureus. Radiographic imaging revealed no abnormalities.

On examination post-washout at the referral hospital, JM appeared systemically well. Routine observations were within normal range. A VAC dressing was in situ on the posteromedial right lower leg set to 125mmHg with suction well applied. The VAC foam sat deep to surrounding tissue, suggestive of a deep wound, although difficult to visualise. Erythema and tenderness were noted at the wound borders with a smooth mass felt in the posterior calf, suggestive of an old haematoma. Pitting oedema was evident to the right knee and the right groin was tender to palpation over the femoral triangle. The left leg was normal on examination and peripheries were neurovascularly intact bilaterally. The remainder of the cardiovascular and respiratory exam was normal.

JM continued to deteriorate the following day with much increased pain in the right ankle. The orthopaedic team performed a subsequent wound washout in theatre where the wound was described as clean with granulating tissue at the base. JM continued to improve over the next two days before developing new pain and erythema in the midfoot and distal calf. An MRI of the right ankle demonstrated two infectious collections with draining sinus. Rupture and retraction of calcaneal tendon and fatty

replacement of both heads of the gastrocnemius and soleus were also noted. This led to increased patient dissatisfaction and revealed a lack of understanding surrounding biologic DMARDs and their use in immunosuppression. A subsequent wound swab later demonstrated pseudomonas and the collections were drained under ultrasound guidance. JM was started on oral clindamycin 450mg three times per day while continuing on IV cephazolin 2g four times per day.

JM continued to improve and was discharged home 15 days after transfer to the referral hospital with a plan to follow up in the rural emergency department for VAC dressing changes. Cephazolin was changed to oral cephalexin 500mg four times per day and JM was continued on oral azithromycin 450mg three times per day. JM was to withhold prednisone 3mg daily, adalimumab 40mg fortnightly and leflunomide 20mg daily until a review in two weeks with both the orthopaedics specialist and infectious diseases specialist as an outpatient.

Discussion

Recommendations are outlined by the American College of Rheumatology and the Canadian Rheumatology Association for the perioperative management of immunosuppressed patients. This included continuing DMARDs such as leflunomide and methotrexate without interruption as there is low or no infection risk demonstrated in a systematic review of three clinical practice guidelines and one consensus statement [5, 6]. Stopping therapy, however, may result in a flare of disease and impede recovery from surgery [5, 7].

Recommendations for withholding biologic DMARD before surgery varied from one week to two months for TNF-alpha inhibitors. A systematic review of 12 clinical guidelines and one consensus statement recommended withholding these agents prior to surgery with the exception of the British Society of Rheumatology which suggested that they could be continued. The timeline for withholding therapy should take into account the clinical scenario, type of surgery (e.g. sterile, septic), and patient comorbidities [5]. Six guidelines suggested that the timing for withholding therapy should be based on the pharmacokinetic properties of the agent used while one recommended withholding biologic DMARDs for 3–5 half-lives and TNF-alpha inhibitors' for one dose cycle [8, 9]. Eight guidelines recommended that biologics may be restarted postoperatively if there is no evidence of infection and wound healing is satisfactory. A Spanish guideline suggested waiting 10–14 days [10] and a Japanese guideline recommended with-holding agents for at least two weeks [11].

Biologic DMARDs increased the risk of serious infection compared to conventional synthetic DMARDs [12, 13]. Side effect profiles including infection risk may differ between medications because of different mechanisms of actions or dosing and most research focuses on the use of TNF-alpha inhibitors [2]. A study of 47, 887 cases demonstrated the rate of surgical site infections was 5.7% in patients using TNF-alpha inhibitors and decreased significantly to 2.8% in patients using conventional DMARDs. This was more than the 1.6% rate of surgical site infections in patients with inflammatory disease not using any agents and 0.8% in other surgical patients without any history of inflammatory disease [14]. This study also significantly demonstrated that the risk of post-operative infection was 10 times higher in patients where agents were stopped less than one administration interval before surgery to compared to those stopped more than one administration interval before surgery [14]. Therefore, it should be recommended to cease biologic DMARDs perioperatively in order to decrease risk of surgical site infections as outlined in table 1.

