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Case Study

Doxycycline-Induced Aphthous Ulcer Following Treatment of Bronchopneumonia in an Elderly Patient with Acute Myocardial Infarction – A Rare Adverse Drug Reaction

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ABSTRACT

Background Doxycycline is a broad-spectrum tetracycline antibiotic that is frequently used to treat zoonotic illnesses, skin and soft tissue infections, atypical bacterial infections, and respiratory tract infections. Aphthous ulcers and other uncommon adverse medication responses involving the oral mucosa have been documented, despite the fact that it is usually well tolerated. If not identified right away, drug-induced aphthous ulcers can seriously hinder oral intake, lower medication adherence, and lengthen hospital stays. Pharmacovigilance and early clinical identification are crucial because elderly individuals with various comorbidities who receive polypharmacy are more likely to experience adverse medication responses.Case ReportA 75-year-old woman was diagnosed with Acute Coronary Syndrome-ST Elevation Anterior Wall Myocardial Infarction (ACS-STEAWMI) due to acute thrombotic blockage of the left anterior descending artery after presenting with significant retrosternal chest discomfort. After a successful first percutaneous coronary intervention with drug-eluting stent insertion, she experienced acute kidney injury, bronchopneumonia with Type I respiratory failure, and significant left ventricular dysfunction. Intravenous piperacillin-tazobactam and oral doxycycline were used as empirical antibacterial therapy for bronchopneumonia. The patient experienced trouble swallowing and decreased oral intake after developing several painful aphthous ulcers involving the oral mucosa around two days after beginning doxycycline. while receiving piperacillin-tazobactam treatment. She also experienced temporary heparin-associated haematuria and hypokalaemia while in the hospital, were treated conservatively without stopping vital cardiovascular medication. Both the Naranjo Adverse Drug response Probability Scale and the WHO-Uppsala Monitoring Center causation evaluation classified the adverse drug response as probable.ConclusionThis case demonstrates how doxycycline-induced aphthous ulcers in an elderly patient with numerous comorbidities and polypharmacy

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can be an uncommon but clinically significant adverse medication event. Complete recovery without compromising treatment of the underlying infection was achieved by promptly identifying the temporal link between doxycycline therapy and mouth ulcers, stopping the suspected medication right away, and providing adequate supportive care. This paper highlights the significance of pharmacovigilance, clinical chemist engagement, and interdisciplinary care in detecting rare adverse drug reactions and enhancing patient safety..

INTRODUCTION

Doxycycline is a broad-spectrum, semisynthetic tetracycline antibiotic, is frequently prescribed for the treatment of respiratory tract infections, skin and soft tissue infections, atypical bacterial infections, sexually transmitted infections, and several zoonotic diseases. By reversibly attaching to the 30S ribosomal subunit, it inhibits bacterial protein synthesis and stops microbial growth, so exerting its antimicrobial effect. Despite being typically well tolerated, doxycycline can cause side effects such photosensitivity, hepatotoxicity, oesophagitis, gastrointestinal discomfort, hypersensitivity reactions, and, less frequently, oral mucosal lesions (Brunton et al., 2023). Aphthous ulcers, sometimes referred to as canker sores or recurrent aphthous stomatitis, are painful, shallow ulcerative lesions that affect the oral mucosa that is not keratinised. Immune dysregulation, genetic predisposition, nutritional deficiencies, infections, local trauma, hormonal changes, psychological stress, and adverse drug reactions are thought to be involved in their pathophysiology, which is still unclear. Because drug-induced aphthous ulcers mimic idiopathic aphthous stomatitis in their clinical appearance, they are quite rare and frequently go undiagnosed. The suggested mechanisms include hypersensitivity reactions, immune-mediated inflammatory responses, direct mucosal toxicity, and changes in epithelial cell turnover brought on by the offending drug (Edwards and Aronson, 2000). Doxycycline has been widely used in clinical practice for many years, there are still few documented cases of doxycycline-induced aphthous ulcers in the literature. Early detection of uncommon adverse drug responses is crucial, as evidenced by the temporal correlation between doxycycline administration and the beginning of severe mouth ulcerations, which completely resolve after stopping the medication and receiving supportive care. This study highlights the early recognition, prompt drug withdrawal, and supportive oral care resulted in complete recovery, emphasizing the importance of pharmacovigilance and ADR causality assessment.

