# Delayed Anaphylaxis to Intravenous Colistin in a Critically Ill Cancer Patient: A Case Report

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## ABSTRACT

**INTRODUCTION:** Anaphylaxis is an acute, life-threatening, multi-system syndrome that has been reported with a wide range of medications. Though anaphylaxis usually has a rapid onset, we describe a patient who developed anaphylaxis to intravenous colistin after 28 days of daily administration.

**CASE PRESENTATION:** A 20 years-old Caucasian male patient, with a history of relapsed acute myeloid leukemia, was transferred from the medical floor to our intensive care unit with septic shock. The source of infection was presumed to be a recto-cecal abscess and arm cellulitis. Cultures were positive for extended spectrum beta-lactamase (ESBL) and carbapenem-resistant enterobacteriaceae (CRE) *Escherichia coli.* for which he was receiving broad spectrum antibiotics, as well as intravenous colistin, started about 4 weeks earlier. On day 2 of ICU admission, and during the administration of colistin, the patient experienced an anaphylactic reaction. He developed hypotension requiring the initiation of norepinephrine, shortness of breath, hypoxia, tachycardia, and tachypnea. The reaction was resolved after supportive therapy but it was thought to be related to septic shock and therefore the patient continued on colistin the following day. The patient tolerated colistin for the next 3 days before developing another similar, but more severe, reaction. Colistin was discontinued and the symptoms resolved following supportive therapy.

**CONCLUSION:** This case highlights the importance of being aware of delayed serious reactions that may occur several weeks after initiation of drug therapy. In addition, successful re-initiation may not necessarily rule out the recurrence of such reactions and therefore close monitoring is crucial.

**KEYWORDS:** Colistin, anaphylaxis, hypersensitivity, cancer, intensive care units

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## Introduction

Colistin, also known as polymyxin E, was introduced to the market more than 50 years ago for the treatment of Gram-negative bacteria. However, its use slowly diminished due to concerns about its nephrotoxicity and neurotoxicity as well as the approval of relatively safer antibiotics. Over the last 2 decades, the use of colistin has re-emerged with the increased prevalence of multi-drug resistant Gram-negative bacteria that are resistant to most available antibiotics and susceptible to colistin.[1,2]

Anaphylaxis is a life-threatening, multi-system syndrome that has been reported with a wide range of medications, with the most common being Non-steroidal anti-inflammatory drugs and beta-lactam antibiotics.[3,4] Though anaphylaxis usually has a rapid onset, cases of delayed anaphylaxis have been reported with certain medications and with the influenza vaccine. In those cases, the onset of the allergic reactions began 12 hours to a few days after treatment.[3-12] In this report, we describe a patient who developed anaphylaxis to intravenous colistin after about a month of daily administration, during which he had no signs or symptoms suggestive of any form of allergies to the medication. In addition, we describe the outcomes following the re-administration of colistin after the initial episode of anaphylaxis.

## Case Report

A 20 year-old Caucasian male patient was transferred from the medical floor to our intensive care unit (ICU) with septic shock. The patient had a history of relapsed acute myeloid leukemia with myelodysplasia-related features, and his most recent chemotherapy was administered about 10 weeks prior to ICU admission. The patient had no underlying co-morbidities and no known drug allergies.

Upon admission to the ICU, the patient was febrile (temperature 39°C), had tachycardia (heart rate 125 beats per minute), and tachypnea (respiratory rate 22 breaths per minute). He was also hypotensive (blood pressure 80/35 mmHg, mean arterial pressure 50) for which he was started on norepinephrine, titrated to a dose of 20 µg/min for a mean arterial pressure (MAP) target of 65 and above. The laboratory results were significant for neutropenia (absolute neutrophil count 216), thrombocytopenia (platelets $85 \times 10^3$/µl), and hypokalemia (potassium 2.8 mmol/L).

