

A Challenging Case Of Amiodarone-Induced Pulmonary Toxicity Presenting As Cryptogenic Organizing Pneumonia Combine With Blue Man Syndrome: A Multidisciplinary Case Report

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Abstract:

Background: Amiodarone is a prevalent antiarrhythmic medication with efficacy and a risk for serious adverse effects, most importantly pulmonary toxicity and dermatologic presentation. Amiodarone pulmonary toxicity (APT) can manifest as interstitial lung disease or cryptogenic organizing pneumonia (COP) mimicking infection or malignancy. Blue Man Syndrome is a rare cutaneous appearance that indicates chronic amiodarone exposure in less than 3% of patient using amiodarone medication.

Case Presentation: A 57-year-old male patient with a history of mitral valve replacement, 8 years amiodarone therapy who was admitted through the emergency department with dyspnea, dry cough, low-grade fever, and skin discoloration for 10 days. He was initially evaluated for community-acquired pneumonia. But, lack of response to antibiotics and presence of a reversed halo sign on high-resolution CT scan also negative sputum, excluding infectious culture etiology, rendered APT as a cause of COP diagnosis. In addition, Blue Man Syndrome was present in the patient, which was an amiodarone dermatologic side effect. Amiodarone withdrawal and multidisciplinary assessment led to radiologic and clinical improvement.

Conclusion: This case stresses the importance of recognizing the pleiotropic toxicities of amiodarone, including pulmonary and cutaneous. Early diagnosis by imaging and clinical correlation and withdrawal of the offending drug in a timely manner are necessary to prevent additional morbidity. Multidisciplinary approach is essential in handling complex adverse drug reactions.

Keywords: Amiodarone-induced pulmonary toxicity, Cryptogenic organizing pneumonia, Blue Man Syndrome, Reversed halo sign, Drug-induced lung disease.

1.Introduction:

Amiodarone-induced pulmonary toxicity (APT) is a reported side effect of amiodarone, a widely utilized antiarrhythmic drug for the management of cardiac arrhythmias such as atrial fibrillation and ventricular tachycardia (1). Amiodarone's pulmonary toxicity occurs in varied forms such as interstitial pneumonitis, pulmonary fibrosis, and cryptogenic organizing pneumonia (COP) (2). COP, further characterized by the reversed halo or atoll sign on imaging, has a clinical presentation of increasingly worsening dyspnea, cough, and sometimes low-grade fever, mimicking infectious pneumonia and

rendering early diagnosis challenging (3,4). Risk factors for APT include high cumulative dose, large extent of treatment, advanced age, and underlying lung disease, with clinical presentation within weeks to many years after initiation of treatment (5). Diagnostic workup is typically consisting of, history, clinical examination, laboratory and radiological tools. high-resolution computed tomography (HRCT), pulmonary function studies, and exclusion of other causes such as infection, malignancy, and autoimmune disease. A multidisciplinary approach that involves the integration of clinical, radiologic, and occasionally histopathologic findings (6). Amiodarone toxicity has cutaneous presentations, most notably "Blue Man Syndrome," a characteristic blue-gray skin coloring of sun-exposed surfaces due to deposition of lipofuscin pigment in the dermis (7). Blue Man Syndrome is dose-dependent, typically irreversible, and significantly impacts patient quality of life due to cosmetic and psychosocial impacts (8). Control of these amiodarone-related toxicities requires an elaborate balance between rhythm control advantages and risks for systemic adverse effects, necessitating dose modification, drug withdrawal, or consider replacement with other treatment modalities (9).

This case report presents a case of coexistence between amiodarone-induced pulmonary toxicity with a cryptogenic organizing pneumonia pattern and Blue Man Syndrome's cutaneous side effect, with very high emphasis on awareness, early diagnosis, and multidisciplinary management in long-term amiodarone-treated patients.

1.1 Rationale:

This case report highlights the clinical complexity and diagnostic challenge of amiodarone-induced pulmonary toxicity presenting as cryptogenic organizing pneumonia combine with the dermatologic manifestation of Blue Man Syndrome. Despite the widespread use of amiodarone, its systemic toxicities may be underappreciated or their diagnosis delayed by clinicians due to heterogeneity presentation and similarity of symptoms with pneumonia or malignancy etc. By documenting and discussing the clinical presentation, radiological features, multidisciplinary diagnosis, and management plan of this patient, this report aims to heighten awareness among clinicians. Prompt recognition, thorough differential diagnosis, and early treatment can significantly alter patient outcomes and decrease long-term morbidity from amiodarone toxicity.

