"Antibiotic-Responsive" drug fever due to the patient's medication-taking behavior: a case report

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ABSTRACT

Background: Drug fever can complicate the diagnosis of recurrent fever, especially when multiple physicians are involved in treatment.

Case Presentation: We report the case of a 56-year-old man with recurrent fever responsive to antibiotics, initially suggesting a persistent bacterial infection. Detailed history-taking revealed that he discontinued minocycline, prescribed for rosacea dermatitis, when starting new antibiotics, and resumed it after the fever subsided. Eosinophilia and a clear improvement in the general condition between fevers led to the suspicion of drug fever. A rechallenge confirmed minocycline-induced fever.

Conclusion: This case emphasizes the importance of thoroughly reviewing medication history and patients' medication-taking behavior when drug fever is suspected.

Keywords: Minocycline, drug fever, medication-taking behavior.

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Background

The diagnosis of sustained fever can be complicated by medication-taking behavior, especially when medications are prescribed by multiple physicians. This report describes a case that was initially suspected to be "antibiotic-responsive" but was ultimately identified as minocycline-induced drug fever.

Factors contributing to poor medication adherence include patient-, physician-, and healthcare system-related factors [1]. Only approximately 50% of patients adhere to their prescribed medications, and care provided by multiple physicians affects medication adherence [1,2]. For example, a systematic review and meta-analysis involving 27 million patients with hypertension between 2010 and 2020 reported that 27%-40% exhibited poor adherence [3]. Additionally, a report conducted in Japan found that 24.7% of patients had discontinued prescribed antibiotics at their own discretion [4].

Case Presentation

A 56-year-old Japanese male patient with recurrent fever was referred by his primary care physician (PCP) to our hospital. He developed a 39°C fever 19 days before the consultation and visited his PCP the next day. The physician prescribed levofloxacin 500 mg/day for 7 days, and the fever subsided after 4 days. However, the fever recurred along with a cough 9 days before the consultation; hence, the PCP prescribed clarithromycin 400 mg/day for 5 days, resulting in fever reduction. While afebrile, the patient had a good appetite and no weight loss. Nevertheless, 3 days before the consultation, he developed a 38.9°C fever and was referred to our hospital. His medical history included atopic dermatitis, for which he had been seeing a dermatologist since the age of 25 years and was being treated with topical tacrolimus ointment and steroids. Additionally, he began taking minocycline for rosacea dermatitis 31 days before the consultation. The patient had no other medical history or history of medication use. There were no known allergies and no previous adverse drug reactions.

On physical examination, the patient was afebrile and had normal vital signs. In the head and neck examination, erythema without tenderness was noted on both cheeks, consistent with rosacea dermatitis. No conjunctival hemorrhage or jaundice was observed. The auricles were not deformed, and the oral cavity and pharynx appeared normal. The thyroid was normally palpable without tenderness. No cardiac murmurs or adventitious breath sounds were detected in the chest. The abdomen was non-tender with no hepatosplenomegaly. No joint swelling or muscle tenderness was noted in the extremities. There was no superficial lymphadenopathy. No abnormalities in the

skin were found other than the face. Blood tests revealed eosinophilia (2030/mcl) and an elevated C-reactive protein level (5.3 mg/dl). No anomalies suggesting neutrophilia, anemia, liver dysfunction, or renal impairment were found. Chest radiography results were normal.

The patient's fever temporarily subsided with antibiotic treatment, raising suspicion of a persistent bacterial infection such as infectious endocarditis. A differential diagnosis was considered, including infectious endocarditis, pneumonia, and occult abscesses (Table 1). However, a review of systems revealed no abnormalities in vital signs such as tachypnea and tachycardia, and no findings suggestive of infective endocarditis, including heart murmurs, conjunctival hemorrhage, Janeway lesions, or Osler nodes. Moreover, his excellent general condition during the intermittent afebrile phases was atypical for a persistent bacterial infection, malignancy, and noninfectious inflammatory disease. In addition, the presence of eosinophilia was inconsistent with a typical bacterial etiology. Detailed inquiries revealed the patient decided not to combine the dermatologist- and PCP-prescribed antibiotics. When he started the newly prescribed antibiotics, he discontinued minocycline; however, he resumed it after the fever subsided (Figure 1). Hence, we suspected minocycline-induced drug fever and conducted a rechallenge, which resulted in a high fever with chills after 4 hours. Subsequently, minocycline was discontinued, and no fever recurrence was observed.

Table 1. *A list of common causes of sustained fever (modified from the reference [5]).*

INFECTION	Bacterial Sinusitis Dental abscesses Endocarditis Tuberculosis Abdominal or pelvic abscess Urinary tract infection Viral Cytomegalovirus Epstein-Barr virus
MALIGNANCY	Leukemia Lymphoma
NONINFECTIOUS INFLAMMATORY DISEASE	Connective tissue diseases Granulomatous disease Vasculitis
MISCELLANEOUS	Drug-induced Factitious fever Thromboembolic disease Thyroiditis

Discussion

We report a case of recurrent fever with an antibiotic-response-like time course following antibiotic administration, which initially led to the consideration of persistent bacterial infections such as infective endocarditis, tuberculosis, and occult abscesses. However, the diagnosis was later reconsidered in light of the patient's preserved general condition during afebrile periods. A detailed history revealed that the patient discontinued minocycline on his own when levofloxacin and clarithromycin were prescribed. He had been intermittently discontinuing and restarting minocycline, which better explained the observed clinical pattern. The patient's condition was not a medication effect, but rather a side effect.