Case Description

A 75-year-old woman got admitted due to the complaints of acute retrosternal chest pain that had been present since 2:00 PM that day, along with one episode of vomiting. Although she had risk factors related to advanced age, she had no prior history of ischaemic heart disease. She was admitted with a blood pressure of 130/80 mmHg, a pulse rate of 90 beats per minute, a respiratory rate of 20 breaths per minute, a room air oxygen saturation of 90%, and a random blood glucose level of 255 mg/dL. Upon physical examination, bilateral basal crepts that were suggestive of pulmonary oedema were found. Acute Coronary Syndrome-ST Elevation Anterior Wall Myocardial Infarction (ACS-STEAWMI) was diagnosed after electrocardiography revealed ST-segment elevation in the anterior leads. Due to hypoxemic respiratory failure, the patient was sent right away to the coronary care unit, where emergency stabilisation with non-invasive ventilation (NIV) was started. In accordance with the usual care procedure for ST-elevation myocardial infarction, she was given loading doses of Ticagrelor 180 mg, Aspirin 300 mg, Atorvastatin 80 mg, and intravenous unfractionated heparin 5000 IU.

The patient had an emergency coronary angiography (CAG) via the right radial artery due to the prolonged chest discomfort and continuous ischaemia. And a two-dimensional echocardiogram showed severe left ventricular systolic dysfunction with an ejection fraction of 30%, global hypokinesia involving all myocardial segments except the basal region, and apical ballooning consistent with extensive anterior wall myocardial infarction. During the post-procedural intensive care stay, the patient developed Type I respiratory failure due to bronchopneumonia and cardiorenal acute kidney injury. The laboratory tests showed elevated blood urea (51 mg/dL) and serum creatinine (1.3 mg/dL). Empirical antimicrobial therapy for bronchopneumonia was started, with intravenous Piperacillin-Tazobactam 4.5 g every 8 hours and oral Doxycycline 100 mg twice daily. The patient showed progressive respiratory improvement, with oxygen saturation rising to 97% and complete resolution of fever. However, after about two days of doxycycline therapy revealed multiple painful aphthous ulcers affecting the buccal mucosa and oral cavity. There was no prior history of recurrent aphthous stomatitis, autoimmune disorders, recent viral infection, or local traumatic injury that could account for the lesions.

Doxycycline-induced aphthous ulcer was suspected based on the temporal association between the start of doxycycline therapy and the development of oral ulceration, as well as the lack of other possible causes. As a result, the cardiologist stopped using doxycycline while continuing to provide intravenous piperacillin-tazobactam as a monotherapy to finish the bronchopneumonia treatment. In order to treat the symptoms of the oral ulcers, Zytee oral gel was used locally twice a day to lessen discomfort and inflammation, and Riboflavin 10 mg tablets were taken once a day to promote mucosal healing. Additionally, the patient was instructed to avoid spicy or acidic meals, eat soft, non-irritating foods, and practise good dental hygiene while recovering. The oral lesions showed a favourable de challenge response over the next several days, with a notable decrease in pain and full healing prior to discharge. After receiving a total of 14,000 IU of unfractionated heparin in addition to intracoronary tirofiban and dual antiplatelet therapy during the same hospital stay, the patient developed heparin-associated haematuria, another adverse medication event. The patient was treated conservatively, with close assessment of urine output, diuretic therapy optimisation, rigorous fluid restriction of 1.5–2 L/day, and ongoing monitoring for bleeding symptoms. Without stopping the necessary dual antiplatelet therapy or jeopardising the patency of the coronary stent, the haematuria totally disappeared. Later the laboratory test showed hypokalaemia with a serum potassium value of 3.1 mmol/L, most likely as a result of rigorous diuretic medication. As a potassium-sparing diuretic, tablet Aldactone (Spironolactone) 50 mg once daily was started by the next day, serum potassium had returned to normal at 3.6 mmol/L. Tablet Meljio before bed to enhance the quality of your sleep and Tablet Welmol 1 g for widespread body aches.