Glucocorticoids including prednisone, methylprednisolone and dexamethasone demonstrate an increased risk of surgical site infection in a dose dependent manner as outlined in table 1 [6]. For patients taking >10mg/day of glucocorticoid, 13.25% experienced post-operative infection compared to 8.76% of patients taking 5-10mg/day and 6.78% of those not taking glucocorticoids in a statistically significant study [2]. Wound healing is also delayed in patients taking glucocorticoids and it is suggested to wean doses to at least <10mg/day [2]. It is suggested to maintain a small dose of glucocorticoid rather than administering perioperative supraphysiologic dose or "stress-dosing" [15].

Surgical site infections remain one of the most common complications associated with surgery in Australia and throughout the world. Immunosuppressive and

immunomodulatory drugs such as DMARDs, biological DMARDs, and glucocorticoids pose a unique risk to surgical patients and highlight the importance of a careful medication history. In addition to this, it is also important to be aware of medications side effects and contra-indications. Once this is considered, there remains a decision to cease or continue medications peri-operatively. The risk must always be weighed against the benefit of continuing medications and as for many inflammatory conditions, the risk of disease flares is often large and debilitating. This is a complex process and often requires the expertise of more than one medical team.

Consent Declaration

Informed consent was obtained from the patient for publication of this case report and accompanying figures.

Acknowledgments

I thank Dr Timothy Gilbey (Murrumbidgee Local Health District) for providing me with the opportunity to complete clinical placements in infectious diseases and introducing me to this case. I thank the Research and Critical Analyses team at the University of Wollongong for encouraging my development of this report.

Learning Points

- It would be appropriate to consider ceasing biologic DMARDs including TNF-alpha inhibitors perioperatively to decrease the risk of surgical site infections in patients taking these agents. The time course of this should be carefully correlated to the pharmacokinetics and half-life of the agent under consideration.
- Glucocorticoids increase the risk of surgical site infections in a dose dependent manner and professionals should consider weaning patients to a dose of <10mg per day.
- Conventional DMARDs have not demonstrated an increase in risk of surgical site infections and these can be safely continued peri-operatively.
- There is a fine balance between the risk of surgical site infections versus benefit of preventing disease flares in ceasing medications perioperatively which often requires the expertise of more than one medial team.

