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Case report

A case of hypersensitivity pneumonitis caused by a humidifier: diagnosis and management in rural practice

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Abstract

Hypersensitivity Pneumonitis (HP) is an allergic interstitial lung disease that arises from type III and IV allergic reactions. During the COVID-19 outbreak, HP was established as having similar manifestations to COVID-19. In remote rural regions of Japan, where respiratory specialists are not readily accessible, HP is not always easy to differentiate, and establishing a definitive diagnosis can be challenging due to insufficient laboratory examinations. Herein, we present a case of a moderately definite diagnosis of acute non-fibrosing HP. The foundation of treatment included antigen avoidance, which necessitates a comprehensive analysis of the patient's medical history. In instances where anomalous chest imaging outcomes are observed, it is imperative to conduct a comprehensive review of the patient's medical history, and to consider the possibility of HP.

Key words: primary care medicine, rural medicine, COVID-19, humidifier lung, hypersensitivity pneumonitis

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Introduction

Hypersensitivity pneumonitis (HP) is an allergic interstitial lung pathology resulting from type III and IV hypersensitivity reactions. In geographically isolated location where pulmonology experts were not readily available in the COVID-19 pandemic, HP was documented to present similarly to COVID-19. The differentiation between these two conditions is often complicated, thereby rendering the establishment of a definitive diagnosis particularly arduous due to the lack of adequate laboratory assessments. However the prompt identification and management of HP are necessary to significantly diminish the likelihood of grave respiratory complications.

The cornerstone of therapeutic intervention is predicated upon the avoidance of antigens, which necessitates a thorough evaluation of the patient's clinical history. The condition may achieve a state of complete remission or escalate to a severe form if it transitions into a chronic state, thereby emphasizing the importance of a comprehensive medical interview.

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Case Presentation

In 2021, a 61-year-old presented with body hypertension, with a recorded temperature of 38.5°C persisting over two weeks. Furthermore, he continued to experience a state of feverishness and a prevailing feeling of unease. The patient was married and worked in an office. His medical history included plaque psoriasis, gastric ulcers, and skin cancer. He had no pets and had smoked 10 cigarettes a day for 40 years. Morning stiffness and arthralgia were not observed.

Notably, the patient did not present with any signs of coughing, although a slight reduction in appetite and a decreased frequency of urination were observed. Furthermore, the patient displayed symptoms of palpitations, which prompted his visit to a medical professional. It is noteworthy that the patient had ceased smoking a month prior, consequently resulting in a weight gain of 9 kilograms. Additionally, the patient had procured an ultrasonic humidifier three years prior and had been using it since December of the prior year, excluding rainy days. To relieve respiratory

distress, the patient resorted to inhaling the steam emitted from the humidifier.

Physical examination revealed severe respiratory distress, categorized as Grade 5 on the modified British Medical Research scale. The patient's level of consciousness was E4V5M6. His vital signs included a pulse of 136 beats/min, a respiratory frequency of 42 breaths/min, a blood pressure of 129/75 mmHg, and a body temperature of 38.6°C. His chest was clear on auscultation. Jugular venous pressure was not elevated, and he showed no peripheral edema in the lower extremities or clubbed fingers. A chest X-ray performed at the first visit revealed no significant abnormalities.

Initial laboratory investigation revealed a white blood cell count of 23,190/μL, with a difference of 92% in the segmented neutrophils, 3.6% in lymphocytes, 0.40% in eosinophils, and 3.2% in monocytes. The platelet count was 37.9×104/μL. His hemoglobin level was 14.8 g/dL (Table 1). Arterial blood gas data at 3 L oxygen administration in the emergency room are shown (Table 2).

