

Teicoplanin Induced Fever Following Treatment of Septic Knee Arthritis: A Case Report

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Introduction

Although much has been published regarding antibiotic-induced fever, especially with the use of betalactamic antibiotics, an extensive literature search did not identify cases of antibiotic induced fever in patients with a prosthetic joint being treated with Vancomycin or Teicoplanin. We report a case of a female patient who developed antibiotic-induced fever while on a 6-week term therapy of intravenous (IV) teicoplanin for management of an infected total knee replacement.

Case

We present a case of a 71 year old caucasian female patient who developed antibiotic-induced fever while on a 6-week term therapy of IV teicoplanin for management of an infected total knee replacement.

Following admission with a diagnosis of septic knee arthritis (SKA) affecting knee replacement, she underwent an extensive washout, removal of metalwork and cemented nail knee. Following the procedure the patient was started on a 2-week course of IV vancomycin whilst awaiting for culture and sensitivities from the microbiology department. Microbiology recommended continued IV vancomycin. Once medically fit, the patient was discharged with outpatient Teicoplanin therapy IV. One week post discharge the patient returned to emergency department with increased temperature (38.5C). Multiple tests were made (full septic screen, MRI of the affected knee and TC-99M labelled leucocyte scan) to rule out unresolved SKA, all of which came back negative.

After case review and discussion with the microbiology department, the possibility of a teicoplanin induced fever was considered. Teicoplanin was stopped and the temperature spikes ceased.

Conclusion

In conclusion, due to the coincidence in time and exclusion of other possible etiological factors, the reported case of continuous fever was most likely drug-induced. Since the therapy was teicoplanin, and since the fever spikes ceased when teicoplanin was stopped, we conclude that this case is a teicoplanin-induced fever. Since this diagnosis, we have identified another case of teicoplanin-induced fever. As with the case presented, fever ceased after stopping the antibiotic therapy.

Background

Although much has been published regarding antibiotic-induced fever, especially with the use of betalactamic antibiotics [1], an extensive literature search did not identify cases of antibiotic induced fever in patients with a prosthetic joint being treated with Vancomycin or Teicoplanin [2]. We report the case of a female patient who developed antibiotic-induced fever while on 6-week term therapy of IV teicoplanin for management of an infected total knee replacement.

Case Presentation

Our patient is a 71-year-old caucasian female who developed septic arthritis

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in December 2016 following a previous right revision knee replacement, performed in May 2009 for an infected unicompartmental knee replacement secondary to insect bite and cellulitis. Her past medical history includes moderate rheumatoid arthritis managed with analgesia and type 1 diabetes mellitus. At admission, she had chronic kidney disease stage 3. As well as this, she suffered from diabetic foot disease, resulting in multiple toe amputations on her right foot over the preceding 6 months. At the time of admission with infection there was an active infected ulcer. The patient reported intolerance of penicillin-based antibiotics.

Following admission, she underwent an extensive washout, with removal of metalwork and cement, and cemented nail arthrodesis of the knee with antibiotic loaded cement (gentamicin 0.5g/mix and vancomycin 2g/mix cement) as a single stage procedure [3]. Following the procedure, and in keeping with the hospital guidelines for treatment of SKA in a prosthetic joint, the patient was started on a 2-week course of IV vancomycin, aiming at a serum vancomycin level of 15-20mg/dl, whilst awaiting culture and sensitivities from microbiology. Samples taken in theatre grew group B streptococcus (GBS). Because of the patient's penicillin sensitivity, the microbiology department recommended continued IV vancomycin.

Over the 2-week period on the orthopaedic ward, C-reactive protein (CRP) reduced from 373 to a stable value of 9 (Figure 1), leucocytes reduced from $15.02 \times 10^9 /L$ on admission to a value $< 9 \times 10^9 /L$, and the patient was able to fully weight bear on her leg, with pain control provided by paracetamol and codeine. The patient was discharged with outpatient IV Teicoplanin therapy.

One week post discharge the patient returned to emergency department with increased temperature (38.5C) (Figure 2) and a raised CRP (58), with suspected unresolved SKA, so the knee joint was aspirated in theatre.

The fluid aspirated was clear, and the microbiology report said "no organisms grown" (Figure 3). As part of the septic screen, a chest XR was requested, which showed possible pneumonia. The patient started a 5-day course of IV amoxicillin and was transferred to the respiratory ward.

At five days, chest XR showed resolution of the pneumonia although the patient continued to spike temperatures. Unfortunately the patient's adherence to antibiotic therapy was not ideal, and after refusing 3 doses of her antibiotics, she had a peak of CRP levels during this treatment (Figure 1). As per hospital protocols, every time this patient had a temperature peak $> 38^{\circ}C$, blood cultures were taken and sent to microbiology, and all blood culture results showed no organisms.