When considering the causes of fever of unknown origin, factors such as infection, connective tissue diseases, and malignancy are commonly considered. However, when the patient's general condition clearly improves during afebrile periods, drug-induced fever should be considered in the differential diagnosis. A 2023 review defines drug fever as a febrile response that meets all the following criteria: (i) onset after drug administration, (ii) resolution within 72 hours after discontinuation of the drug without specific treatment, (iii) no other identifiable cause based on medical history, physical examination, laboratory tests, or imaging, and (iv) no recurrence of fever within 72 hours after defervescence [6]. A retrospective

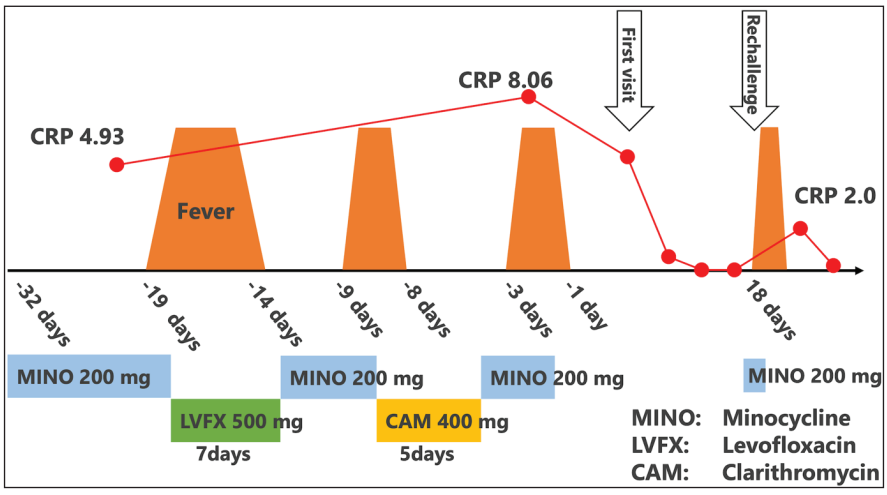


Figure 1. *The course of symptoms and medications.*

study at a single institution in Japan reported that drug fever accounted for 5.7% of hospitalized patients presenting with fever [7].

Whether intentionally or unintentionally, patients may not report their exact medication usage; therefore, medical staff should specifically ask about their use of medicines and other treatments to rule out drug-induced fever. It is important to ensure that all medications taken within the past month, including those prescribed by other physicians and over-the-counter drugs, are accounted for [8]. Patients often cannot accurately report their medication history and may not bring either the medications or a recent list of them [9]. Utilizing pharmacy records from community pharmacists may provide more comprehensive information regarding the medication history of hospitalized patients [9].

Initially, the drug-induced fever developed approximately 13 days after the minocycline prescription, and the interval between administration and fever onset progressively shortened. This suggests an immune response as the underlying mechanism of drug-induced fever [10]. Drug hypersensitivity elicits different immune responses depending upon the nature of the drug and varies between individuals. For instance, drug-induced immune hemolytic anemia are type II hypersensitivity reactions, whereas, drug-induced hypersensitivity syndrome, is a type IV hypersensitivity reaction. Drug fever may be categorized as a type III reaction among the four classical types of allergic responses [11]. In patients with serum sickness, a condition similar in nature to drug fever, decreased levels of serum C3 and C4 have been observed, along with immune complex deposition in the vasculature, supporting its classification as a type III reaction. However, drug fever may also elicit type IV or delayed type hypersensitivity reaction, as seen in the case of drug fever induced by Vinca alkaloids [12]. Even if the patient was asymptomatic during the prior administration, sensitization may have occurred, and re-exposure can trigger symptoms. In addition, prior exposure to a drug of the same class has been associated with a shortened latency period before the onset of drug fever [13]. Research on whether atopic dermatitis constitutes a risk factor for drug fever remains insufficient. A pediatric study conducted in China reported that atopic dermatitis posed a risk for delayed-type drug hypersensitivity, with an odds ratio of 8.2 [14]. However, another report found that atopic dermatitis was not a significant risk factor for drug hypersensitivity induced by antimicrobial agents [9]. When drug-induced fever is suspected in mild cases, a rechallenge can be safely performed to facilitate diagnosis. However, rechallenges are contraindicated in patients with severe liver injury, lymph node swelling, or suspected drug-induced hypersensitivity syndrome.

Conclusion

This case underscores the importance of considering drug-induced fever in the differential diagnosis of recurrent fever, especially when eosinophilia is present. A detailed medication history and awareness of patient medication-taking behaviors are essential to avoid unnecessary antibiotic use and misdiagnosis of persistent bacterial infections.

What is new

This case underscores the importance of considering drug-induced fever in the differential diagnosis of recurrent fever, especially when eosinophilia is present. A detailed medication history and awareness of patient medication-taking behaviors are essential to avoid unnecessary antibiotic use and misdiagnosis of persistent bacterial infections.

Acknowledgment

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List of abbreviations

PCP Primary care physician

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Consent for publication

Written informed consent was obtained from the patient.

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Ethical approval

Ethical approval is not required at our institution for anonymous case reports.

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Summary of case

1	Patient (gender, age)	56 years, male
2	Final diagnosis	Minocycline-induced drug fever
3	Symptoms	Recurrent fever
4	Medications	NA
5	Clinical procedure	Minocycline was discontinued
6	Specialty	Internal medicine