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**Furazolidone-induced pulmonary toxicity in *Helicobacter pylori* infection: A report of two cases and a literature review**

pulmonary toxicity of furazolidone

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## Abstract

### BACKGROUND

*Helicobacter pylori* (*H. pylori*) infection is a global problem, causing significant morbidity and mortality. Furazolidone is recommended to eradicate *H. pylori* infections in China owing to the highly associated antibiotic resistance.

### CASE SUMMARY

This article presents two cases of lung injury caused by furazolidone treatment of *H. pylori* infection and the relevant literature review. Two patients developed symptoms, including fever, cough, and fatigue after receiving a course of furazolidone for *H. pylori* infection. Chest computed tomography showed bilateral interstitial infiltrates. Laboratory studies revealed elevated blood eosinophil count. After discontinuing furazolidone with or without the use of corticosteroids, the symptoms improved rapidly. A Pubmed database literature search revealed three reported cases of lung injury suggestive of furazolidone-induced pulmonary toxicity.

### CONCLUSION

Clinicians should be aware of the side effects associated with the administration of furazolidone to eradicate *H. pylori* infection.

**Key Words:** furazolidone; *Helicobacter pylori* infection; pulmonary hypersensitivity; Case report

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**Core Tip:** Furazolidone should be used as a treatment option for *H. pylori* eradication in China because of high antibiotic resistance. We present two cases of furazolidone-

induced pulmonary hypersensitivity determined by the Naranjo Adverse Drug Reaction Probability Scale score. Clinicians should be aware of the adverse effects of furazolidone, especially as it is widely used in the treatment of *H. pylori* infection in China.

## INTRODUCTION

*Helicobacter pylori* (*H. pylori*) infection is highly prevalent worldwide and is the leading cause of gastritis, peptic ulcers, and gastric cancer [1]. *H. pylori* remains the most common human bacterial pathogen, infecting approximately half of the global population [2]. The overall *H. pylori* infection rate has declined gradually over the past 3–4 years owing to ongoing interventions, education, improved sanitation, and water quality. However, the incidence was high (46.7 %) between 2006 and 2018 [3]. The most commonly recommended therapy worldwide is a standard dose of proton-pump inhibitor (PPI)-based regimen consisting of a PPI, clarithromycin, amoxicillin, and/or metronidazole [4]. However, the eradication rate of standard therapy is less than 80%, with the increasing drug resistance of *H. pylori* [5]. Furazolidone, a conventional drug administered for decades in the developing countries to eradicate *H. pylori* infections, has low resistance rates [6]. The Fifth Chinese National Consensus Report recommended the administration of furazolidone as a treatment option for *H. pylori* eradication in China because of its high antibiotic resistance [7].

The side effects of furazolidone are mild and well-tolerated by most patients [8]. Common furazolidone side effects include gastrointestinal reactions [4], including nausea, vomiting, diarrhea, and allergic reactions characterized by fever and rash [9]. Pulmonary hypersensitivity induced by furazolidone administration for the treatment of *H. pylori* infection is uncommon and rarely reported. Therefore, furazolidone-induced pulmonary toxicity goes largely unrecognized, prolonging diagnosis and leading to irreversible pulmonary complications.

Here, we present two cases of furazolidone-induced pulmonary hypersensitivity determined using the Naranjo Adverse Drug Reaction Probability Scale score (score: 11). Furthermore, we review the literature to improve our understanding of the side effects of furazolidone.

## **CASE PRESENTATION**

### ***Chief complaints***

progressive fatigue and cough lasting 1 wk.

### ***History of present illness***

A 38-year-old woman presented at our hospital complaining of progressive fatigue and cough lasting 1 wk. There was no history of pyrexia, weight loss, night sweats, chest tightness, dyspnea, or rash.

### ***History of past illness***

Her medical history revealed that she underwent cesarean section in 2017. Chronic non-atrophic gastritis caused by *H. pylori* infection was diagnosed 6 mo before her presentation. Eighteen days prior, she was prescribed rabeprazole (10 mg), potassium bismuth citrate (600 mg), amoxicillin (1 g), and furazolidone (100 mg) twice daily for 2 wk, to treat the *H. pylori* infection.

### ***Personal and family history***

Furthermore, the patient had never smoked and had no occupational exposure or a history of allergies.