After that the patient's clinical condition had considerably improved. She showed full recovery from bronchopneumonia, aphthous ulcers, haematuria, and acute renal injury. She was also haemodynamically stable and maintained normal oxygen saturation without breathing support. Ticagrelor, aspirin, atorvastatin, bisoprolol, Tide Plus, Nodosis, Rabium DSR, and Sucrafil-O syrup were among the medications prescribed by guidelines when she was released. A low-fat cardiac diet, a daily fluid intake of 1.5–2 L, rigorous adherence to prescribed medications, and a follow-up appointment after 16 days were all recommended for her. Both the Naranjo Adverse Drug Reaction Probability Scale and the WHO-Uppsala Monitoring Center causation assessment

rated the reaction as Probable based on the temporal connection, improvement after stopping doxycycline, and lack of other explanations.

DISCUSSION

Doxycyline is a broad-spectrum antimicrobial activity and superior oral bioavailability, doxycycline, a second-generation tetracycline antibiotic, is widely used in the treatment of respiratory tract infections, atypical pneumonia, skin and soft tissue infections, sexually transmitted infections, and a number of zoonotic diseases. Hepatotoxicity, photosensitivity, hypersensitivity reactions, gastrointestinal irritation, oesophagitis, and, in rare cases, oral mucosal lesions are among the side effects of doxycycline, despite the fact that it is typically considered a safe and well-tolerated antimicrobial medication. Because the clinical presentation of drug-induced aphthous ulcer is similar to that of idiopathic recurrent aphthous stomatitis, it is a rare adverse drug reaction that is frequently overlooked. Direct cytotoxic effects on the oral epithelium, delayed hypersensitivity reactions, immune-mediated inflammatory responses, and altered epithelial cell turnover leading to localised mucosal ulcers are among of the suggested reasons, while the precise mechanism is still unknown.

1: Laboratory Investigations

PARAMETER	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6
Haemoglobin	14.2 g/dl	13.8 g/dl	12.1 g/dl	12.18 g/dl	-	-
Total WBC	18,680 cells/cu.mm	-	-	-	-	-
Platelet count	3.46 L/Cu.mm	-	-	-	-	-
Blood Urea	19 mg/dl	23 mg/dl	51 mg/dl	51 mg/dl	58 mg/dl	60 mg/dl
Serum Creatinine	0.9 mg/dl	1.0 mg/dl	1.3 mg/dl	0.9 mg/dl	0.8 mg/dl	0.9 mg/dl
Serum Sodium	137 mmol/L	-	-	141 mmol/L	-	141 mmol/L
Serum Potassium	4.0 mmol/L	4.8 mmol/L	4.4 mmol/L	3.4 mmol/L	3.1 mmol/L	3.6 mmol/L
Bicarbonate	21.0 mmol/L	-	-	26	-	28
Blood Glucose	255 mg/dl	-	150 mg/dl	-	133 mg/dl	-

During hospitalisation for Acute Coronary Syndrome-ST Elevation Anterior Wall Myocardial Infarction (ACS-STEAWMI), the patient experienced painful aphthous ulcers around two days after starting oral doxycycline medication for bronchopneumonia. A clinical examination revealed several painful ulcerative lesions affecting the oral mucosa, which caused severe discomfort and made swallowing difficult. The oral lesions could not be explained by the patient's history of recurrent aphthous stomatitis, autoimmune diseases, malnutrition, recent viral infections, or local traumatic injury. Doxycycline was highly supported as the causal agent by the close temporal link between doxycycline administration and ulcer development, followed by full healing following drug cessation and the start of topical symptomatic therapy. Drug-induced aphthous ulcers are diagnosed mainly through clinical evaluation and meticulous exclusion of other possible causes. After stopping doxycycline on the third day of treatment, the patient's pain gradually decreased and the oral ulcers completely healed before being discharged, with no recurrence. The adverse medication response was classified as Probable/Likely according to the WHO-Uppsala Monitoring Center (WHO-UMC) causality assessment

standards. In a similar vein, the Naranjo Adverse Drug Reaction Probability Scale evaluation revealed a probable causative relationship between doxycycline treatment and the emergence of aphthous ulcers.