2. Case report:

A 57-year-old man with a history of mitral valve replacement before 8 years and on long-term amiodarone therapy presented with progressive dyspnea, dry cough, fever, chills, and asthenia for 10 days. Physical examination revealed bilateral crepitations, hypoxemia, and characteristic blue-gray pigmentation of the skin. Radiological studies, including HRCT, revealed characteristic radiological findings suggestive of cryptogenic organizing pneumonia, namely the reversed halo sign. Septic screening tests eliminated infectious etiologies, other lab and radiology to eliminate of suspicious malignancy, and thyroid disease, thereby after exclusion for them the diagnosis of amiodarone-induced pulmonary toxicity confirmed. Improvement in the patient's clinical and radiological status with amiodarone discontinuation and replacement with beta-blocker, start steroid prednisolone 40 mg Po OD x 8 weeks then tapered over 4 weeks. and supportive care emphasizes the key importance of multidisciplinary collaboration for such intricate clinical presentations.

Presentation to the Emergency Room:

The patient had presented to the emergency room with a 10-day history of paroxysmal fever with chills, dry cough, and shortness of breath. He was complaining of generalized weakness and weight loss noticed for the last 3 weeks not measured by the patient but his dress became unfit. The patient had denied chest pain, orthopnea, paroxysmal nocturnal dyspnea, hemoptysis, palpitations, leg edema, or recent exposure to Chemical, sick patient or confirmed tuberculosis patient. Even with his complex cardiac history of prior mitral valve replacements and chronic amiodarone therapy the initial suspect was community-acquired pneumonia, but concern for acute cardiac or drug-toxicity complications was evident. The minimal hypoxia, bilateral fine crepitations on chest examination, and blue-gray skin discoloration raised suspicion for systemic effects of amiodarone toxicity. The patient was admitted for further management evaluation and treatment.

Clinically when presented, the patient was oriented and alert but had signs of respiratory distress. His vital signs were as follows: temperature 37.8°C, heart rate 104 bpm, respiratory rate 26 breaths/min, blood pressure 110/68 mmHg, and oxygen saturation 88% on room air. Chest auscultation was positive for bilateral fine crepitations, more on the left. Cardiovascular examination S1+ loud S2, no murmurs or other heart sounds. Of specific mention was the bluish-gray discoloration of sun-exposed portions of the patient's skin.

Table (1) : Vital Signs Monitoring Table:

Parameter	Value	Normal Reference
Oxygen Saturation (SpO ₂) on RA	88%	≥94% (on Room Air)
Heart Rate (HR)	104	60-100 beats/min
Respiratory Rate (RR)	26	12-20 breaths/min
Blood Pressure (BP)	110/68	Systolic: 90-120 mmHg, Diastolic: 60-80 mmHg
Temperature (Temp)	37.8	36.5-37.5 °C

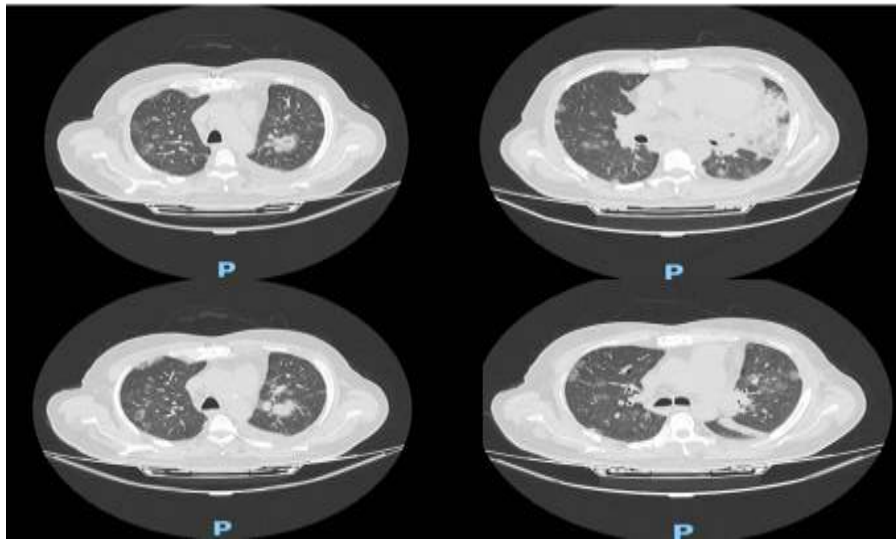
Table (2) : Laboratory Findings:

Test	Result	Reference Range
Albumin	40.63 g/L	35 - 52 g/L
Alkaline Phosphatase (ALP)	147.20 U/L	46 - 116 U/L
ALT (GPT)	25.90 U/L	10 - 50 U/L
AST (GOT)	55.30 U/L	0 - 50 U/L
Bilirubin (Total)	22.745 µmol/L	5 - 21 µmol/L
GGT	216.50 U/L	15 - 55 U/L

BUN	4.00 mmol/L	1.3 - 3.3 mmol/L
Creatinine	122.589 µmol/L	64 - 104 µmol/L
C-Reactive Protein (HS)	24.5 mg/dL	0 - 0.8 mg/dL
WBC	10.25 x10 ⁹ /L	4 - 11 x10 ⁹ /L
RBC	6.15 x10 ¹² /L (H)	4.3 - 5.7 x10 ¹² /L
Hemoglobin (HGB)	124 g/L (L)	130 - 170 g/L
Hematocrit (HCT)	0.406 L/L	0.367 - 0.471 L/L
MCV	66 fL (L)	85 - 110 fL
MCH	20.2 pg (L)	29 - 37 pg
RDW	24.7 % (H)	11.8 - 15.6 %
Platelet Count	258 x10 ⁹ /L	150 - 400 x10 ⁹ /L
Neutrophils %	74.6 %	40 - 80 %
Lymphocytes %	10.7 % (L)	20 - 40 %
Monocytes %	14.2 % (H)	2 - 10 %
Eosinophils %	0.1 % (L)	1 - 6 %
Basophils %	0.4 % (L)	1 - 2 %
Free T3 (FT3)	5.48 pmol/L	3.1 - 6.8 pmol/L
Free T4 (FT4)	18.62 pmol/L	12 - 22 pmol/L
TSH	3.68 µIU/mL	0.27 - 4.2 µIU/mL
pH	7.28	7.35 – 7.45
PaCO₂ (mmHg)	60	35 – 45
PaO₂ (mmHg)	48	80 – 100
HCO₃⁻ (mmol/L)	26	22 – 26
O₂ Saturation %	78%	95 – 100%
Lactate (mmol/L)	3.5	0.5 – 2.0
Blood Culture (Anaerobic)	No Growth	No growth
Blood Culture (Aerobic)	No Growth	No growth
Sputum Culture	No Bacterial Growth	No growth

The table 2 shows elevated liver enzymes (ALP, AST, GGT) and bilirubin, suggesting hepatobiliary involvement . Renal markers reveal mildly raised creatinine, indicating possible renal impairment. CBC shows anemia with microcytosis, high RDW, and relative lymphopenia/monocytosis. ABG indicates hypoxemic respiratory failure with acidosis, while cultures reported no bacterial growth.

Figuer 1 : Chest CT: Pulmonary Infiltrates in Both Lungs (Lung Window)

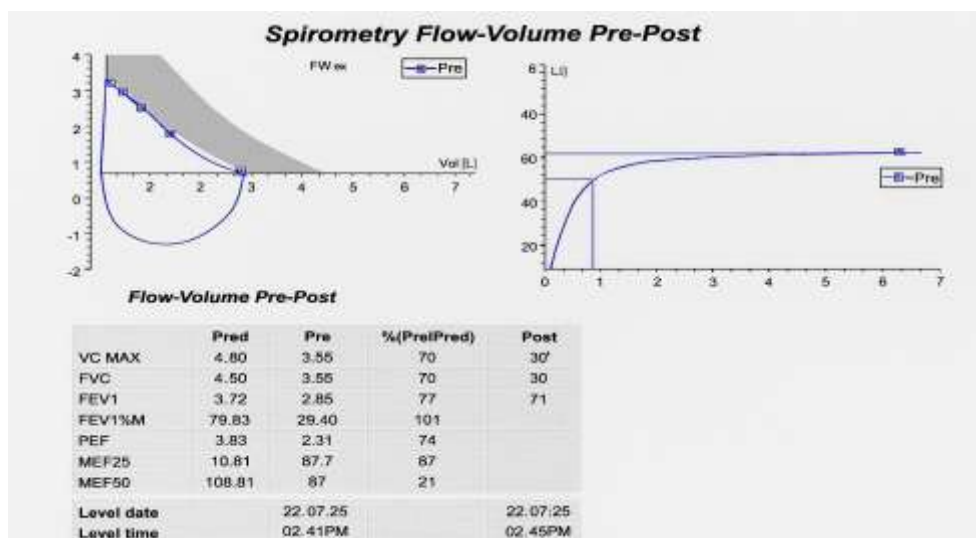


Evidence of non-homogenous ill defined consolidation containing air bronchogram, is seen involving left upper lobe lingular segment , Reverse halo's sign & multiple ground glass nodules largest seen at the left upper lobe measuring 3x2.5cm for close follow up

No significant mediastinal shift for correlation with clinical data.