The source of infection was presumed to be a recto-cecal abscess that he developed as a complication following an appendectomy that was performed 7 weeks earlier. The patient was admitted to the hospital with febrile neutropenia secondary to the recto-ceccal abscess about 6 weeks prior to his transfer to the ICU. Given the patient's thrombocytopenia, surgical intervention for source control was postponed until platelet recovery and he was maintained on broad spectrum antibiotics, meropenem and vancomycin, as well as micafungin. Upon admission to the hospital, amikacin was also started, but discontinued 5 days later once the culture results showed no growth. On day 12 of hospital admission, he developed right arm cellulitis associated with an abscess. The cultures taken from the blood and arm abscess were positive for extended spectrum beta-lactamase (ESBL) and carbapenem-resistant enterobacteriaceae (CRE) *Escherichia coli*. The patient was started on colistin, with a loading dose of 9 million units infused over 90 minutes, followed by a maintenance dose of 3 million units infused over 60 minutes every 8 hours. Since the patient was still febrile and neutropenic, he was kept on meropenem and vancomycin, and micafungin was switched to amphotericin B.

During his ICU stay, the patient continued on colistin and meropenem, tigecycline was added, and amphotericin B was switched to micafungin. By the second day of ICU admission, the patient's blood pressure improved and norepinephrine was discontinued, but he remained febrile. However, on that day, and during the administration of the morning dose of colistin (day 28), the patient developed a severe reaction that consisted of hypotension (Blood pressure was 85/40 mmHg, MAP was 55) requiring the re-initiation of norepinephrine, shortness of breath, hypoxia (oxygen saturation level 91%), tachycardia (heart rate 147 beat per minute), tachypnea (respiratory rate 30 breath per minute), with a flushed face. Colistin was immediately held, and adrenaline, chlorpheniramine and hydrocortisone were given. Laboratory tests showed a new onset of leukocytosis (WBC: $19.3 \times 10^3$/μl, increased from $1.9 \times 10^3$/μl) and acute kidney injury (serum creatinine: 1.2 mg/dL, increased from 0.7 mg/dL). Given that the patient had been admitted with septic shock and had been on colistin for a prolonged duration with no complications, the clinical judgment at that time was that the symptoms were related to the patient's critical illness rather than colistin. The plan was to continue colistin treatment and closely observe the patient during administration. The following day, leukocytosis was resolved, the patient's renal function was back to its baseline, and norepinephrine was discontinued. Over the next 3 days, the patient received colistin without any complications.

However, on day 5 of ICU admission and day 31 of colistin treatment, the patient developed another similar, but more severe reaction during the administration of colistin. The patient became hypotensive and required re-initiation of norepinephrine, had shortness of breath, hypoxia (oxygen saturation level was 90%) and a flushed face. In addition, the patient was noted to have generalized erythema in his upper limbs. Supportive therapy was administered, which consisted of adrenaline, hydrocortisone, and chlorpheniramine. Laboratory results were significant for leukocytosis (WBC: $17.3 \times 10^3$/μl), acute kidney injury (serum creatinine: 1.4 mg/dL) and an increase in total bilirubin level (total bilirubin: 2.79 mg/dL, increased from 0.88 mg/dL). Based on the clinical assessment of both the critical care and infectious disease teams, the reaction was considered as an anaphylactic reaction to colistin and therefore it was discontinued. The patient was maintained on meropenem, tigacycline, and amikacin. According to the Naranjo scale, which is a scale used to assess the causality of adverse drug reactions, this adverse event was rated as probable with a score of 7.

Two days later, norepinephrine was discontinued and all abnormal laboratory results resolved. After 2 more days, the patient's condition stabilized and he was transferred to the floor on piperacillin/tazobactam, tigecycline, and amikacin. However, the following day, he developed ventricular fibrillation and died during cardiopulmonary resuscitation.

