Mimicking pneumonia with septic shock: A case report and literature review

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Abstract. Hydrochlorothiazide (HCTZ) is a commonly used diuretic antihypertensive drug that can cause electrolyte disorders, hyperglycemia and hyperuricemia as well as rare life-threatening adverse drug reactions. These include non-cardiogenic pulmonary edema, interstitial pneumonia, angioedema and aplastic anemia. The present report describes a case of a 59-year-old man who developed a hypersensitivity reaction to HCTZ. Specifically, the patient presented with symptoms of cough, chest tightness and shortness of breath, with pneumonic consolidation on chest CT and elevated levels of white blood cell count, neutrophil percentage, C-reactive protein and procalcitonin. A presumptive diagnosis of severe pneumonia was made initially. However, during the gradual recovery of the patient through treatment, he mistakenly ingested HCTZ containing losartan potassium intended for another patient, which resulted in symptoms similar to those observed upon admission. Upon further inquiry into the medical history, it was revealed that the patient had also taken irbesartan/HCTZ 4 h prior to hospitalization. There was no evidence of a pathogenic infection. Therefore, HCTZ-induced anaphylactic reaction was considered to be the most likely etiology for his severe shock. Treatments including epinephrine, methylprednisolone and respiratory support were administered. After 7 days, the patient was transferred from the Respiratory Intensive Care Unit [The Affiliated Jiangning Hospital of Nanjing Medical University (Nanjing, China)] to a general ward. During the follow-up, 12 months after advising the patient to discontinue HCTZ, there had been no recurrence of the aforementioned symptoms. At the time of publication, the patient is currently alive.

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Introduction

Hydrochlorothiazide (HCTZ) is a widely used diuretic antihypertensive drug that reduces the blood volume and dilates blood vessels to lower peripheral vascular resistance, which serves to alleviate mild hypertension (1). HCTZ acts on the renal tubules primarily by inhibiting the sodium-chloride cotransporter in the proximal part of the tubules (2). This inhibition reduces the reabsorption of sodium and water, leading to increased urinary excretion. The overall effect aims to lower blood pressure and treat edema (2). Despite its efficacy, HCTZ has been associated with several adverse effects, including hyponatremia, hypokalemia, hypotension, phototoxicity and even pulmonary edema and interstitial pneumonia (3). Since the inaugural report documenting the case of HCTZ-induced non-cardiogenic pulmonary edema in 1968 (4), this rare but severe adverse drug reaction has been reported in >60 cases to date (5-7). However, the primary mechanism underlying HCTZ-induced pulmonary edema remain unclear. In patients with mild reactions such as nausea, vomiting and diarrhea, the symptoms will typically resolve spontaneously upon the discontinuation of HCTZ. However, in critically ill individuals with anaphylactic shock caused by HCTZ, resolution is commonly achieved with diuretics, respiratory support and norepinephrine (8). The present report describes a case of HCTZ-induced acute pulmonary edema with anaphylactic shock, which was initially misdiagnosed as severe pneumonia with septic shock. Due to an unintended re-exposure to HCTZ, HCTZ-induced anaphylactic reaction was finally confirmed. During the therapeutic process, the patient once developed systemic capillary leak syndrome (SCLS; Clarkson's disease). The present case highlights the importance of recognizing the potential for HCTZ-induced adverse reactions, particularly in patients with atypical clinical presentations, to promptly diagnose and treat these rare but potentially life-threatening adverse events.

