Clinical Critical Care

E-ISSN 2774-0048

VOLUME 34 NUMBER 1

JANUARY-DECEMBER 2026

Clinical Critical Care

Clinical Critical Care
Volume 34, Article ID e260007, 6 pages
https://doi.org/10.54205/ccc.v34.274793

CASE REPORT

eISSN 2774-0048

Refractory hypotension in amyloidosis patient: A case report

Kamonchanok Boonsri, Surat Tongyoo

Division of Critical care, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, 10700

OPEN ACCESS

Citation:
Boonsri K, Tongyoo S. Refractory hypotension in amyloidosis patient: A case report. Clin Crit Care 2026; 34: e260007.

Received: April 13, 2025
Revised: January 18, 2026
Accepted: January 20, 2026

Data Availability Statement:
All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author. (Kamonchanok Boonsri, email address: kamonc.boon@gmail.com)

Funding:
This case report did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interests:
The authors declare that they have no competing interests.

Corresponding author:
Kamonchanok Boonsri
Division of Critical care, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, 10700
Tel: (+66) 2-419-8534
Fax: (+66) 2-419-8534
E-mail: kamonc.boon@gmail.com

ABSTRACT:

Introduction: Shock is a critical condition resulting from circulatory failure and is commonly observed in intensive care settings. It arises from four primary mechanisms, including hypovolemic, cardiogenic, distributive, and obstructive shock. However, some cases lack an identifiable cause or present with conditions mimicking sepsis. Rare causes, such as autonomic dysfunction, manifest through cardiovascular abnormalities like orthostatic hypotension and abnormal vasovagal responses. We reported here a case of autonomic dysfunction with amyloidosis due to its uncommon nature and significant influence on mortality rates. Timely and precise diagnosis, coupled with effective treatment, has the potential to be life-saving for the patient.

Case presentation: A 73-year-old female with a past medical history of curative breast cancer 15 years ago, sick sinus syndrome status post DDDR 3 years ago, and previous heart failure with an unremarkable coronary angiography result, presented for evaluation of progressive dysphagia. Following admission for esophagogastroduodenoscopy, she developed clinical symptoms consistent with septic shock and acute kidney injury with volume overload, which resolved after appropriate treatment. Subsequently, the patient experienced unexplained hypotension accompanied by periorbital ecchymosis, prompting a skin biopsy, serum protein electrophoresis, and free light chain testing, ultimately leading to a diagnosis of AL amyloidosis. After discussing the treatment plan, the patient opted for palliative care, and pharmacotherapy was provided as part of supportive management.

Conclusions: Refractory hypotension in AL amyloidosis poses a multifaceted clinical challenge, requiring a thorough and individualized treatment approach that considers the unique circumstances and therapeutic requirements of each patient.

Keywords: AL amyloidosis; Autonomic dysfunction; Hypotension; Case report

INTRODUCTION

Shock represents the clinical manifestation of circulatory failure, leading to insufficient cellular oxygen utilization. It is a frequent occurrence in critical care settings, impacting approximately one-third of patients in intensive care units [1]. Shock results from four possible pathophysiological mechanisms, including hypovolemic, cardiogenic, distributive, and obstructive shock. Each mechanism disrupts the body's ability to maintain adequate tissue perfusion and oxygen delivery [1].

In addition to the aforementioned causes, there are cases when the diagnosis is still obscure and the cause of shock is not easily identified. For instance, in a study of patients admitted with suspected septic shock, 7.4% had no identifiable cause of shock, while 11% exhibited conditions that mimicked sepsis [2]. Rare causes of shock include autonomic dysfunction, idiopathic capillary leak syndrome (Clarkson Syndrome), hemophagocytic lymphohistiocytosis (HLH), and systemic mastocytosis [3, 4].

The common findings in autonomic dysfunction occur in the cardiovascular regulation and consist of an abnormal vasovagal response and orthostatic hypotension [3]. There are various causes of autonomic dysfunction, one of the most common being amyloidosis. This case report explores the clinical presentation, diagnostic challenges, and management of autonomic dysfunction in a patient with AL amyloidosis. We reported this case due to its rarity and substantial impact on mortality. With accurate diagnosis and appropriate treatment, it has the potential to be life-saving for the patient.

KEY MESSAGES:

- Persistent hypotension after apparent recovery from septic shock should prompt reassessment for non-shock mechanisms.
- In systemic AL amyloidosis, autonomic dysfunction can cause refractory hypotension despite stable perfusion indices.
- Characteristic clinical clues such as periorbital ecchymosis and macroglossia may facilitate early suspicion and histopathologic confirmation remains essential for diagnosis.
- Recognition of autonomic dysfunction allows appropriate supportive therapy, avoids unnecessary escalation of vasopressors, and supports individualized care planning aligned with patient goals.