- atelectatic bands seen at bilateral lower lobes.
- No gross enlarged mediastinal lymph nodes.
- Cardiomegaly and previous open heart thoracotomy sutures.
- **Mild left pleural effusion-/+ thickening.**

Figure 2 : Spirometry flow-volume curve:



Spirometry shows reduced FVC and FEV1 with preserved FEV1/FVC ratio, indicating a restrictive ventilatory pattern. Flow rates are decreased, consistent with moderate restriction. No clear obstructive defect is seen.

Figure 3 : Clinical photograph of hand discoloration at exposure area:

Management Strategies:



Initial Plan of management:

The patient was empirically started on intravenous antibiotics cefotaxime 1 gm I.V BID, later escalated to piperacillin-tazobactam 3.75 gm I.V TID and moxifloxacin 400 Mg Po OD. Supportive measures included IV paracetamol for fever and oxygen therapy. Upon the CT chest reports and lack of improvement, suspicion shifted from pneumonia to drug-induced lung injury. Since the clinical picture was highly suggestive of amiodarone induced toxicity, we used the Naranjo Adverse Drug Reaction Probability Scale and our patient received a score of 6, suggesting a probable adverse drug reaction (Table 3).

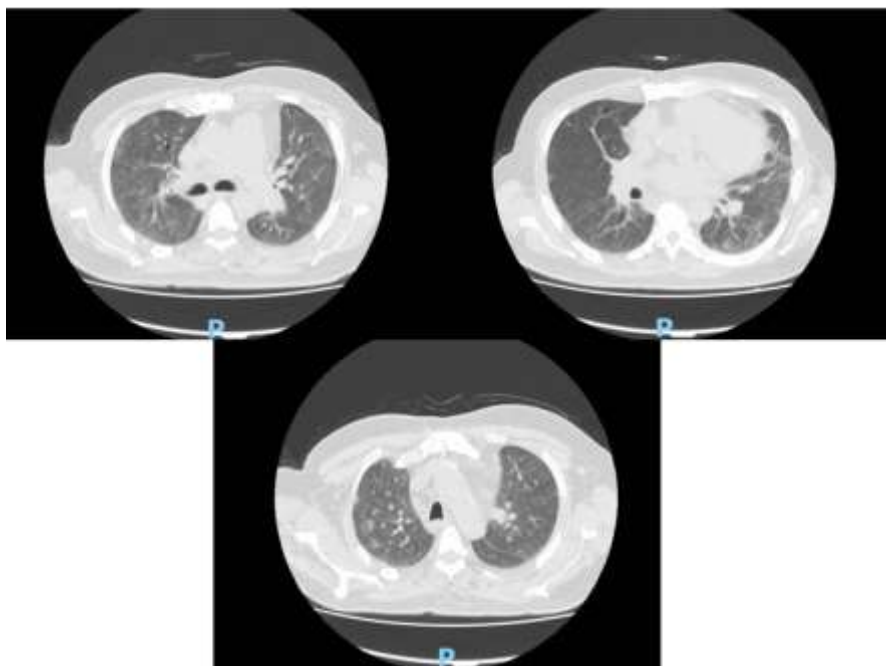
Table 3: Naranjo Adverse Drug Reaction Probability Scale* (Total score 5-8 : A probable drugreaction, with a reasonable temporal sequence to support the reaction)

No.	Question/Scoring Yes/ No/ Do not know or unavailable	Yes	No	NA
1	Are there previous conclusive reports on this reaction?	1	0	0
2	Did the adverse event appear after the suspected drug was given?	2	-1	0
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	1	0	0
4	Did the adverse reaction appear when the drug was re-administered?	2	-1	0
5	Are there alternative causes that could have caused the reaction?	-1	2	0
6	Did the reaction reappear when a placebo was given?	-1	1	0
7	Was the drug detected in any body fluid in toxic, concentrations?	1	0	0
8	Was the reaction more severe when the dose was increased/increasing or less severe when the dose was decreased?	1	0	0
9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	1	0	0
TOTAL				