Case report

A 59-year-old man presented to the Emergency Department, Jinling Clinical Medical College of Nanjing Medical University (Nanjing, China) in December, 2021 because of continuous symptoms of cough, chest tightness and shortness of breath for 4 h. The past medical history of the patient was long-lasting hypertension. The patient had taken amlodipine besylate to control his elevated blood pressure (BP) for 20 years. However, 1 week before his presentation to the hospital, the care physician added irbesartan/HCTZ to the antihypertensive regime. The patient denied any history of allergy to antibiotics. On physical examination, notable vital signs of the patient included a temperature of 38.9˚C (reference, 36.3-37.2˚C), heart rate of 120 beats/min (reference, 60-120 beats/min), respiratory rate (RR) of 32 times/min (reference 13-21 times/min) and BP of 82/48 mmHg (reference, between 90/60 and 120/80 mmHg). Comprehensive clinical assessment revealed elevations of white blood cell (WBC) count, neutrophil percentage, C-reactive protein (CRP) levels, procalcitonin (PCT) levels and interleukin-6 levels. Arterial blood analysis revealed a pH of 7.45, arterial oxygen tension 59.9 mmHg and arterial carbon dioxide tension 30.4 mmHg. No pathogens were found in the sputum, blood or urine specimens (Table I). A chest CT demonstrated bilateral lung inflammation, minimal pleural effusion and interstitial pulmonary edema (Fig. 1). The patient underwent image evaluation via CT of the thorax and chest (SOMATOM drive; Siemens Medical Solutions; Siemens Healthineers). A standard protocol was applied: The patient was in supine position and the tube voltage and tube current was 2x100 kV and 40-1600 mAs with a scan from the lung apex to the diaphragmatic angle. Scan direction was cranio-caudal (slice thickness, 0.5-5 mm) to obtain axial and coronal images. Pulmonary embolism was initially excluded. Based on the clinical presentation and exam findings, the patient was diagnosed with septic shock secondary to severe pneumonia. Early goal-directed therapy was initiated, including rehydration and empirical broad-spectrum antibiotics, with meropenem (dose, 1 g; administrated every 8 h) added for 4 days.

Despite ongoing treatment, the respiratory failure of the patient persisted. Therefore, the patient was transferred to the Department of Respiratory and Critical Care Medicine, The Affiliated Jiangning Hospital of Nanjing Medical University (Nanjing, China) in December, 2021 with laboratory results similar to those observed during the hospitalization at the Jinling Clinical Medical College of Nanjing Medical University (Table I). Physical examination of the patient revealed cyanosis with BP of 145/80 mmHg, RR of 20 breaths/min and a temperature of 36.3˚C. An echocardiogram was performed. It revealed that although limited by a poor window, a normal ventricular ejection fraction was observed with no areas of hypokinesis. A chest CT revealed sporadic pulmonary inflammation and minimal pleural effusion (Fig. 2). Pneumonia with sepsis was persistently suspected. The patient immediately received cefoperazone/sulbactam (dose, 3 g; administrated every 8 h) and moxifloxacin (dose, 0.4 g; administrated every 24 h) alongside non-invasive ventilation. The vital signs of the patient stabilized on day 9 following hospitalization. Despite negative findings for bacteria in blood, urine, stool and sputum cultures, the respiratory failure of the patient persisted.

The patient then experienced an unintended recurrence of severe symptoms on day 10, with an increased RR of 35 times/min and a drop in BP to 60-70/40-45 mmHg. The patient also developed a fever with a maximum body temperature of 38.5˚C and chills. Therefore, he was transferred to the Respiratory Intermediate Care Unit (RICU) and underwent a battery of laboratory tests (Table I). Chest X-rays performed in the RICU did not reveal any progression of pulmonary infection or interstitial edema (Fig. 3). Pulmonary CT angiography did not detect any newly-formed emboli. Samples were collected for sputum, blood and urine cultures, finding no microorganisms. Extensive physical examination, laboratory tests and echocardiography were conducted, which ruled out endocarditis and autoimmune diseases.

The medical history of the patient was thoroughly investigated, where the possibility of other underlying causes was explored. It was then revealed that the patient recently had HCTZ added to his antihypertensive medication regimen, which he ingested on two occasions before admission. After the first dose of HCTZ, symptoms of chest tightness and wheezing were relieved after resting initially. However, after the second dose of HCTZ, 7 days later, the patient experienced more severe symptoms, necessitating hospitalization. During the hospital stay, all oral antihypertensive medications were discontinued, which resulted in a marked improvement in his condition with systemic treatment. On day 9, a new patient was admitted to the same ward who had been receiving daily doses of losartan potassium/HCTZ tablets for hypertension. On day 10 the patient mistakenly took losartan potassium/HCTZ (dose, 12.5 mg HCTZ in combination with 50 mg losartan potassium) due to a mix up and the close proximity of the bedside table of another patient. The patient experienced shock within minutes. This raised concerns about HCTZ-induced anaphylactic shock. Subsequently, the condition of the patient swiftly improved with fluid administration, norepinephrine infusion, dexamethasone and oxygen supplementation. This further confirmed the hypothesis that the patient experienced a severe allergic reaction following the administration of HCTZ. On day 20, WBC, neutrophil percentage, CRP, PCT and pulmonary imaging results suggested patient recovery (Fig. 4; Table I). The patient was provided specific instructions to completely avoid HCTZ in the future after being discharged after 23 days of hospitalization. A monthly follow-up was conducted by telephone, with no similar episodes noted in 12 months. The patient is still alive at the time of publication.