Risks of further knee surgery were very high and in order to confirm active sepsis around the knee spacer, MRI scan and a TC-99M labelled leucocyte scan [4] were requested. Both investigations were negative. Malignancy was excluded on the basis of normal tumour markers.

After case review and discussion with microbiology, the possibility of a teicoplanin induced fever was considered. Teicoplanin was stopped and the temperature spikes ceased (Figure 4).

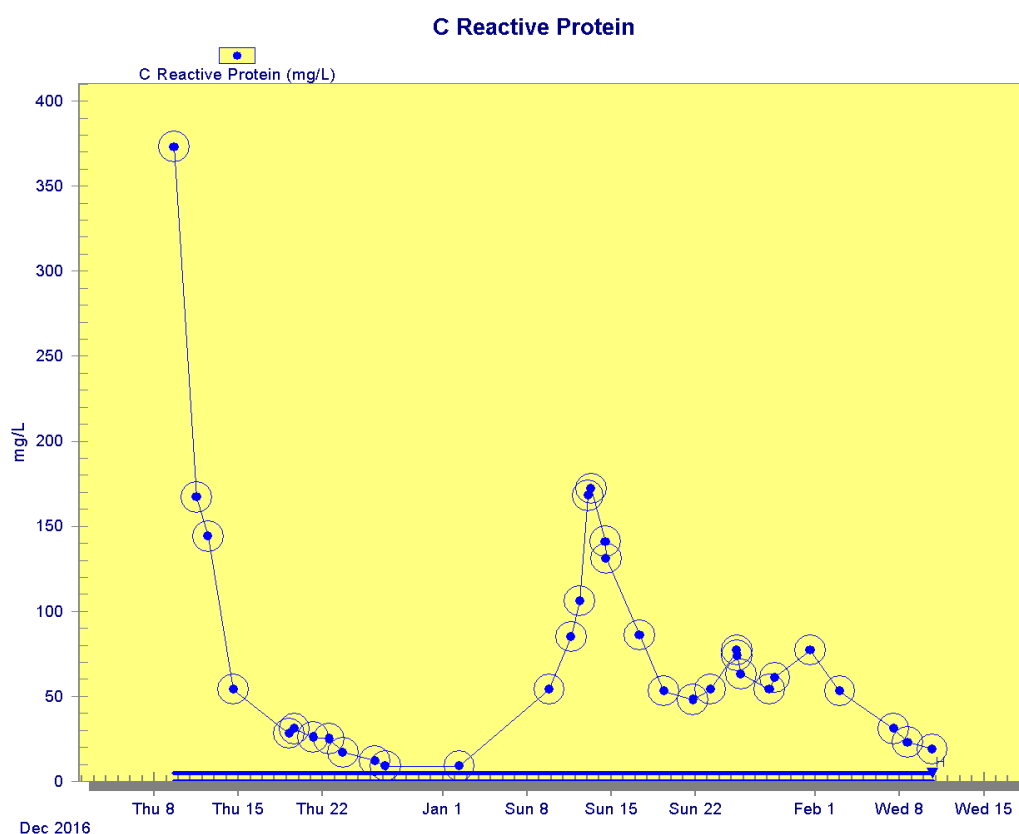


Figure 1: CRP values (mg/L) over the patient's stay in hospital



Specimen Type : Aspirate Knee	
Microscopy	
Gram stain	
Leucocytes	+ (Scanty)
Epithelial cells	Nil
No organisms seen	
Aspirate/Tissue Culture	
No growth	
Extended Anaerobic Culture	
No growth	
Enrichment Broth Culture	
No growth	

Figure 3: Microbiology results from knee aspirate

The patient was discharged from the medical ward, fully weight bearing, with no antibiotics. This patient was seen in the orthopaedic outpatient clinic 4 weeks after discharge, with full blood count, electrolytes, urea and a CRP, all of which were normal.

Discussion

We reviewed the ways antibiotics could induce fever. Pathophysiologically, a drug might cause fever by five principal mechanisms: interference with peripheral heat dissipation, alteration of central temperature regulation, evocation of either a cellular or humoral immune response, exogenous pyrogenicity, and the direct damage of tissues (Table 1) [5].

We found that, for new generation beta-lactams, the aetiology of fever induction could be due to the side chain attached to their core moiety [1]. As for teicoplanin, we could not find

