Vancomycin Dependent Pancytopenia - a rare side effect: A case report

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ABSTRACT Background: Vancomycin is an anti-microbial agent which is preferred for the treatment of bacteremia, endocarditis, pneumonia, cellulitis, catheter infection and osteomyelitis. Pancytopenia is one of the rare side effects of vancomycin treatment, and there are few presentations in the literature on this issue. **Case Summary:** Here, we presented three cases with vancomycin related pancytopenia. All three cases were treated with vancomycin for different infections and healed with appropriate therapeutic interventions. **Conclusion:** Vancomycin dependent pancytopenia is a severe and life-threatening condition. Clinicians should keep this condition in mind to prevent related complications with appropriate medical support.

KEYWORDS Vancomycin, side effect, pancytopenia

Introduction

Vancomycin is a tri-cyclic glycopeptide antibiotic which inhibits cell wall synthesis by preventing the addition of N-acetylmuramic acid and N-acetylglucosamine to the peptidoglycan matrix of the cell wall and by this way inhibits bacterial replication. Vancomycin is the first step for methicillin-resistant, coagulase positive or coagulase-negative staphylococcus infections (bacteremia, endocarditis, pneumonia, cellulitis and osteomyelitis [1].

Even though vancomycin is known to be a relatively safe drug, it may have side effects like fever, red man syndrome, phlebitis, nephrotoxicity, autotoxicity, thrombocytopenia, fixed drug eruption, Steven-Johnson syndrome, toxic epidermal necrolysis, leukocytoclastic vasculitis [2]. In the literature, in a search using 'vancomycin' and 'pancytopenia' terms, five vancomycin linked pancytopenia cases were detected [1, 3-5]. In this work, we report three interesting and different cases with pancytopenia related to intravenous (iv) vancomycin treatment. The primary objective of this paper is to draw the attention of physicians to this unwanted side effect.

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Case presentations

Case 1

An 83-year old female was admitted to emergency service with fewer and productive cough lasting for one week. In the physical examination, blood pressure was 180/100 mmHg, the pulse rate was 114/ min, body temperature was 38 °C. In patient's both lungs, there were crepitant rales. On thorax CT, bilateral pleural effusion and ground glass opacities in the lungs were observed. The patient was hypertensive for five years and had an arteriovenous fistula (AVF) because of chronic kidney failure for hemodialysis (HD) preparation. For bacterial pulmonary infection Ceftriaxone/Clarithromycin combination was started, and in the 2nd day, in blood culture, methicillin-resistant vancomycin sensitive Staphylococcus aureus was grown. Ceftriaxone/Clarithromycin combination was switched to vancomycin. In renal dose, vancomycin iv 1000 mg/ 72 hours was started. Changes in the complete blood count values were shown in Table 1.

In the 10th day of the treatment, pancytopenia was observed in blood count. In physical examination, the patient did not have a fever. In the follow-up, pleural effusion was not detected in the thoracic X-Ray imaging; no bacterial growth was detected

Table 1 Changes in the complete blood count in Case 1.

Time (day)	Day 1	Day 10	Day 11*	Day 13
HGB (g/dL)	10	8.7	7.9	7.5
HCT (%)	30	25.8	23.9	22.8
WBC (/µL)	11.4	2.1	0.4	3.4
PLT (/µL)	162.1	123.3	96.6	90.1
*When vancomycin stopped, and G-SCF started HGB: Hemoglobin, HCT: Hematokrit, WBC: White Blood Cell, PLT: Platelet				

in the blood and urinary culture. Similarly, while the infection was in the tendency to regress, in the complete blood count, pancytopenia, primarily neutropenia, deepened in the 11th day of treatment. As no reason was thought to cause pancytopenia except vancomycin, vancomycin was stopped, and in renal dose, iv teicoplanin 200mg/ 72h was started. In the same day, arterial blood oxygen saturation values dropped, and the patient was connected to mechanical ventilation. This serious state of the patient was thought to be due to severe neutropenia and 5 mcg/kg/day subcutaneous granulocyte stimulating factor (G-CSF) was started. 2 days after G-CSF (on the 13th day of the treatment), in the complete blood count analysis, cells tended to increase and G-CSF was stopped. In the 14th day of the treatment, three days after the start of G-CSF, cardiac arrest was developed in the patient following sudden hypotension and ventricular fibrillation. The patient did not answer to resuscitation, and she died.

