CASE REPORT

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Asymptomatic Eosinophilia Induced by Systemic Colistin Therapy: A Brief Case Report

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ABSTRACT Colistin is a polymyxin group antibiotic, and colistimethate-sodium is the prodrug form of colistin and is inactive. Colistin is often the last optional drug for nosocomial infections caused by multidrug-resistant gram-negative microorganisms. We present a case of asymptomatic eosinophilia due to systemic colistin therapy. The increasing trend of absolute eosinophil counts appeared with recurrent colistin therapy and decreased when colistin was discontinued. The Naranjo Adverse Drug Reaction Probability Scale score was 7, and this score was classified as "probable" for this case. Clinicians should consider this drug reaction in a patient with eosinophilia and avoid unnecessary laboratory tests and treatments.

Keywords: Colistin; colistimethate sodium; eosinophilia; drug reaction

Eosinophilia is defined as a peripheral eosinophil count (PEC) greater than or equal to 500 cells/μL. Besides; hypereosinophilia, the eosinophil count is over 1,500 cells/μL.[1] It may be observed in various diseases such as infections, allergies, neoplasms, and primary hematologic malignancies. Also, eosinophilia affects 25% of patients on parenteral antibiotics. Drug-induced eosinophilia can be seen as asymptomatic; also, it can be seen in different clinical pictures ranging from mild to severe hypersensitivity reactions (HSRs). Asymptomatic eosinophilia is mostly associated with penicillins, cephalosporins, and fluoroquinolones, among antimicrobials.[2]

Colistin (polymyxin E) was discovered in 1949 as a polycationic peptide antimicrobial, and it is administered as a prodrug form, namely colistimethate-sodium (CMS). Colistin is often the last optional drug for nosocomial infections caused by multidrug-resistant (MDR) gram-negative microorganisms, especially carbapenemase-producing *Enterobacter spp*., *Pseudomonas aeruginosa*, and *Acinetobacter baumanni*.[3] The common adverse effects of colistin are dizziness, numbness, tingling, prickling and burning sensation. Also, colistin may induce renal and neurological adverse effects. On the other hand, colistin may cause mild to severe HSRs and eosinophilia, according to previous reports.[4]

Here we presented a case with early-onset of eosinophilia due to parenteral colistin therapy.

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An 84-year-old female patient was hospitalized with a loss of consciousness in the neurologic intensive care unit (ICU). Her past medical history included hypertension, tremor, allergic asthma, coronary artery disease, and Type 2 diabetes mellitus. She was

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admitted to the hospital with a history of rib fracture 4 weeks ago. Her chronic medications are acetylsalicylic acid, nebivolol, losartan, hydrochlorothiazide, insulin degludec, insulin aspart and metformin. Meropenem, sertraline, enoxaparin, insulin glargine, insulin aspart, domperidone, amlodipine, levodopa-benserazide, pantoprazole, furosemide, and cyanocobalamin were given to patients for other conditions throughout colistin treatment. No significant drug-drug interactions were detected between medications of the patient according to the UpToDate software system.

Intravenous (IV) colistin therapy was initiated to treat *A. baumanni*-related nosocomial pneumonia. Due to normal renal function, following a daily 300 mg IV loading dose, IV colistin therapy was maintained at 150 mg twice daily. On the second day of therapy, PEC started to increase, and on day 7, the upper limit (500/μL) was exceeded. At the beginning of colistin treatment, the eosinophil count (200/μL) increased by 1,590% and reached the maximum value of 3,380/μL. On the 17th day (February 22, 2021) of colistin therapy, *Serratia marcescens* was isolated in the patient's blood culture. Because of *S. marcescens* intrinsic colistin resistance, colistin treatment was discontinued, and antimicrobial therapy was continued with meropenem. One day after discontinuation of colistin, a decrease in PEC was observed. The eosinophil count (3,380/μL), which was high after the colistin treatment was terminated, decreased by 47.6% and reached 1,770/μL until the start of the second treatment. On the 4th day (February 26, 2021) of meropenem therapy, due to the history of infection with MDR microorganism and hospitalization in the ICU, colistin was added to her treatment empirically with a diagnosis of sepsis. With the restart of colistin therapy, the PEC increased once again. The eosinophil count (1,770/μL) at the start of the second colistin treatment increased by 78.0% and reached a maximum value of 3,150/μL. Colistin therapy was completed on March 9, 2021, and PEC started to decrease simultaneously. Within 8 days of colistin discontinuation, the PEC (440/μL) returned to below the upper limit (Figure 1).