A literature review was performed using search engines, such as PubMed (https://pubmed.ncbi.nlm.nih.gov/), Wiley Online Library (https://onlinelibrary.wiley.com/), Web of Science (https://www.webofscience.com/) and NCBI (https://www.ncbi.nlm.nih.gov/), with the following key words: 'Hydrochlorothiazide', 'mechanism', 'anaphylactic reaction', 'adverse drug reactions', 'pneumonia', 'pulmonary edema', 'Clarkson's disease' and 'treatment'. Cases that presented adverse reactions caused by other thiazide diuretics or the coadministration of HCTZ with other medications were excluded. Inclusion criteria involved matching symptoms, similar medication history, comparable biochemical results, imaging manifestations and clinical outcomes.

Table I. Laboratory data.

Variable	Reference range[a]	Day 1 of hospitalization	Day 5 of hospitalization	Day 10 of hospitalization	Day 20 of hospitalization
Blood					
Hemoglobin (g/l)	130-175	167	138	179	138
Hematocrit (%)	40-50	49	42.5	55.5	43.1
White-cell count (x10^9/l)	3.5-9.5	20.05	6.48	5.4	12.58
Neutrophils	1.8-6.3	19.21	4.54	4.79	10.06
Lymphocytes	1.1-3.2	0.18	1.02	0.52	1.81
Monocytes	0.1-0.6	0.64	0.52	0.07	0.54
Eosinophils	0.02-0.52	0	0.36	0.01	0.1
Basophils	0-0.06	0.02	0.04	0.01	0.07
Platelet	125-350	208	207	250	279
Differential percentage (%)					
Neutrophils	40-75	95.8	70.1	88.8	79.9
Lymphocytes	20-50	0.90	15.7	9.6	14.4
Monocytes	3-10	3.20	8.0	1.3	4.3
Eosinophils	0.4-8	0	5.6	0.2	0.8
Basophils	0-1	0.02	0.6	0.1	0.6
C-reactive protein (mg/l)	0.1-10	36	5.08	42.17	<0.05
Procalcitonin (ng/ml)	0-0.5	42.14	3.84	27.61	1.80
IL-6 (ng/l)	0-7	696.3	0	-	-
D-dimer (mg/l)	0-0.55	8.52	0.75	1.20	0.25
B-type natriuretic peptide (μg/l)	300-450	104.7	-	272	-
Cardiac troponin I (μg/l)	0.01-0.02	0.048	<0.01	<0.01	-
Creatine kinase MB (μg/l)	2-7.2	7	<2	<2	-
Prothrombin time test (sec)	9-15	12.8	11.8	13.5	11
Prothrombin time test-international normalized ratio (%)	0.8-1.2	1.12	1.09	1.24	1.02
Activated partial thromboplastin time (sec)	20-40	27.9	32.7	36.2	33.6
Thrombin time (sec)	14-21	19.4	14.5	15.1	13.9
Arterial blood gas					
pH	7.35-7.45	7.45	7.44	7.39	7.45
Partial pressure of O_2 (mmHg)	80-108	59.9	53	73	67
Partial pressure of CO_2 (mmHg)	35-45	30.4	36	34	40
Lactate (mmol/l)	0.5-2.5	3.1	0.8	3.2	1.1
Total protein (g/l)	65-85	49.2	57	50.6	59.5
Albumin (g/l)	40-55	26.6	35.1	30.5	35.6
Urea nitrogen (mmol/l)	3.1-8	7.0	6.81	7.04	8.8
Creatinine (μmol/l)	57-97	105.1	76.4	80.1	70.3
Glucose (mmol/l)	3.9-6.1	12.3	4.97	9.5	5.0
Total bilirubin (μmol/l)	0-26	18.4	24.6	8.6	16.3
Direct bilirubin (μmol/l)	0-8	6.7	11.9	4.1	5.0
Alanine aminotransferase (U/l)	9-50	22	41	31.2	21.4
Aspartate aminotransferase (U/l)	15-40	26	37.2	18.5	14.4
Alkaline phosphatase (U/l)	45-125	52	-	56.9	-
Blood					
Bacteria	None	None	None	None	None
Urine					
Bacteria	None	-	None	None	None
Sputum					
Bacteria	None	None	None	None	None

[a]Reference values are affected by many variables, including the patient population and the laboratory methods used. None, no bacteria were detected in the samples; -, the examination for this aspect was not conducted.