Case 2

A 72-year-old male was admitted to emergency service with a headache and difficulty in breathing for three days. In physical examination, blood pressure was 170/90 mmHg, pulse rate was 110/min, body temperature was 38 °C. In patient's both lungs, there were crepitant rales. In the thoracic CT, there were bilateral pleural effusion and collapse consolidation in the adjacent locations of effusion. It was learned that the patient had had kidney failure under hypertension background and an AVF was opened for HD preparation in another centre four weeks ago, and at the same time, a permanent HD program has been started. For vascular access, a catheter was temporarily placed into the right jugular vein. We have not detected any other source of infection other than the catheter. Hypervolemia findings were regressed by HD, and classical hemodialysis regime was continued three days a week. In renal dose, vancomycin 1000mg/ 72h and after each HD 2 g iv ceftazidime were started. In the 3rd day of the treatment, methicillin-resistant vancomycin sensitive Staphylococcus aureus was grown in the blood culture taken from the catheter; therefore, ceftazidime was stopped, and vancomycin continued. By pulling out the catheter, HD program continued from AVF as AVF got mature. Changes in the complete blood count values were shown in Table 2.

In the 3rd day of the treatment, pancytopenia was observed. The patient did not have a fever during a physical examination. In the follow-up, in the chest X-ray, there was no fluid load, and there was no bacterial growth in control blood and urinary cultures. Similarly, while consolidations of infection were in the tendency to regress, in the 6th day, definitive pancytopenia

Table 2 Changes in the complete blood count in Case 2.

Time (day)	Day 1	Day 3	Day 6*	Day 22
HGB (g/dL)	10.2	7.5	7.4	9.8
HCT (%)	30.6	23.8	23.3	28.8
WBC (/µL)	11	3.8	4.1	6.8
PLT (/µL)	135	78	66.9	123
*When vancomycin stopped, and G-SCF started.				

Table 3 Changes in the complete blood count in Case 3.

Time (day)	Day 1	Day 3	Day 5*	Day 6	Day 21
HGB (g/dL)	7.3	6.7	5.7	8.0	9
HCT (%)	23.8	21.5	17.7	23.3	27.8
WBC (/µL)	11.2	10.8	9.4	8.6	8.9
PLT (/µL)	182.4	61.3	38.9	41.2	131.9
*When vancomycin stopped, and G-SCF started.					

was detected during complete blood count. No reason causing pancytopenia was considered, except for vancomycin. Consequently, vancomycin was stopped. In renal dose, iv teicoplanin 200 mg/ 72h was started. After three-week long antibiotic treatment, there was no growth in the blood culture; therefore, antibiotic treatment terminated. Twenty-two days after stopping vancomycin, complete blood count turned to normal and patient was discharged.

Case 3

A 55-year-old female was brought to emergency service with one-month long lack of appetite, weight loss, discomfort in foot ankles. It was learned that the patient was bedridden because of ankylosing spondylitis sequelae for five years and she has not been medicated for six months. In physical examination, blood pressure was 80/60 mmHg, pulse was 100/min, body temperature was 37 °C, her tongue was dry, and she was cachectic. In both of patient's ankles, there were ulcerative swellings with flux. In the laboratory tests, urea was 184,5 mg/dL, creatinine was 2,97 mg/dL, WBC was 11,2 /μL, HGB was 7.3 g/dL, HTC was % 23,8 and PLT was 182,4 /μL, c-reactive protein (CRP) was 223,1 mg/L. The patient was hospitalized in the nephrology service. Isotonic fluid replacement was started. Five days later, kidney functions got better (urea:41 mg/dL, creatinine:0,72 mg/dL). Cellulitis was considered to be due to bacterial infection; therefore, ampicillin/sulbactam was started. Methicillin-resistant vancomycin sensitive Staphylococcus aureus was grown in the smear taken from the ankle. Vancomycin was started iv 1mg/ 12 h. Changes incomplete blood count values were shown in Table 3.

