Tigecycline-induced Drug Fever and Leukemoid Reaction
A Case Report
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Abstract: In this study, we describe a patient in whom tigecycline-induced drug fever and leukemoid reaction (LR) after 3 weeks of therapy for pneumonia.

A 62-year-old man developed aspiration pneumonia on February 1, 2015. He had received multiple antibiotics at another hospital, but did not respond well. Disease rapidly progressed, and he was referred to our department on February 14. We adjusted the antibiotic therapy to tigecycline + vancomycin, and added voriconazole to empiric antifungal therapy. Pneumonia largely improved, and we discontinued vancomycin and voriconazole on February 28. With tigecycline monotherapy, his clinical status remained stable.

On March 7, he developed high fever and LR (white blood cell count: 38.25 × 10^9/L). Erythrocyte sedimentation rate and C-reactive protein were elevated, and CD8⁺ T cells had been abnormally activated. After a careful physical examination and laboratory investigation, we confirmed that primary infection did not progress and no other cause was evident. So we figured fever and LR might be induced by tigecycline. After discontinuing tigecycline and adding low-dose steroid, fever and LR totally resolved in 3 days, which further confirmed our diagnosis.

According to this case and literature review, drug-induced hypersensitivity should be considered in the differential diagnosis of fever and LR when the therapeutic duration of tetracycline approximates 3 weeks. Monitoring T-cell subsets may facilitate early diagnosis. When necessary, we should discontinue the suspected drug to confirm diagnosis.

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Abbreviations: CRP = C-reactive protein, CT = computed tomography, DEX = dexamethasone, ESR = erythrocyte sedimentation rate, LR = leukemoid reaction, WBC = white blood cell.

INTRODUCTION
Tigecycline, the first-in-class glycylcycline tetracycline antimicrobial agent, is the 9-t-butyglycylamido derivative of minocycline. With glycyl-amino substitutions at position 9, tigecycline has more broad-spectrum, anti-infective activities (Figure S1, http://links.lww.com/MD/A492). Clinically, adverse events of tetracycline antimicrobial agents commonly include gastrointestinal discomfort (nausea and vomiting), liver dysfunction, impairment of renal function, and so on. Drug fever and leukemoid reaction (LR) are rarely caused by tetracycline antibiotics, with only several cases reported to be associated with minocycline. Here, we describe a case in which fever and LR developed 3 weeks after initiation of tigecycline therapy for pneumonia. To the best of our knowledge, this is the first case report of tigecycline-induced drug fever and LR in the world. This study was approved by the Institutional Review Board of Peking Union Medical College Hospital. Informed consent has been obtained from the patient for publication of this case report.

CASE
A 62-year-old man developed pneumonia after vomiting and aspirating on February 1, 2015. Sputum culture was positive for Klebsiella pneumoniae (multidrug-resistant, sensitive to tetracycline). Chest computed tomography (CT) scan showed effusions in bilateral lower lobes, with the right side more significant, and bilateral pleural effusions (Figure S2A, http://links.lww.com/MD/A492). He had received piperacillin, tienam, teicoplanin, and sulperazone monotherapy or combination at another hospital, but did not respond well. Disease rapidly progressed. He developed type I respiratory failure and underwent tracheotomy on February 11, and was referred to our department 3 days later. Medical, family, and psychosocial history was not significant. On physical examination, he was weak and unconscious, with hyperthermic (38.7°C), hypertension (149/75 mm Hg), and tachypnea (30 beats per minute). Auscultation revealed that bilateral breath sounds were rough, and bilateral lower breath sounds were weak. We adjusted the antibiotic therapy to 50 mg tigecycline + 1 g vancomycin q12h. Meanwhile, we added voriconazole 0.2 g q12h to empiric antifungal therapy. He gradually came back to consciousness and his temperature normalized (37.3°C). Signs and symptoms of pneumonia largely improved. Repeat chest CT scan showed bilateral pleural effusions were less than before, but the remaining was unchanged (Figure S2B, http://links.lww.com/MD/A492). Vancomycin and voriconazole were discontinued on February 28. With tigecycline monotherapy, his clinical status remained stable.

On March 7, our patient developed scattered rash on both lower extremities, and his temperature reached 39.0°C on the same night (Fig. 1). His general status was well, and signs and symptoms of pneumonia did not worsen. His white blood cell...
(WBC) count was 38.25 x 10^9/L (from 13.34 x 10^9/L 1 d earlier), with 83.2% neutrophils, 0.2% eosinophils, and 9.8% lymphocytes (Fig. 1). Blood smear did not identify naïve blood cells. Erythrocyte sedimentation rate (ESR) was 58 mm/h and C-reactive protein (CRP) was 108 mg/L. Blood culture and T-SPOT.TB were both negative. G-test was <100 pg/mL. T-cell subsets showed CD8^+ T cells were abnormally activated (CD8^−DR 73.8%, CD8^+CD38^+ 94.0%). Repeat chest CT scan did not indicate any progression of the primary infection (Figure S2C, http://links.lww.com/MD/A492). Since fever and LR cannot be explained by primary infection and no other cause was evident after a careful physical examination and laboratory investigation, we figured fever and LR were induced by tigecycline, which was the only agent he was receiving at that time.

After discontinuing tigecycline on March 9, rash recessed, WBC count came down, and his temperature gradually came down in 48 hours, which is appropriate to the t1/2 of tigecycline (42.4 h); this helped to demonstrate that fever and LR were induced by tigecycline, which was the only agent he was receiving at that time.

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Contributors: Q-QS, LQ, G-RR, and X-JM looked after the patient, and R-XC and Z-JL collected the data. All authors contributed to the report. Written consent to publication was obtained.

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