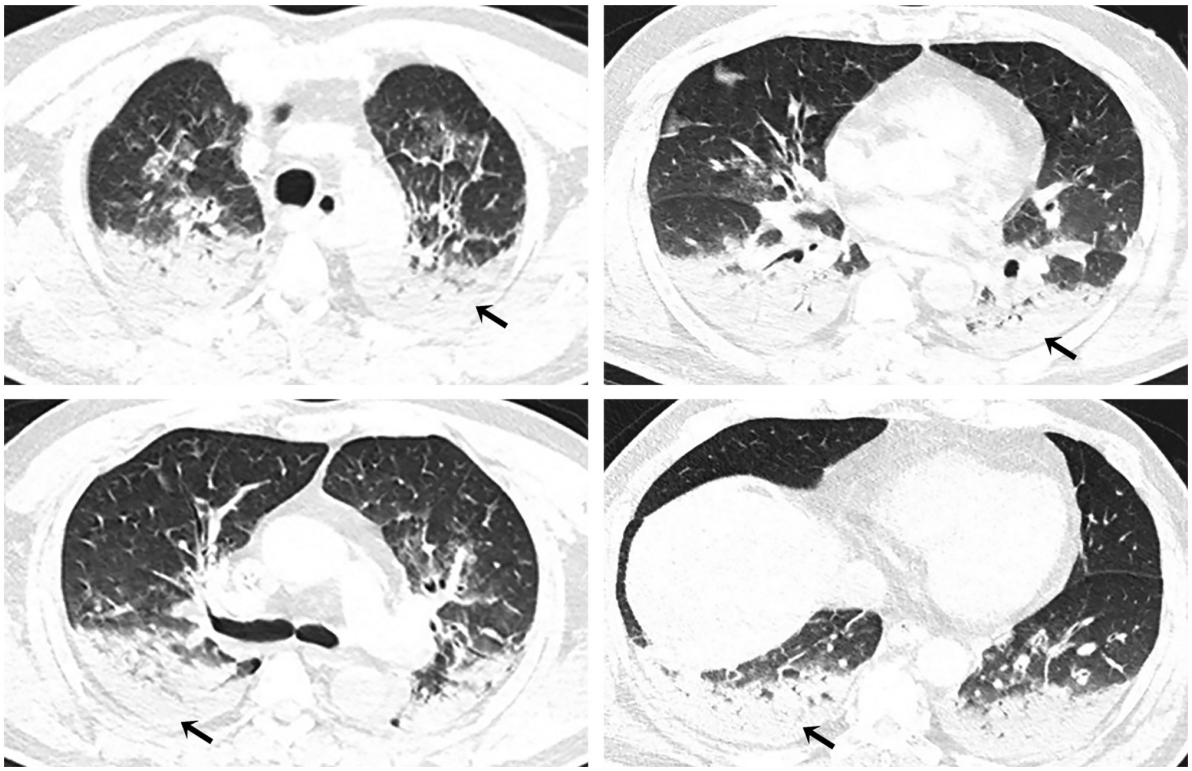

Figure 1. Chest CT on day 1 of hospitalization revealing bilateral lung inflammation and interstitial pulmonary edema with bilateral minimal pleural effusion (arrows).