In the 3rd day of vancomycin, pancytopenia was developed. In the 5th day, while cellulitis was in the tendency to recover, pancytopenia tended to deepen. Rectal bleeding was observed related to thrombocytopenia. Patient's fever was normal, and her chest X-ray was normal. There was no bacterial growth in blood and urinary cultures. As no reason causing pancytopenia was observed except vancomycin; it was stopped, and

teicoplanin was started. Heart failure symptoms were observed due to anaemia; therefore, two units of erythrocyte transfusion was applied. After transfusion, haemoglobin increased. Rectal bleeding stopped. In the 18th day, reticulocyte count was 7.2% (corrected reticulocyte 4.2%), and 13 days after stopping vancomycin, blood cell counts increased, and the patient was discharged.

In the haematological investigations of three cases, there were normocytic, normochromic anaemia, eosinophilia (no eosinophilia in the third case) and leukocytopenia with thrombocytopenia in peripherical blood count. No pathology indicating leukaemia, or any other haematological diseases were detected in the peripherical smear. Reticulocyte was lower than 0.1%. No abnormal finding, except pancytopenia, was detected in other laboratory examinations including coagulation profile. Vitamin B12 and folate levels were normal. Additionally, no iron deficiency was detected. Patients did not have any allergy against any known medication.

Discussion

Pancytopenia is a rare side effect of vancomycin. Probable mechanisms include bone marrow suppression, sequestration and peripheral cell destruction. Some authors claim the opposite of bone marrow suppression based on the bone marrow biopsy results (hyperplasia and hypoplasia of granulocyte series) [4]. On the other hand, cytopenia was claimed to develop in an immunological context by Drygalsi et al. [2] with the discoveries of vancomycin dependent thrombocyte reactive antibodies and by Schwartz [6] with the discoveries of anti-neutrophil antibodies. In our cases, to detect the relationship between vancomycin and pancytopenia, the Naranjo probability scale [7] was used. Our three patients got the score of 7; consequently, they fit into Naranjo probable relation.

Pancytopenia inducing effects of drugs such as ceftriaxone, clarithromycin, ceftazidime, ampicillin-sulbactam, have not been reported. In our all three cases, paracetamol was being used by patients before using and after the cessation of vancomycin treatment, and therefore, pancytopenia cannot be related to this. Because of timing relation between the start of vancomycin and the reduction in blood cells, we speculated the vancomycin as the cause of pancytopenia. Also, the absence of clinical findings like sequestration (like portal hypertension and splenomegaly) or peripheral destruction (icterus or microangiopathy) was supportive. Also, the absence of an atypical cell or haematological disorder in peripheric smear was supportive for side effects caused by vancomycin.

There are several treatment options in patients who have adverse reactions related to vancomycin. Sanche et al. presented a case in which teicoplanin was used instead of vancomycin in case of neutropenia [8]. Another option reported in the literature is the use of G-CSF [9]. Transfusion is recommended for the cases in which there are vancomycin dependent dramatic thrombocytopenia and bleeding [10]. During the acceptance to the hospital, in our first and second cases, anaemia in blood counts was considered to be due to renal diseases, and in the third case, anaemia in the blood count was considered to be due to ankylosing spondylitis. In the first case, there was a reduction in all three blood cell series. We stopped vancomycin and started teicoplanin. Teicoplanin was used in low dose in our case because a high dose of teicoplanin also may cause pancytopenia [11]. We applied G-SCF because there was dramatic neutropenia and the spontaneous resolution of neutropenia after stopping antibiotic would take time (1-22 days, six days in average) [12]. The puzzling aspect of the patient was the reason for his sudden death. As it is known, the primary cause of mortality in kidney diseases is the cardiovascular conditions [13]. Ischemic heart disease being the main reason, we thought that this was the factor inducing hypotension and ventricular fibrillation. However, we are not certain that G-CSF has any contribution to a patient's health. Therefore, one must be careful when using G-CSF in vancomycin-induced neutropenia. In the second case, there was a reduction in all three blood cells in average levels. We just stopped vancomycin and started teicoplanin. Twenty-two days after stopping vancomycin, we observed an increase in WBC. We discharged patient with a cure with the continuum of his three times a week classic dialysis program. Also, in third case, there was a reduction in all three blood cell series.