### ***Physical examination***

Physical examination revealed the following <sup>2</sup> vital signs: temperature, 37 °C; heart rate, 95 beats/min; respiratory rate, 20 breaths/min; blood pressure, 112/86 mmHg; and oxygen saturation, 98% in room air. Pulmonary examination revealed bilateral coarse

breath sounds. Other physical examinations, including cardiac examinations, were unremarkable.

### ***Laboratory examinations***

Routine blood tests revealed an elevated eosinophil ratio (10.9%; reference range, 0.4–8%) and blood eosinophil count ( $0.55 \times 10^9/\text{L}$ ; reference range,  $0.02\text{--}0.52 \times 10^9/\text{L}$ ). We observed a rapid erythrocyte sedimentation rate (44 mm/h; reference range, 0–26 mm/h) and elevated immunoglobulin E (966 IU/mL; reference range, 0–87 IU/mL). The electrolyte panel, renal function, hepatic function, thyroid function, glucose level, tumor markers, and antinuclear antibodies were normal.

### ***Imaging examinations***

Computed tomography (CT) of the chest revealed bilateral interstitial infiltrates, mainly manifested as interlobular septal thickening and nodules (Figure 1A).

## **CHIEF COMPLAINTS FOR CASE 2**

a 1-day history of fever and a mild cough

## **HISTORY OF PRESENT ILLNESS FOR CASE 2**

A 36-year-old woman presented with a 1-day history of fever and a mild cough. She did not complain of weight loss, night sweats, chest tightness, dyspnea, or rash.

## **HISTORY OF PAST ILLNESS FOR CASE 2**

Twelve days before her presentation, she was diagnosed with *H. pylori* infection and treated with omeprazole (20 mg), potassium bismuth citrate (600 mg), amoxicillin (1 g), and furazolidone (100) mg twice daily.

## **PERSONAL AND FAMILY HISTORY FOR CASE 2**

The patient had never smoked and denied alcohol consumption.

### **PHYSICAL EXAMINATION FOR CASE 2**

Her vital signs at the outpatient clinic were as follows: temperature, 38.5 °C respiratory rate, 18 breaths/min; heart rate, 80 beats/min; and blood pressure, 116/74 mmHg. Chest auscultation revealed bilateral coarse breath sounds, while the other general examination results were normal.

### **LABORATORY EXAMINATIONS FOR CASE 2**

Although the WBC and neutrophil counts were within the normal ranges, the eosinophil ratio (9.8%) and C-reactive protein (11.2 mg/L; reference range, 0–10 mg/L) were elevated. The electrolyte panel, renal function, hepatic function, and cardiac workup results were normal.

### **IMAGING EXAMINATIONS FOR CASE 2**

Chest CT showed bilateral interstitial infiltrates, including patchy hyperdense foci, combined with thickening of the interlobular septa and nodules (Figure 2A).

### **FINAL DIAGNOSIS**

The two patients were diagnosed with furazolidone-induced lung injury based on the findings.

### **TREATMENT**

For case 1, the patient received a 6 days treatment with intravenous prednisone (40 mg/day). Then the intravenous administration of prednisone was replaced with oral administration, and the dose was gradually reduced over a week. For case 2, due to the adamant refusal of oral corticosteroids administration and hospitalization, only furazolidone was discontinued, and antipyretic treatment was administered.

### **OUTCOME AND FOLLOW-UP**

For case 1, the fatigue and cough rapidly subsided. The eosinophil ratio was 0.3%, and chest CT showed significant absorption of bilateral interstitial infiltrates (Figure 1B). The patient did not show any similar symptoms during the follow-up period. For case 2, the symptoms improved rapidly, and chest CT after 1 mo revealed obvious absorption of bilateral interstitial infiltrates (Figure 2B).

## DISCUSSION

*Helicobacter pylori* infection is a family-based, population-wide disease that causes significant morbidity and mortality as it causes peptic ulcers and gastric cancer. It poses a major health threat to the Chinese families and society through increasing the economic and medical burden of the country [3]. In 2020, a meta-analysis, including 670,572 participants from 26 provinces of mainland China, reported that the overall prevalence was 63.8% between 1983 and 1994, 57.5% between 1995 and 2005, and 46.7% between 2006 and 2018 [10]. The infection rates vary greatly among different geographical regions and are much higher in the rural areas [10]. The discovery that *H. pylori* causes most duodenal ulcers and approximately two-thirds of gastric ulcers is seminal. Furthermore, *H. pylori* has been estimated to increase lifetime risk of gastric cancer by 1.5%–2.0% [11]. Previous studies reported that *H. pylori* eradication for gastric cancer prevention is cost-effective in China [12].