A mild increase in KL-6 and an increase in SP-D were observed in the blood draw, thus prompting a suspicion of interstitial lung disease. Consequently, a mycoplasma test

Table 1 Laboratory data

	Patient values	Normal values
Hematology		
White blood cells	23,190/μL	3,300–8,800
Neutrophil	92.70 %	38.5–80.5
Lymphocyte	3.60 %	16.5–50.0
Eosinophil	0.40 %	0–8.5
Monocyte	3.20 %	2.0–10.0
Hemoglobin (Hb)	14.8 d/dL	13.7–16.8
Platelets count (PLT)	37.9×10^4 /μL	$15.8–34.8\times10^4$
Biochemistry		
Total protein	7.1 g/dL	6.6–8.1
Total-Bilirubin	0.8 mg/dL	0.4–1.5
Aspartate transaminase (AST)	26 IU/L	13–30
Alanine transaminase (ALT)	40 IU/L	10–42
Alkaline phosphatase (ALP)	359 IU/L	38–113
Blood urea nitrogen (BUN)	12.5 mg/dL	8.0–20.0
Creatinine Cre	0.9 mg/dL	0.65–1.07
Sodium (Na)	137 mEq/L	138–145
Potassium(K)	4.3 mEq/L	3.6–4.8
Chloride (Cl)	104 mEq/L	101–110
Serology		
C-reactive protein (CRP)	5.15 mg/dL	0.00–0.14
Krebs von den lungen (KL-6)	366 U/mL	0–500
Pulmonary Surfactant Protein-D (SP-D)	209.6 ng/dL	0–110
Beta-D-glucan	6.9 pg/mL	0–20.0
Influenzae antigen	negative	negative
Mycoplasma IgM	negative	negative
Urinaysis		
Legionella antigen	negative	negative
Pneumococcal antigen	negative	negative

Table 2 Arterial blood gas

Parameter	Patient value	Normal range
pH	7.404	7.35 to 7.45
Arterial O_2 pressure (PaO_2)	57.9 Torr	75 to 100
Arterial CO_2 pressure ($PaCO_2$)	45.3 Torr	35 to 45
Bicarbonate (HCO_3^-)	23.2 mEq/L	22 to 26
Base exces (BE)	−0.2 mEq/L	−2 to 2
Percutaneous oxygen saturation (SpO_2)	84%	94 to 100
Alveolar-arterial oxygen difference (A-aDO_2)	41.4 Torr	0 to 20

was performed to distinguish it from atypical pneumonia; however, results were negative. Subsequent PCR testing was carried out for COVID-19, yielding negative findings. Computed tomography (CT) images revealed a mosaic pattern, with regions of ground-glass opacity observed predominantly in the superior lobes of both lungs (Figure 1).

Due to the patient's compromised respiratory condition, a course of empiric therapy with ABPC/SBT 1.5 g q6h was initiated to investigate the possibility of bacterial pneumonia. Given the prevailing prevalence of COVID-19 in the surrounding vicinity, screening for COVID-19 was also conducted, yielding negative results. Subsequently, on the eighth day after admission, a consultation was sought from the Respiratory Medicine Department. At that time, enhancements in the patient's overall health condition and respiratory function were noted (Table 3).

Based on medical imaging results and the assessment of medical history, a suspicion of HP arising from the use of a humidifier was raised. Subsequently, sputum culture revealed the presence of *Pseudomonas aeruginosa*. Following discharge, the use of a humidifier was explicitly forbidden, with no apparent exacerbation of symptoms. An assessment was conducted to avoid duplicating the clinical signs and symptoms caused by contact with the environment. Furthermore, no recurrence of symptoms was noted. Although the water in the humidifier was visually clean, and water culture was performed, no fungal culture could be obtained.

One-month post-hospital discharge, CT scan revealed gradual resolution of the observed ground glass opacities (Figure 2).

Discussion

HP can be categorized into three distinct phases: the acute, subacute, and chronic phases. The acute phase can further be divided into the nonfibrotic and fibrotic HP phases. This case presents a moderately definite diagnosis of acute non-fibrosing hypersensitivity pneumonitis. The classification of nonfibrotic and fibrotic HP has been shown to indicate the progression and prognosis of the disease, as documented in the Japanese guidelines[1].