## Discussion

In this report, we describe a case of delayed anaphylaxis associated with the administration of intravenous colistin. Delayed hypersensitivity reactions are T-cell mediated and typically begin 48 to 75 hours after drug administration. It may also involve other cells like monocytes, neutrophils, and eosinophils.[5] Several factors have been linked to an increased risk of drug-induced anaphylaxis such as older age, intravenous administration, African-American race, interruption of prior therapy, and decreased platelet activating factor (PAF) acetylhydrolase activity.[3] Although many of the patient's medications were intravenous, in this case it is unique in that the onset of anaphylaxis was about a month after daily administration of colistin and the patient had no signs or symptoms suggestive of drug-related allergies prior to developing the first reaction. In addition, the re-administration of colistin after the initial reaction did not result in any anaphylactic manifestations until 3 days later.

The report highlights the importance of being aware of such serious reactions that may occur several weeks after the initiation of treatment. In addition, a successful re-challenge of the medication may not necessarily rule out the recurrence of such reactions and therefore close monitoring is crucial.

Petrodimopoulou et al described a case of delayed anaphylaxis associated with the administration of intravenous colistin in a 42-year-old male patient with chronic osteomyelitis due to Pseudomonas aeruginosa.[6] However, unlike our case, that patient had demonstrated hypersensitivity reactions prior to developing anaphylaxis. During the 24-day treatment with intravenous colistin, rash, and pruritus were reported on 3 occasions for which he was treated with antihistamines. Eight months later, the patient was admitted to the hospital due to a relapse and intravenous colistin was initiated. During the

administration of the first dose of colistin, the patient developed severe anaphylaxis, with generalized pruritus and erythema, hypotension, dyspnea, vomiting, diarrhea, and feeling of imminent death. A skin prick and intradermal test were both positive for colistin hypersensitivity and thus an IgE-mediated mechanism was suggested for that allergic reaction.[6] Since our patient was in the hospital during the entire time of colistin administration, it is unlikely that he developed any signs or symptoms of hypersensitivity that were unrecognized by the healthcare team prior to the first reported episode of anaphylaxis. We did not perform a skin test to confirm the allergic reaction, as it was clinically judged after the 2 episodes that colistin was likely the cause. With the first episode, it was initially thought that it was related to his admission diagnosis of septic shock. The second reaction demonstrated that the first reaction was most likely anaphylaxis to colistin and occurred again after the re-administration of colistin.

Cases of delayed anaphylaxis have been described with intravenous ondansetron, some of which were reported after receiving multiple doses with no adverse effects.[7-9] In a 1-year old pediatric girl with stage-IV neuroblastoma, anaphylaxis was reported with the 56th dose of ondansetron though the patient received earlier doses with no adverse reactions.[8] Montañez et al3 described cofactors that may increase the risk of anaphylaxis in patients, like the concomitant use of medication (Non-steroidal anti-inflammatory drugs, proton pump inhibitors, or angiotensin-converting enzyme), the presence of other medical conditions (asthma, cardiovascular diseases, or mastocytosis), emotional stress, and the use of alcohol.

We hypothesize that the lack of any noticeable allergic reactions prior to the development of the delayed anaphylactic condition may be related to the immunocompromised condition of patients with cancer as well as neutropenia. Recent studies have suggested that neutrophils are closely associated with the initiation of allergic inflammation and allergic sensitization, as well as being associated with the severity of the reaction.[13] Furthermore, it has been suggested that neutrophil recruitment stimulates the development of allergic cutaneous inflammation, which may provide some insight regarding the absence of major skin reactions prior to the development of anaphylaxis in our patient, as well as in other reported cases.[13] However, this does not explain why it took a few days for the development of the second anaphylactic reaction in our patient since his neutropenia had resolved.

## Conclusion

Clinicians should be aware of delayed serious reactions that may occur several weeks after initiation of therapy. In addition, successful re-initiation may not necessarily rule out the recurrence of such reactions and therefore close monitoring is crucial.

## Author Contributions

WA, LN, FA, and NM were involved in concept and supervision. All authors were involved in data analysis and case report writing. All authors have read and approved the final version of this report for submission.

## Informed Consent for Publication

Not applicable.

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