Optimal clinical management and treatment approaches are unknown and evolve in response to the changing antimicrobial resistance patterns [11]. In many parts of the world, triple therapy with PPI, clarithromycin, amoxicillin, or bismuth-based quadruple therapy with PPI, bismuth, tetracycline, and metronidazole, is the most commonly administered first-line treatment regimen [4]. In China, the rate of *H. pylori* resistance to antibiotics, including clarithromycin, metronidazole, and levofloxacin, is increasing [7]. Recent studies reported that the resistance rates to clarithromycin, metronidazole, and levofloxacin were 20–50%, 40–70%, and 20–50%, respectively [13]. Furthermore, *H. pylori* can be resistant to multiple antibiotics [13]. Previous studies reported that the

dual resistance of *H. pylori* to clarithromycin and metronidazole is approximately 25% [14]. Therefore, implementing these regimens in China may result in significantly lower eradication rates.

Furazolidone is a synthetic nitrofuran monoamine oxidase inhibitor with broad-spectrum antimicrobial activity [15]. However, its therapeutic effect on *H. pylori* infection cannot be ignored. Currently, the resistance rates of *H. pylori* to furazolidone are low (0%–1%) [13]. Because it rarely produces resistance, it can be readministered after a treatment failure. Therefore, some national and regional guidelines for *H. pylori* infection recommend furazolidone as a component of rescue therapy [11]. However, furazolidone has been administered in a few high-quality eradication studies, and there is a lack in randomized trials. Additionally, concerns about its safety and use have resulted in its unavailability in the United States and European Union [4]. However, due to antibiotic resistance, it is recommended as empirical first-line therapy for *H. pylori* infection in China [7]. With the increasing use of furazolidone in China, its related side effects should be fully recognized and monitored.

The most common side effects of furazolidone are gastrointestinal reactions, including nausea and abdominal pain [4, 15]. Furazolidone-related allergic reactions are clinically common and are characterized by fever (1.8%) and rash (0.3%) [10]. One study reported that rash and fever were the most frequent clinical findings in antibiotic-induced drug reactions, with eosinophilia and systemic symptoms [16]. Pulmonary hypersensitivity is uncommon; however, it often leads to fatal damage [16]. Drug-induced pulmonary hypersensitivity and interstitial lung disease may be mediated by T cells; however, they are primarily affected by antibody-mediated factor functions (I–III) [17].

Following furazolidone treatment for *H. pylori* infection, the patients reported in this case report developed pulmonary hypersensitivity. The Naranjo probability score indicated that the adverse events could be drug-related. Using the search algorithm

“furazolidone” and “pulmonary” or “lung”, we searched the PubMed database (as of May 2022). Three cases of pulmonary hypersensitivity were attributed to furazolidone; however, these included other bacterial infections. In all the reported patients, symptoms developed during or immediately after furazolidone administration, with prominent pyrexia and dyspnea (Table 1) [18-20]. Chest radiograph revealed bilateral interstitial infiltrates with subsequent eosinophilia.

Our cases were similar to the three previously reported cases of furazolidone pulmonary hypersensitivity, with minor differences. Both patients developed symptoms during their furazolidone treatment. The three previously reported cases had severe symptoms, including significant pyrexia, dyspnea, and bibasilar crackles. The symptoms and physical signs in our cases were milder than those of the previous studies as there was no dyspnea or obvious crackles. This could be attributed to racial differences with respect to drug susceptibility or factors related to medication dosage and duration. However, the eosinophil levels were elevated during the early disease stages. Lung imaging revealed bilateral interstitial infiltrates. However, since only the radiographs of the patients have been shown in the past, the specific imaging findings of the chest CT are unknown. Both cases in our report showed interlobular septal thickening and nodules on the chest CT. Furthermore, the symptoms improved rapidly and significantly without recurrence after discontinuing furazolidone and the concurrent steroid administration.

## **CONCLUSION**

This report highlights two rare cases of pulmonary hypersensitivity caused by furazolidone during treatment of *H. pylori* infection. Clinicians should be aware of the side effects of furazolidone, especially because it is widely used in China to treat *H. pylori* infection. The possibility of furazolidone-induced pulmonary hypersensitivity can be recognized based on the medical history, elevated eosinophil levels, and pulmonary

interstitial infiltrates. Appropriate and timely treatment is required to prevent drug-induced damage.

#### **ACKNOWLEDGEMENTS**

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