During the COVID-19 epidemic, certain diagnostic procedures, such as bronchoalveolar lavage (BAL), pulmonary function tests, lung biopsy, and other tests, were not con-

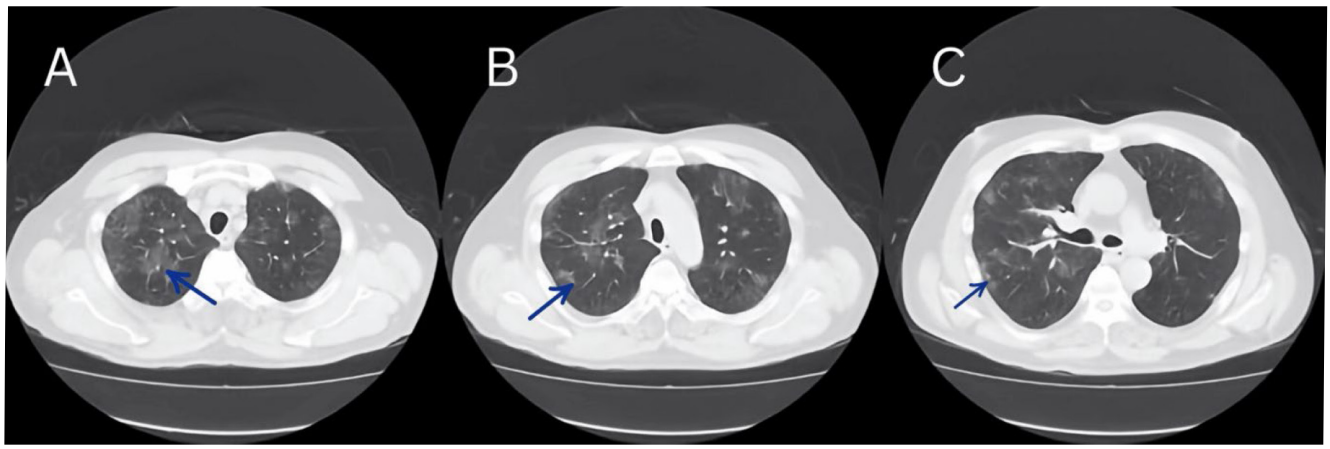

Figure 1 Chest computed tomography (CT) on arrival.
Chest CT reveals the presence of ground glass opacity, as indicated by the arrows.
ABC in order from pulmonary apex.

Table 3 Progress chart

Date	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Body temprature (celsius)	38.5	37.8	38	37.4	37.4	37.3	36.8	36.7
Heart rate	82	77	86	85	80	84	80	76
SpO_2 (%)	94	93	94	96	95	97	96	96
Oxygen dose (L)	5	5	3	3	1	1	1	0
WBC	23,190			11,610			9,250	
C-reactive protein	5.15			7.88			3.98	
ABPC/SBT 1.5 g	q6h	q6h	q6h	q6h	q6h	q6h	q6h	q6h

WBC: white blood count; ABPC/SBT: ampicillin/sulbactam.