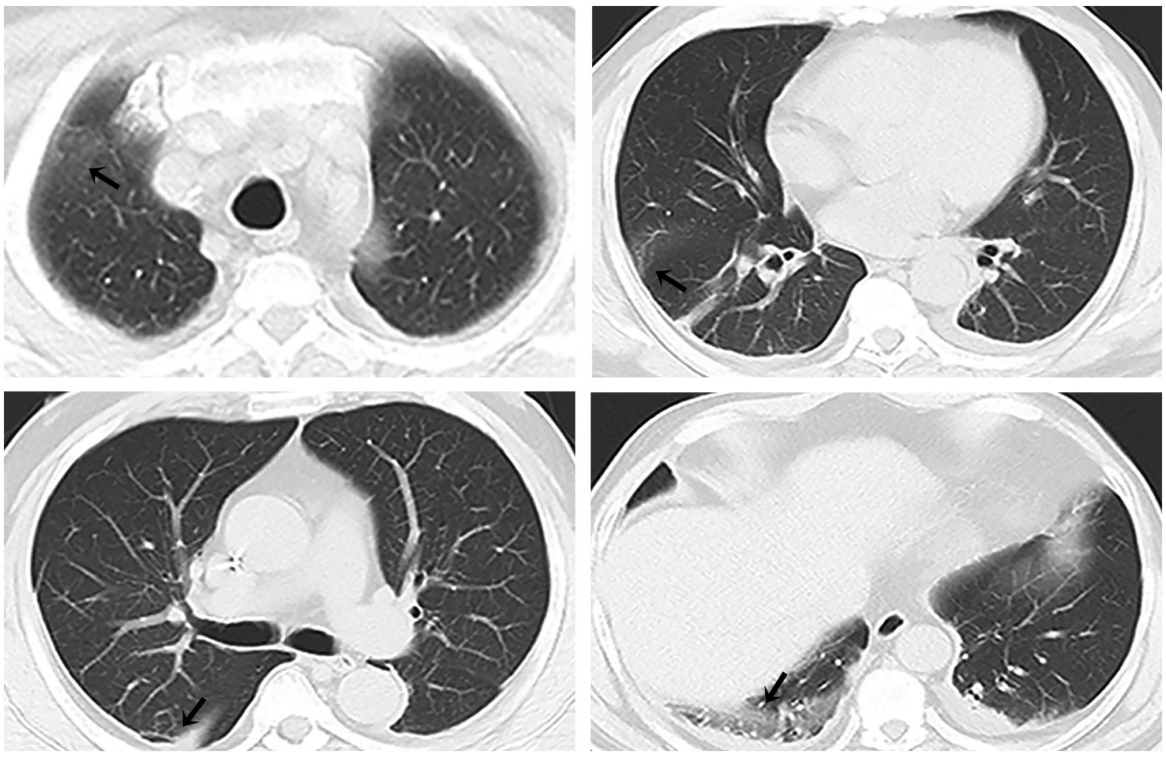

Figure 2. Chest CT on day 5 of hospitalization showing bilateral scattered pulmonary infection and minimal pleural effusions (arrows).

Discussion

The hypersensitivity reaction to HCTZ rarely presents with pneumonia-like symptoms, and there have only been two reported cases worldwide with such a presentation (7,9). The present study was the first to report a case within China of severe allergic shock attributed to HCTZ. Septic shock can appear similar to anaphylaxis, with symptoms including

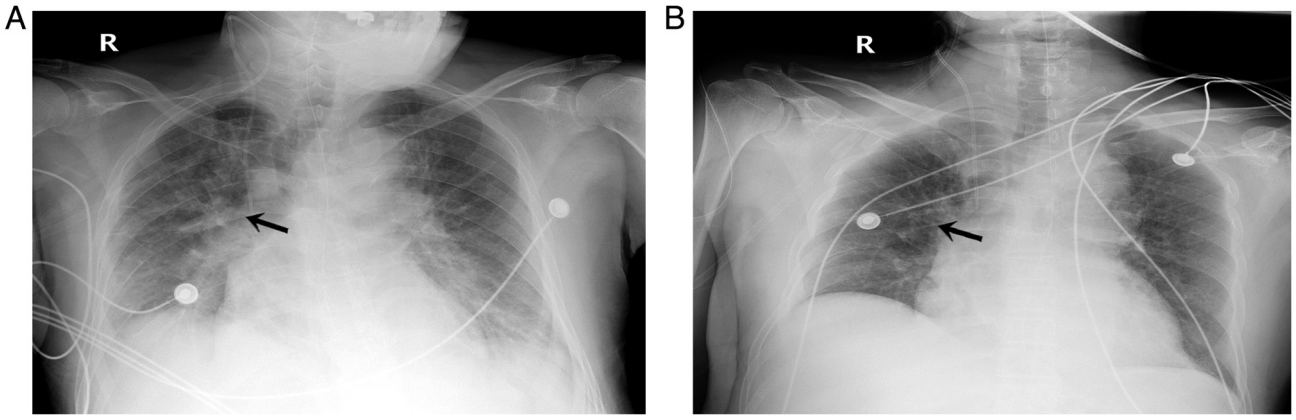

Figure 3. Chest X ray showing bilateral scattered pulmonary infection and minimal pleural effusions (arrows). (A) day 10 and (B) day 12 of hospitalization. R, right side.