Complete blood counts and biochemistry tests were followed daily during the colistin therapy. However, no other value was significantly increased except PEC. Also, renal impairment, electrolyte imbalances, and cutaneous reactions were not developed. On the other hand, subjective signs (such as itching) could not be evaluated because of loss of consciousness. There has not been a significant alteration in any treatment during the colistin therapy period affecting blood test values, including PEC.

To evaluate colistin-induced eosinophilia probability as an adverse drug reaction, The Naranjo Adverse Drug Reaction Probability Scale was used. The total score was 7, classified as "probable" in the Naranjo Scale (Table 1).[5]

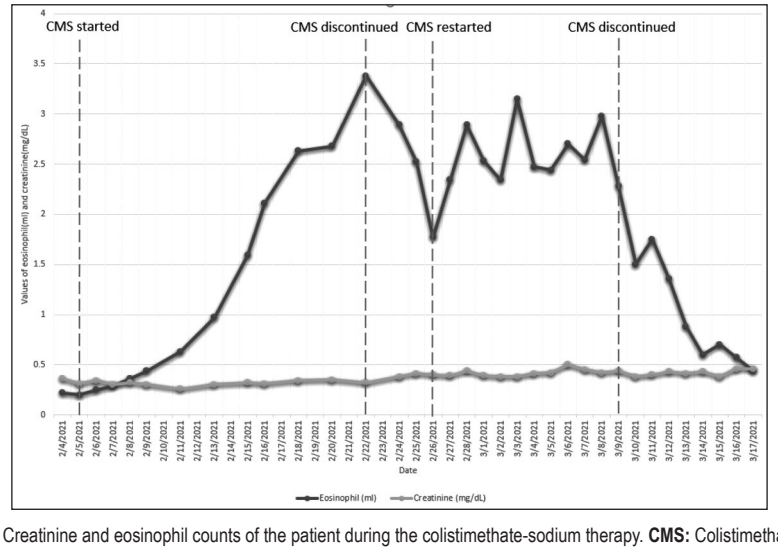

FIGURE 1: Creatinine and eosinophil counts of the patient during the colistimethate-sodium therapy. **CMS:** Colistimethate-sodium.

TABLE 1: Obtained scores for the patient in Naranjo Adverse Drug Reaction Probability Scale.[5]

Naranjo Adverse Drug Reaction Probability Scale	
Questions	**Score**
Are there previous conclusive reports of this reaction?	1
Did the adverse event appear after the drug was given?	2
Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was given?	1
Did the adverse reaction reappear upon readministering the drug?	2
Were there other possible causes for the reaction?	0
Did the adverse reaction reappear upon administration of placebo?	0
Was the drug detected in the blood or other fluids in toxic concentrations?	0
Was the reaction worsened upon increasing the dose?	1
Or was the reaction lessened upon decreasing the dose?	
Did the patient have a similar reaction to the drug or a related agent in the past?	0
Was the adverse event confirmed by any other objective evidence?	0
Total score	7

Written informed consent was obtained from the patient's legal guardians for the publication of this case report and patient information.

DISCUSSION

This is the first case report, including an adult patient who experienced eosinophilia with colistin therapy to the best of our knowledge. There is only one study on eosinophilia associated with parenteral CMS therapy in neonatal patients. In the study of Al-Lawama et al., they reported 21 newborns who were treated with parenteral CMS. Fourteen (67%) patients had elevated eosinophil counts during colistin therapy in their study. Nevertheless, it had not included eosinophil counts after cessation of colistin therapy.[6] Additionally, in another study, 2 adult patients treated with high-dose aerosolized colistin therapy developed eosinophilia.[7]

The exact mechanism of drug-induced eosinophilia is unknown. Eosinophilopoiesis can be elicited in the bone marrow by three cytokines: granulocyte-macrophage colony-stimulating factor, interleukin-3 (IL-3), and IL-5, with IL-5. These cytokine levels could be elevated by medications and can cause eosinophilia.[8] Evaluation of unexplained eosinophilia needs a variety of tests such as quantitative serum immunoglobulin levels, serum troponin, echocardiogram, pulmonary function tests, bone marrow biopsy, antineutrophil cytoplasmic antibodies, FIP1L1/PDGFRA analysis, etc. besides routine complete blood cell count and routine chemistry values.[8]