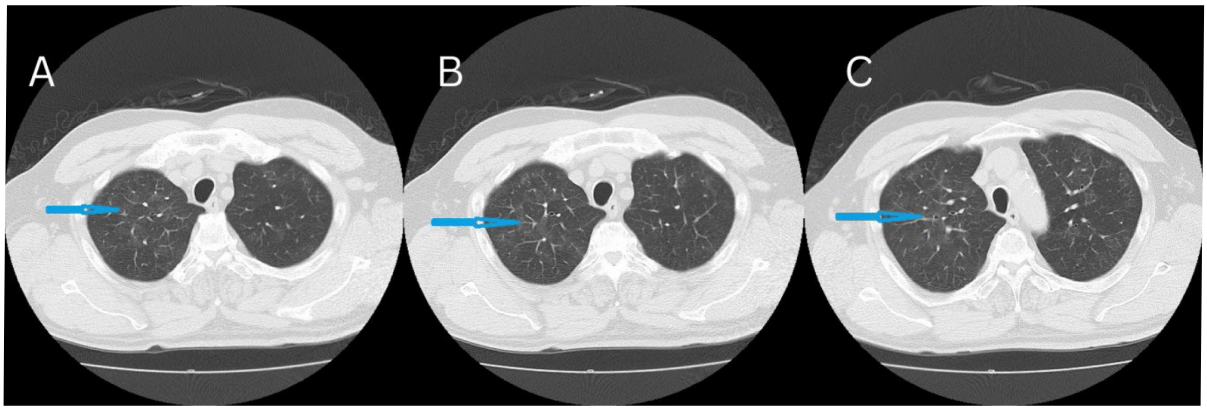

Figure 2 Chest computed tomography (CT) post-hospital discharge.
CT scan of the chest was conducted one month following the patient's discharge from the hospital. Arrows indicate the dissolution of ground glass opacity. ABC in order from pulmonary apex.

ducted due to suspicion of COVID-19 infection. Typically, BAL is recommended for differential diagnosis as it aids in distinguishing between various conditions, such as eosinophilic pneumonia and pneumocystis pneumonia. Consequently, the diagnosis relies heavily on the patient's medical history, diagnostic imaging, and physical examination, as outlined in Table 4[2].

Prior studies have reported that COVID-19 occurs as a manifestation of HP, meaning that achieving an accurate and definitive diagnosis of HP may require invasive tests[3]. At the relevant time in the pandemic situation, there were restrictions on performing the test itself; even today, when COVID-19 infections are classified as class 5 under the Japanese Infectious Disease Control Law (aligning with the classification of the Influenza virus), there are still likely to be significant limitations on diagnosis in remote areas where respiratory physicians are lacking. In addition, a comprehensive report has been published regarding an innovative strategy for the serodiagnosis of HP[4]. Although the diagnosis of HP is predominantly based on exposure identification[5].

In this case, as antigen avoidance was indeed feasible and fibrosis did not manifest, the administration of oxygen alone would have been sufficient treatment. As in the present case, in actual clinical practice, antigen avoidance testing may not be performed when a patient's condition improves smoothly, as the patient automatically becomes antigen-avoidant upon hospitalization. Furthermore, many cases of fibrotic HP do not exhibit clinical improvement, thus, the absence of clinical improvement in the antigen avoidance test does not exclude the possibility of a diagnosis of fibrotic HP[6].

HP is regarded as either a type III or type IV allergic response, in which specific antibodies or sensitized lymphocytes triggered by the repeated inhalation of fungi, bacteria, or heterologous animal proteins interact with the causative antigen locally within the pulmonary system. In addition to the type III hypersensitivity reaction, endotoxins can affect the lungs through the trans-airway and trans-vascular pathways, leading to concentration-dependent pulmonary injury[7].

Table 4 Significant predictors of hypersensitivity pneumonitis

Variables	Odds ratio (95% CI)
Exposure to a known offending antigen	38.8 (11.6–129.6)
Positive precipitating antibodies	5.3 (2.7–10.4)
Recurrent episodes of symptoms	3.3 (1.5–7.5)
Inspiratory crackles	4.5 (1.8–11.7)
Symptoms 4–8 hours after exposure	7.2 (1.8–28.6)
Weight loss	2.0 (1.0–3.9)

Endotoxin measurement in rural medicine

The measurement of endotoxin in general hospitals is practically difficult and often does not contribute to changes in treatment strategy compared with measurements in hospitals where test results are not immediately available. HP is a disease that can be completely cured if diagnosed in the acute phase with identification of the causative antigen. Therefore, early diagnosis and identification of the cause of HP are very important. When patients are diagnosed with atypical pneumonia or COVID-19 infection, it is essential to conduct a detailed medical interview, investigate their living environment, and interview them, keeping HP in mind.

Conclusion

Herein, we report a case of moderately definite HP, which showed disease remission and was ultimately diag-

nosed based on typical imaging findings and medical history. A definitive diagnosis of hypersensitivity pneumonitis is difficult, particularly in remote area, while a detailed interview and physical examination are important in situations where medical resources are limited. During the COVID-19 pandemic, it is imperative to closely observe treatment progression. The use of humidifiers increased during the COVID-19 outbreak, prompting a thorough assessment of the possible implications of hypersensitivity pneumonitis linked to this practice.

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