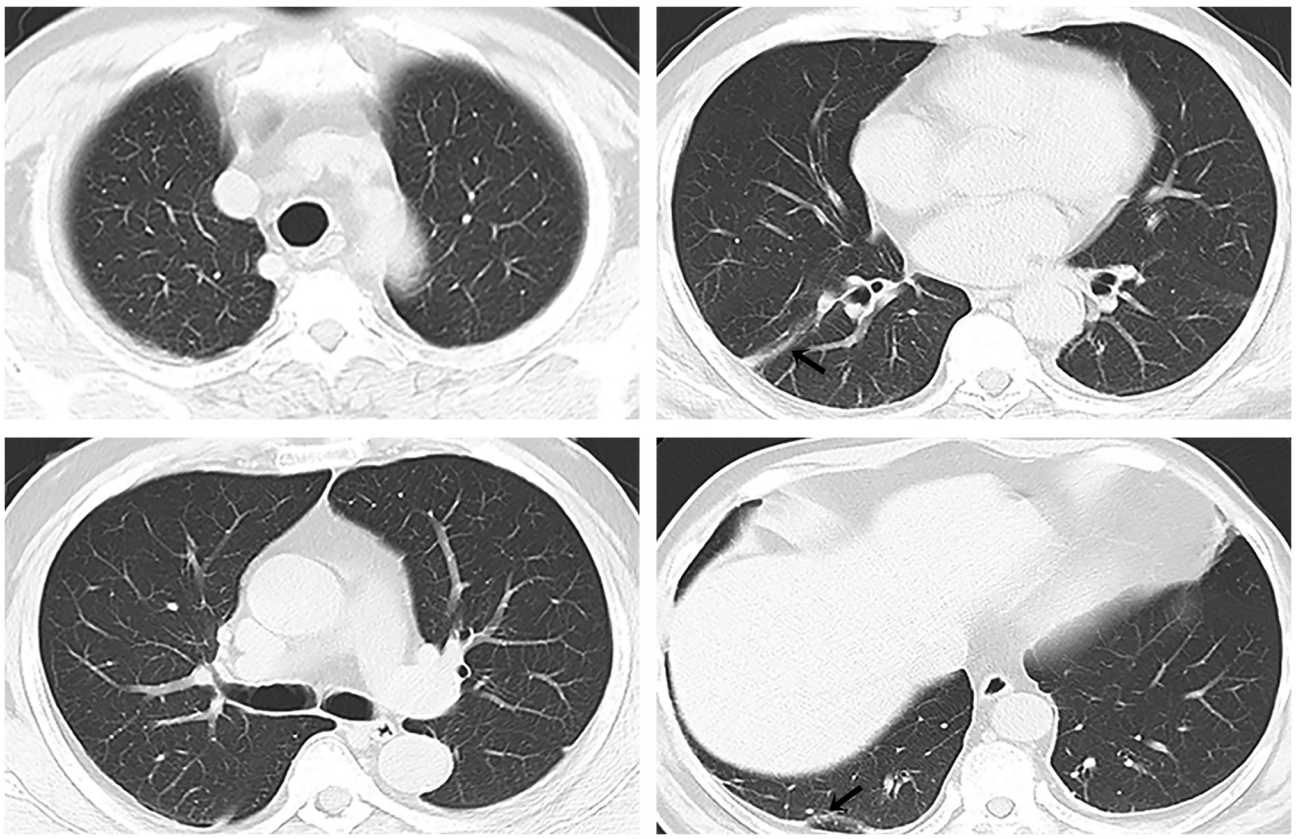

Figure 4. Chest CT on day 20 of hospitalization showing almost normal pulmonary imaging features (arrows).