References

1. Australian Commission on Safety and Quality in Health Care. Approach to Surgical Site Infection Surveillance. Sydney: Australian Commission on Safety and Quality in Health Care; 2017. Available from: https://www.safetyandquality.gov.au/sites/default/files/migrated/Approaches-to-Surgical-Site-Infection-Surveillance.pdf.
2. George MD, Baker JF, Winthrop K, Alemao E, Chen L, Connolly S, et al. Risk of Biologics and Glucocorticoids in Patients With Rheumatoid Arthritis Undergoing Arthroplasty. Annals of internal medicine. 2019; 170(12):825-36. Available from: https://www.acpjournals.org/doi/abs/10.7326/M18-2217. DOI: 10.7326/m18-2217.
3. Benjamin O, Bansal P, Goyal A, Lappin SL. Disease modifying anti-rheumatic drugs. StatPearls [Internet]: StatPearls Publishing; 2020. Available from: https://pubmed.ncbi.nlm.nih.gov/29939640/
4. Krause ML, Matteson EL. Perioperative management of the patient with rheumatoid arthritis. World Journal Orthopedics. 2014; 5(3):283-91. Available from: https://pubmed.ncbi.nlm.nih.gov/25035831. DOI: 10.5312/wjo.v5.i3.283
5. Bombardier C, Hazlewood GS, Akhavan P, Schieir O, Dooley A, Haraoui B, et al. Canadian Rheumatology Association recommendations for the pharmacological management of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs: part II safety. The Journal of rheumatology. 2012; 39(8):1583-602. Available from: https://pubmed.ncbi.nlm.nih.gov/22707613/. DOI: 10.3899/jrheum.120165
6. Baker JF, George MD. Prevention of infection in the perioperative setting in patients with rheumatic disease treated with immunosuppression. Current rheumatology reports. 2019; 21(5):17. Available from: https://pubmed.ncbi.nlm.nih.gov/30847768/. DOI: 10.1007/s11926-019-0812-2
7. Goodman SM, Menon I, Christos PJ, Smethurst R, Bykerk VP. Management of perioperative tumour necrosis factor α inhibitors in rheumatoid arthritis patients undergoing arthroplasty: a systematic review and meta-analysis. Rheumatology (Oxford, England). 2016; 55(3):573-82. Available from: https://pubmed.ncbi.nlm.nih.gov/26447162/. DOI: 10.1093/rheumatology/kev364
8. Royal College of Nursing: Rheumatology Biologics Working Party. Assessing, managing and monitoring biologic therapies for inflammatory arthritis Guidance for rheumatology practitioners. London: The Royal College of Nursing; 2003.
9. Rezaieyazdi Z, Sahebari M, Khodashahi M. Preoperative Evaluation and Management of Patients Receiving Biologic Therapies. The archives of bone and joint surgery. 2019; 7(3):220-8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6578481/.
10. Tornero Molina J, Sanmartí Sala R, Rodríguez Valverde V, Martín Mola E, Marenco de la Fuente JL, González Álvaro I, et al. [Update of the Consensus Statement of the Spanish Society of Rheumatology on the management of biologic therapies in rheumatoid arthritis]. Reumatologia clinica. 2010; 6(1):23-36.
11. Koike R, Harigai M, Atsumi T, Amano K, Kawai S, Saito K, et al. Japan College of Rheumatology 2009 guidelines for the use of tocilizumab, a humanized anti-interleukin-6 receptor monoclonal antibody, in rheumatoid arthritis. Modern rheumatology. 2009; 19(4):351-7. Available from: https://pubmed.ncbi.nlm.nih.gov/19590933/. DOI: 10.1007/s10165-009-0197-6

12. Ito H, Kojima M, Nishida K, Matsushita I, Kojima T, Nakayama T, et al. Postoperative complications in patients with rheumatoid arthritis using a biological agent – A systematic review and meta-analysis. Modern rheumatology. 2015; 25(5):672-8. Available from: https://pubmed.ncbi.nlm.nih.gov/25671400/. DOI: 10.3109/14397595.2015.1014302
13. Franco AS, Iuamoto LR, Pereira RMR. Perioperative management of drugs commonly used in patients with rheumatic diseases: a review. Clinics (Sao Paulo). 2017; 72(6):386-90. Available from: https://pubmed.ncbi.nlm.nih.gov/28658439/. DOI: 10.6061/clinics/2017(06)09
14. Scherrer CB, Mannion AF, Kyburz D, Vogt M, Kramers-de Quervain IA. Infection Risk After Orthopedic Surgery in Patients With Inflammatory Rheumatic Diseases Treated With Immunosuppressive Drugs. Arthritis Care & Research. 2013; 65(12):2032-40. Available from: https://pubmed.ncbi.nlm.nih.gov/23861140/. DOI: 10.1002/acr.22077
15. Goodman SM, Springer B, Guyatt G, Abdel MP, Dasa V, George M, et al. 2017 American College of Rheumatology/American Association of Hip and Knee Surgeons Guideline for the Perioperative Management of Antirheumatic Medication in Patients With Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroplasty. Arthritis & Rheumatology. 2017; 69(8):1538-51. Available from: https://pubmed.ncbi.nlm.nih.gov/28620948/. DOI: 10.1002/art.40149