Hospital Course and Follow-Up:

Radiological imaging revealed the presence of a reversed halo sign in the left lung, pointing toward the diagnosis of cryptogenic organizing pneumonia. Amiodarone was discontinued following discussion with cardiology, and the patient was monitored for resolution of pulmonary and dermatologic status. There were no other infectious or malignancy-related etiologies. Clinical and radiologic improvement was observed in the following days. Patient discharged and follow up in the clinic as outpatient, Feels better, regard SOB, cough, asthma, allergy, now no fever, SaO₂ 94% , three months later the CT scan shows Significant improvement regarding consolidation the labs also repeated and shows Normal LFT & RFT “

Figuer 4 : CT Showing Patchy Infiltrates and Ground-Glass Densities in Both Lungs

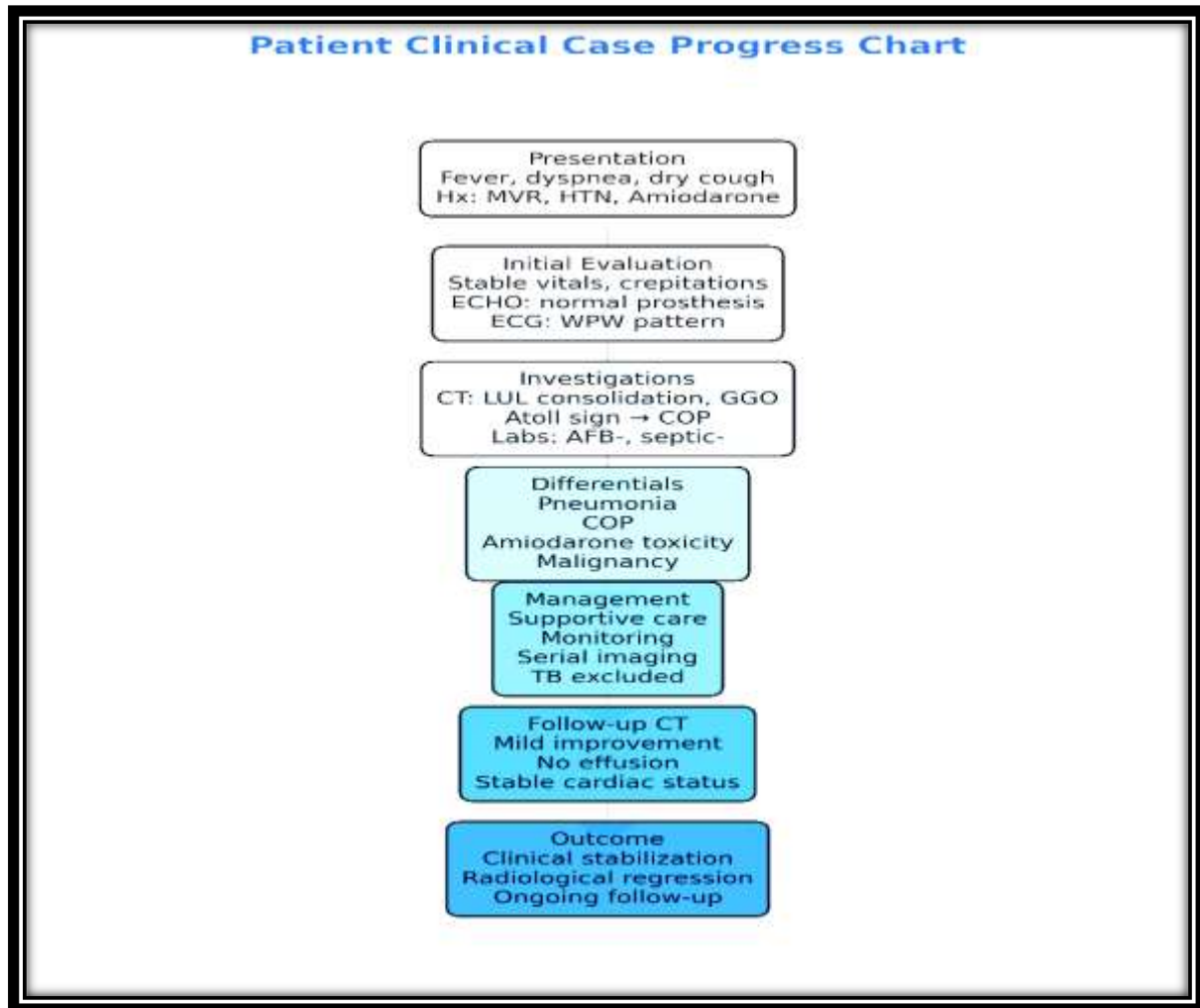


The CT illustrate improvement if the consolidation and nodules bilaterally

Role of a Multidisciplinary Team in Complex Cases:

The management of this patient is a prime example of the critical importance of a multidisciplinary process. Communication between pulmonology, cardiology, infectious disease, dermatology, radiology, and pharmacy was the accurate diagnosis of amiodarone-induced cutaneous and pulmonary toxicity. Each specialty fulfilled its role in both the ruling out of alternative diagnoses and the development of a safe and effective management plan. This case is a demonstration of how multidisciplinary care can optimize outcomes in difficult medical presentations.

Figure 5 : Patient Clinical Case Progress Chart



3.5 Discussion:

This case presents the difficulty in evaluating pulmonary infiltrates in a patient with a significant cardiac history that includes prior mitral valve replacement, hypertension, and amiodarone exposure. Initial symptoms of fever, dyspnea, and dry cough initially raised suspicion for an infection of the lower respiratory tract, most notably community-acquired pneumonia. However, with the history of prosthetic valve surgery and cardiac comorbidities in the patient, prosthetic valve endocarditis was appropriately considered and successfully excluded by echocardiography that documented normal prosthetic function and absence of vegetations. The chest CT radiological findings were lingular consolidation with air bronchogram and multiple bilateral ground-glass opacities. Of particular importance was the fact that the atoll (reversed halo) sign was present, as this pattern has associated with cryptogenic organizing pneumonia (COP) but may also appear in infection or drug-induced lung damage. Amiodarone pulmonary toxicity (so-called "Cordarone lung") was also a prime differential diagnosis in this patient considering his known use of the medication and the exposure duration. Infectious etiologies, including tuberculosis, were ruled out with negative sputum AFB, negative septic screen, and supportive laboratory findings. Management was guided by a multidisciplinary approach using clinical observation, serial imaging, and work-up for infection. Follow-up CT imaging demonstrated mild resolution of the radiologic findings, which correlated with clinical stabilization, thereby supporting an evolving pneumonia with possible overlapping organizing pneumonia compared to progressive malignancy or severe drug-induced toxicity. More broadly, the literature supports these diagnostic considerations. Amiodarone pulmonary toxicity is a well-documented complication, incidence 1–5% based on dose and duration of treatment, which characteristically manifests as diffuse ground-glass

opacities, consolidations, or interstitial patterns on CT(10). Similarly, the atoll (inverted halo) sign, while not absolutely pathognomonic, has been repeatedly characterized as a classic imaging finding in COP, with descriptions of its presence in up to 20% of cases. These overlapping features highlight the diagnostic challenge in distinguishing infection, organizing pneumonia, and drug-induced lung disease, particularly in the presence of complex comorbidities. Here, the combination of clinical assessment, infection exclusion, recognition of imaging hallmarks, and serial follow-up imaging remains crucial(11). In summary, this case illustrates the importance of a stepwise and multidisciplinary evaluation of pulmonary infiltrates in patients with cardiac comorbidities and potential drug-related issues. The collective effort of the healthcare team chest physicians, cardiologists, radiologists, and laboratory services enabled the timely exclusion of endocarditis, the careful consideration of amiodarone toxicity as a possibility, and the confirmation of gradual improvement consistent with pneumonia and also organizing pneumonia.

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Conclusion:

Amiodarone-induced pulmonary toxicity, particularly when it presents as cryptogenic organizing pneumonia in association with skin manifestations, is a tremendous diagnostic challenge due to its nonspecific clinical and radiologic presentation that mimics more common entities like community-acquired pneumonia. In this case, the recognition of systemic manifestations including Blue Man Syndrome and radiologic patterns was crucial to making the diagnosis. Amiodarone was discontinued and multidisciplinary management led to clinical improvement, noting that drug-induced lung disease must be suspected in a patient who has unexplained respiratory symptoms. One must be aware of the side effects of amiodarone and be under active surveillance in order to minimize risks and promote patient safety in those requiring long-term therapy.

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