Similarly, we stopped vancomycin, started teicoplanin. HGB was reduced to 5,7 g/dl especially because of the contributions of the rectal bleeding which is caused by severe thrombocytopenia as a result of negative side effects of vancomycin. With the addition of anaemia symptoms, two units of erythrocyte replacement were done. After transfusion, in the 2nd day, haemoglobin was increased, and interestingly, rectal bleeding stopped. After transfusion, there was no hemolytic reaction. According to the conclusions driven from our third case, vancomycin dependent pancytopenia occurs because of bone marrow suppression [4] rather than an immunological aetiology [2,7]. Therefore, we would like to emphasize that there is no inconvenience in doing erythrocyte replacement in vancomycin related severe anaemia.

In conclusion, although it is rare, the results of vancomycin dependent pancytopenia are serious. Even though it can regress, this potential side effect can complicate the clinical progress of the patient with cases like bone marrow suppression and bleeding diathesis. Physicians should be careful about this side effect, and blood counts should be frequently followed especially in patients who use long term iv vancomycin or have a history of vancomycin side effects. Vancomycin should be stopped as soon as the first finding of any haematological anomaly appears.

Disclosure Statement

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Competing Interests

Written informed consent obtained from the patient for publication of this case report and any accompanying images.

References

1. Gupta S, Sharma S, Menon N et al. Case report of vancomycin-induced pancytopenia. Rev Soc Bras Med Trop. 2016; 49(2):258-9.

2. Von Drygalski A, Curtis BR, Bougie DW et al. Vancomycin-induced immune thrombocytopenia. N Engl J Med 2007; 356: 904-910.

3. Carmichael AJ, AlZahawi MF. Drug points: Pancytopenia associated with vancomycin. Br Med J 1986; 293:1103.

4. Rocha JL, Kondo W, Baptista MI et al. Uncommon vancomycin-induced side effects. Braz J Infect Dis 2002; 6:196-200.

5. Bruniera FR, Ferreira FM, Saviolli LR et al. The use of vancomycin with its therapeutic and adverse effects: a review. Eur Rev Med Pharmacol Sci 2015; 19: 694-700.

6. Schwartz MD. Vancomycin-induced neutropenia in a patient positive for an antineutrophil antibody. Pharmacotherapy 2002; 22:783-788.

7. Naranjo CA, Busto U, Sellers EM et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.

8. Sanche SE, Dust WN, Shevchuk YM. Vancomycin-induced neutropenia resolves after substitution with teicoplanin. Clin Infect Dis 2000;31:824-5.

9. Lai KK, KleinjanJ, Belliveau P. Vancomycin-induced neutropenia treated with granulocyte colony-stimulating factor during home intravenous infusion therapy. Clin Infect Dis 1996;23:844-5.

10. Mohammadi M, Jahangard-Rafsanjani Z, Sarayani A et al. M. Vancomycin-induced Thrombocytopenia: A Narrative Review. Drug Saf. 2017;40:49-59.

11. Choi HM, Choi MH, Yang YW. Case of Teicoplanin-Induced Pancytopenia Caused by Excessive Dosing. Am J Ther. 2016; 23:307-10.

12. Morris A, Ward C. High incidence of vancomycin-associated leukopenia and neutropenia in a cardiothoracic surgical unit. J Infect 1991; 22: 217-23.

13. Wald R, Yan AT, Perl J et al. Regression of left ventricular mass following conversion from conventional hemodialysis to thrice weekly in-centre nocturnal hemodialysis. BMC Nephrol. 2012; 19. 13(1):3.