hypotension, fever, increased heart rate and respiratory distress (7). The elevated CRP and PCT levels in the present case, coupled with the elevated WBC and neutrophil differential counts, initially made the correct diagnosis difficult until the symptoms recurred after an unintended re-challenge with HCTZ. After ruling out pulmonary embolism, bronchial asthma and cardiogenic shock, severe pneumonia with sepsis was suspected based on the CT imaging changes and high levels of WBC, neutrophil count, CRP levels and PCT levels in the patient. However, the imaging features of bilateral pulmonary inflammation and interstitial pulmonary edema largely disappeared and the levels of inflammatory indicators decreased rapidly during the hospitalization, which was not consistent with the typical course of sepsis (10). Due to the patient experiencing severe chest tightness and wheezing after the accidental HCTZ re-challenge, it was concluded that the patient had an allergic reaction to HCTZ, which was the cause of these pathological changes. Since 1968, similar reports have appeared with a number of proposed mechanisms (7-19). Bernal and Patarca (20) proposed that granulocyte infiltration and IgG deposition could be the underlying pathogenesis of pulmonary edema induced by HCTZ in patients. In separate previous studies, one case exhibited markedly elevated neutrophils and virtually absent eosinophils in alveolar lavage

fluid (19), whilst in another report positive basophil activation tests were reported in two cases (18). Another proposed hypothesis is that the drug can trigger inflammatory cells into releasing inflammatory mediators, leading to vasodilatation and extravasation of fluid (21).

Pulmonary edema and anaphylactic shock induced by HCTZ are uncommon and can be misdiagnosed as sepsis with severe pneumonia (7). Consequently, the diagnosis of HCTZ-induced reactions is frequently only considered upon re-exposure with serious adverse effects (16). The present case is at least partially consistent with the characteristics of a previous case reported by Mineo and Cheng (7), where the patient had multiple episodes of septic shock until the allergic reaction to HCTZ was correctly identified. During the course of the gradual recovery of the present case, an inadvertent re-administration of HCTZ occurred, promptly precipitating shock-like symptoms reminiscent of those observed prior to hospitalization. Concurrently, a severe HCTZ hypersensitivity reaction prompted vasodilation and capillary fluid leakage, exacerbating profound anaphylactic shock. This was supported by the laboratory findings revealing hemoglobin >170 g/l and hematocrit >0.5, which indicated hemoconcentration. These acute physiological changes are reminiscent of those observed in SCLS (Clarkson's disease) (22). To date, there have been no reported cases documenting the rapid onset of SCLS following anaphylactic shock induced by HCTZ. However, severe cases of SCLS can result in cardiovascular collapse, shock and even mortality.

It was also observed that the levels of PCT and CRP were markedly elevated in the present case. Conventionally, such elevations are attributed to severe bacterial infections (23). However, previous studies have suggested that PCT may also be elevated under various non-infectious inflammatory conditions, including anaphylactic reactions to medications (14,24). Therefore, in the presence of a specific drug history and recurrence of similar symptoms, drug-induced anaphylaxis should be considered as a potential cause of PCT elevation and other indices of infection in the absence of bacterial infection.

It is evident that effective treatment and management for drug-induced pulmonary edema and anaphylaxis mainly comprises supportive treatment (25). This treatment strategy generally involves providing respiratory support, administration of norepinephrine and discontinuing the suspected offending agent (17). Although steroids have been used empirically, there is a lack of data to support their efficacy in such cases. Similarly, the clinical utility of antihistamines in these scenarios remains unproven. In two previously reported cases, veno-venous extracorporeal membrane oxygenation was effectively used as a salvage therapy to restore lung function in patients with HCTZ-induced pulmonary edema and anaphylaxis (9,25).

In summary, it is essential to consider the rare but potentially life-threatening occurrence of non-cardiogenic pulmonary edema associated with HCTZ in the clinic. In the present case, whilst the clinical presentation may suggest severe sepsis following pneumonia, a thorough evaluation of the medication history and disease progression of the patient is crucial for a more accurate diagnosis and designation of treatment regimens. Further research is required to investigate the genetic predisposition to thiazide-induced pulmonary edema and to identify the underlying etiology through bronchoalveolar lavage or biopsies in affected patients.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

YFG, QQL, ZXW and PZ were responsible for data collection and the writing of the draft manuscript. PZ and XP provided supervision. LQW and PZ were responsible for reviewing, editing the presentation of data and figures. BW and LW were responsible for the concept of the review, supervision and for reviewing and editing the manuscript. XWZ and LQW were responsible for formulating the treatment plan used for the patient. XP analyzed and revised the critically important mechanisms involved in the HCTZ-induced adverse reaction. XP and XWZ confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient prior to the publication of the present case report.

Competing interests

The authors declare that they have no competing interests.

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