Mechanism	Agents
Altered thermoregulation	Anticholinergic agents (eg., antihistamines, atropine, tricyclic antidepressants), cimetidine
	levothyroxine, monoamine oxidase inhibitors
	phenothiazines, sympathomimetic agents (eg., amphetamine, cocaine, epinephrine, 3,4-methylene dioxymethamphetamine)
	Administration Related
	Amphotericin B, bleomycin, cephalosporins, paraldehyde and pentazocine (intramuscular injection), vaccines and allergic extracts, vancomycin
Pharmacologic action of the drug	Antineoplastic agents (e.g.6-mercaptopurine, bleomycin, chlorambucil, cisplatin, cytosine arabinoside, L-asparaginase, streptozocin, vincristine)
	heparin, penicillin, warfarin
	Idiosyncratic Reaction
Hypersensitivity Reaction	Anesthetic agents (e.g., enflurane, halothane alone or in conjunction with succinylcholine, isoflurane), chloramphenicol, dopamine-2-receptor antagonists (eg., haloperidol, phenothiazines, thiothixene), methyldopa, infururation, primaquinephosphate
	quinidine, quinine, sulfonamides
	Allopurinol, antimicrobial agents, carbamazepine
	heparin, methyldopa, phenytoin, procainamide, quinidine, quinine, sulfonamides

Table 1: Mechanism of drug fever and the agents implicated

any references regarding this matter. We have considered the possibility of an allergic reaction, but given normal eosinophil levels throughout the patient's stay (all readings < 0.5 x10⁹ /L) we believe that this is an idiosyncratic effect of teicoplanin.

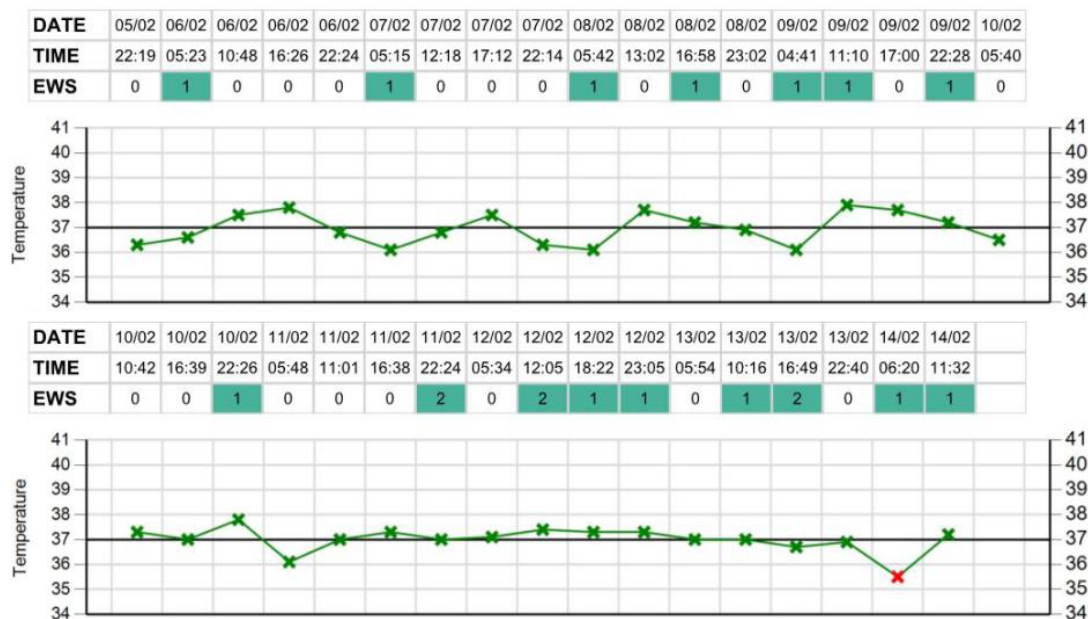


Figure 4 : Temperature values (degrees Celsius) showing resolution of temperature spikes

Conclusions

Due to the coincidence in time and exclusion of other possible etiological factors, the reported case of continuous fever was most likely drug-induced. Since the therapy was teicoplanin, and since the fever spikes ceased when teicoplanin was stopped, we concluded that this case was a teicoplanin-induced fever.

Following this diagnosis, we have identified another case of teicoplanin-induced fever. As with the case presented, fever resolved after discontinuation of antibiotic therapy.

In practice, most clinicians assume a diagnosis of infection when patients present with fever. Management includes a search for an infection with empirical treatment if clinically indicated. This is a process that is logical and safe, but it can lead to the frequent overuse of antibiotics, and high risk surgical procedures.

This case emphasises the importance of being vigilant, particularly when patients don't respond in the way we expect. Careful case review and discussion with colleagues in microbiology is critical so that less common causes of persistent or recurrent fever are identified. In orthopaedics, long term antibiotic treatment is not uncommon and persistent or recurrent fever in the setting of an infected joint replacement may involve further aggressive surgery. We should be vigilant with these patients, and monitor closely once we have discharge them from hospital, so that we do not overlook the possibility of antibiotic induced fever phenomenon.

Declarations

Ethics approval and consent to participate. The patient was

contacted and informed that we want to publish her case to help the scientific community, and to raise awareness about this issue. The patient has given consent to publish, and was also informed that none of the details given were going to be sufficient to identify her.

Regarding Table 1, copyright for use of image has been obtained.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AA - reviewed medical notes and wrote case

SP - read case report and offered input on format and expanded clinical ideas.

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