Like generally accepted definitions, we defined eosinophilia as any absolute eosinophil counts (AEC) greater than or equal to 500/μL and hypereosinophilia as any AEC greater than or equal-1,500/μL. Drug-induced eosinophilia often prompts concern for an impending HSR. The principal of clinical consideration is that PEC is associated with many severe HSRs, including organ-specific reactions (immune-mediated nephritis, hepatitis, and pneumonitis, etc.), and drug rash eosinophilia and systemic symptoms syndrome, severe cutaneous adverse reactions, Stevens-Johnson's syndrome/toxic epidermal necrolysis, etc.[1] There were no clinical signs or symptoms other than significant eosinophilia in the present case report.

Eosinophilia is most associated with penicillins, cephalosporins, and fluoroquinolones, among antimicrobials. Our patient was treated with meropenem and colistin concomitantly. Meropenem therapy was started 7 days before initiation of IV colistin and continued with no evidence for eosinophilia. However, after the 1st day of colistin therapy, PEC increased; this observation has eliminated the possibility of meropenem-associated eosinophilia. Also, the PEC began to decrease shortly after the discontinuation of colistin (Figure 1). Creatinine levels of the patient did not change during the therapy. Therefore, we thought that there is no risk of increasing colistin concentration due to decreased renal excretion. The observed reaction occurs with the exposure of colistin at therapeutic concentrations. However, we could not confirm this consideration because therapeutical drug monitoring for colistin is not available in the hospital laboratory.

In a prospective cohort study, evaluating drug-induced eosinophilia with parenteral antibiotics showed that the median day of therapy until the onset of eosinophilia was 15 days. Nevertheless, the study did not mention the duration of the therapies and eosinophil counts after discontinuing the medications. The study concluded that older patients with multiple comorbidities are at high risk of developing

eosinophilia. Also, outpatient parenteral antimicrobial therapy is prone to eosinophilia due to long-term antimicrobial exposure.[1]

One case report about prominent eosinophilia associated with warfarin administration reported that the PEC increased to over 1,000/μL on the twenty-second day after the initiation of warfarin therapy and reached the level of 3,961/μL on day 44. Nineteen days after the cessation of therapy, PEC decreased to 800/μL.[9] In the present case, the PEC started to elevate on the 2nd day of colistin therapy and reached 1,590/μL within 10 days. Followed by the discontinuation of therapy, PEC turned to the normal range within 8 days. The difference from previous reports may be related to many parameters such as age, weight, underlying diseases, or altered laboratory parameters (creatinine, hepatic function levels, etc). Furthermore, colistin therapy (dosage, duration of therapy, pharmacokinetics, and pharmacodynamic parameters) may influence PEC.

In conclusion, eosinophilia is a rare side effect of colistin. Herein, asymptomatic eosinophilia due to systemic colistin therapy was presented. Patients with drug-induced asymptomatic eosinophilia may not require treatment besides close monitoring. Based on our experience, we recommend clinicians be aware of systemic colistin therapy-induced eosinophilia because it may be associated with severe consequences. However, prospective trials are needed to explain the association of colistin-induced eosinophilia.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *İzgi Bayraktar;* ***Design:*** *İzgi Bayraktar, Emre Kara;* ***Control/Supervision:*** *İzgi Bayraktar, Emre Kara, Meliha Çağla Sönmezer, Kutay Demirkan, Mehmet Akif Topçuoğlu;* ***Data Collection and/or Processing:*** *İzgi Bayraktar, Emre Kara, Mehmet Akif Topçuoğlu;* ***Analysis and/or Interpretation:*** *İzgi Bayraktar, Emre Kara, Meliha Çağla Sönmezer;* ***Literature Review:*** *İzgi Bayraktar, Emre Kara;* ***Writing the Article:*** *İzgi Bayraktar, Emre Kara, Meliha Çağla Sönmezer;* ***Critical Review:*** *Meliha Çağla Sönmezer, Emre Kara, Kutay Demirkan, Mehmet Akif Topçuoğlu.*

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