In order to guarantee sufficient antibiotic coverage for bronchopneumonia, the adverse medication reaction was managed by stopping doxycycline immediately and continuing intravenous piperacillin-tazobactam. Topical Zytee oral gel, which had local analgesic and anti-inflammatory properties, and Riboflavin 10 mg once daily, which encouraged epithelial regeneration and sped up mucosal healing, were used as symptomatic treatments. The patient also experienced temporary haematuria while in the hospital after receiving a cumulative dosage of unfractionated heparin in addition to intracoronary tirofiban and dual antiplatelet medication. Without stopping necessary antithrombotic medication, the bleeding episode was stopped with close observation, hydration restriction, and supportive care optimisation. Additionally, spironolactone was successfully used to treat hypokalaemia brought on by strong diuretic therapy. Although the prevalence of doxycycline-induced mouth ulcers is still quite rare, similar cases have been documented in the literature. The majority of published studies, which are in line with the patient's prognosis, describe full recovery after stopping doxycycline and receiving supportive local treatment. There are, however, few examples of older adults with several concomitant medical problems and an acute myocardial infarction. As a result, this case provides important information on the incidence of this rare adverse drug reaction in a patient with significant cardiovascular risk who is taking several drugs.

Because the adverse drug reaction was identified early and treated immediately without compromising the treatment of the underlying respiratory illness, our patient showed a favourable clinical outcome when compared to previously published studies. While stopping doxycycline removed the causal agent, continuing piperacillin-tazobactam guaranteed successful treatment of bronchopneumonia. Before being released from the hospital, the patient's aphthous ulcers completely healed, and during follow-up, they continued to be clinically stable. In order to maximise patient safety and therapeutic outcomes, this case highlights the significance of keeping a high index of suspicion for uncommon medication-induced oral lesions, especially in elderly patients receiving polypharmacy. It also emphasises the necessity of multidisciplinary collaboration between doctors, clinical pharmacists, nurses, and other healthcare professionals.

CONCLUSION

This case highlights the importance of recognizing **Doxycycline-induced Aphthous Ulcer** as a rare but clinically significant adverse drug reaction, particularly in elderly patients receiving multiple medications for complex medical conditions. Early identification of painful oral ulceration, careful evaluation of the temporal relationship between drug administration and symptom onset, and exclusion of alternative causes are essential for establishing the diagnosis. Prompt discontinuation of the suspected drug, along with appropriate supportive management using topical therapy and nutritional supplementation, resulted in complete resolution of the oral lesions without compromising the treatment of the underlying respiratory infection. The importance of pharmacovigilance and interdisciplinary cooperation between doctors, clinical chemists, nurses, and other medical specialists in the early identification, evaluation, recording, and treatment of adverse drug reactions is further highlighted by this instance. Due to various comorbidities, polypharmacy, and altered physiological

responses, elderly individuals with acute cardiovascular diseases are especially susceptible to drug-related problems.

Reporting rare adverse medication events, like doxycycline-induced aphthous ulcers, enhances pharmacovigilance databases, adds to the body of current scientific literature, and raises healthcare providers knowledge. Increased awareness of these uncommon responses could help with early identification, save pointless tests, reduce patient suffering, and encourage safer and more sensible use of doxycycline in clinical settings.

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Abbreviations

ACS – Acute Coronary Syndrome
STEAWMI – ST-Elevation Anterior Wall Myocardial Infarction
LAD – Left Anterior Descending Artery
PCI – Percutaneous Coronary Intervention
DES – Drug-Eluting Stent
LV – Left Ventricle
EF – Ejection Fraction
AKI – Acute Kidney Injury
ADR – Adverse Drug Reaction
WHO-UMC – World Health Organization–Uppsala Monitoring Centre

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this case report.

Authors' Contribution

All authors participated in patient care, ADR identification, data collection, literature review, manuscript preparation, critical revision of the manuscript, and approval of the final version.

Summary

Doxycycline-induced aphthous ulcer is an uncommon adverse drug reaction that can significantly affect oral intake and patient comfort. In this elderly patient admitted with acute myocardial infarction and bronchopneumonia, oral ulceration developed soon after initiation of doxycycline and resolved following drug withdrawal and supportive treatment. This case highlights the importance of recognizing rare medication-related adverse events, performing appropriate causality assessment, and promoting pharmacovigilance to improve medication safety.

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