CASE PRESENTATION

A 73-year-old female with a past medical history of curative breast cancer 15 years ago, chronic hepatitis B, sick sinus syndrome status post dual-chamber pacemaker implantation (DDDR) 3 years ago, a previous coronary angiography (CAG) performed 19 years ago that showed no significant findings, and previous heart failure in the last 3 months before this admission. A previous echocardiogram performed 4 months ago showed eccentric left ventricular hypertrophy (LVH) without dilatation, with mildly reduced left ventricular systolic function (LVEF 45% by modified Simpson's method), hypokinesis of the basal-mid-apical septal left ventricular wall, and grade II diastolic dysfunction. The right ventricle was of normal size with borderline systolic function with tricuspid annular plane systolic excursion (TAPSE) of 17 mm and tricuspid valve lateral systolic velocity (TV Lat S Vel) of 10.2 cm/s, and the right atrium was not dilated. Moderate tricuspid regurgitation (TR) was present, along with mild pulmonary hypertension (right atrial pressure 15 mmHg, pulmonary artery pressure 47/19 (29) mmHg), and minimal pericardial effusion. The patient presented with several episodes of dyspnea and syncope, which were managed as acute decompensated heart failure.

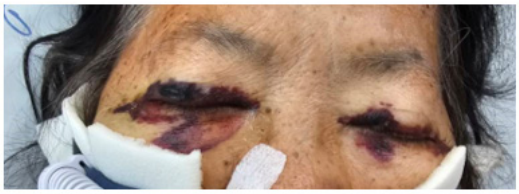
The current admission was prompted by progressive dysphagia for one month. An esophagogastroduodenoscopy (EGD) was performed, which revealed an esophageal mass. The pathological findings were highly suggestive of well-differentiated squamous cell carcinoma. Following the procedure, the patient developed hemodynamic instability accompanied by signs of impaired tissue perfusion, including oliguria and hyperlactatemia. She was initially diagnosed with septic shock of unclear source, prompting aggressive resuscitation. Due to the development of pulmonary edema and acute respiratory failure, she was intubated and transferred to the intensive care unit.

On the first day of ICU admission, physical examination revealed a blood pressure of 80/54 mmHg and a heart rate of 60 beats per minute with a paced rhythm. Her jugular venous pressure was mildly elevated, and her breath sounds revealed fine crepitation in both lower lungs. Her lower extremities were cool with mild bilateral pitting edema. Ecchymosis was observed in both periorbital areas, and macroglossia was noted (Figure 1). The electrocardiogram showed a left bundle branch block (LBBB) with paced rhythm, while the chest radiograph demonstrated bilateral patchy opacities consistent with pulmonary edema. Transesophageal echocardiography (TEE) (Figure 2) showed increased left ventricular wall thickness with myocardial speckled appearance, mildly reduced left ventricular systolic function (LVEF 41.73% by the Teicholz method, from 45% previously), grade II diastolic dysfunction, elevated left ventricular end-diastolic pressure (LVEDP) with an E/e' ratio of 25, and minimal pericardial effusion. Laboratory results showed leukocytosis (WBC 12,150 cells/μL) with a predominance of neutrophils (93.9%), normal hematocrit and platelet count, abnormal renal function with oliguria (BUN 90.3 mg/dL, creatinine 2.43 mg/dL, eGFR 19.15 mL/min/1.73 m^2), serum lactate of 3.9 mmol/L, normal liver function, normal coagulogram, normal urine examination, and negative blood cultures. Based on the overall clinical picture, the initial diagnosis was septic shock complicated by acute kidney injury and volume overload. Continuous renal replacement therapy and supportive ICU management were initiated, and esophageal malignancy was strongly suspected. A systematic evaluation was subsequently undertaken to exclude alternative causes of shock. Cardiogenic shock was considered unlikely, as echocar-

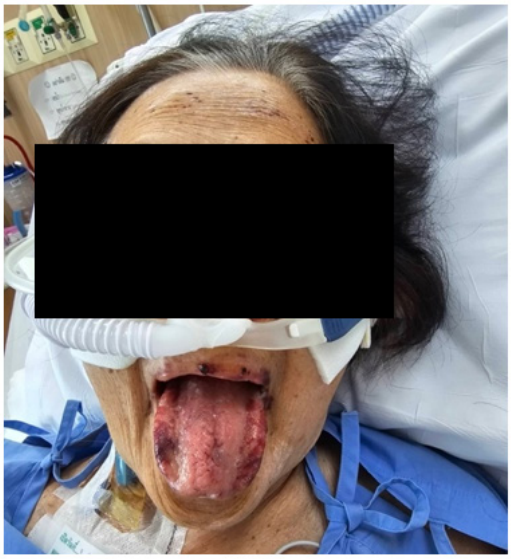
diography revealed only mildly reduced systolic function without evidence of acute deterioration, severe valvular pathology, or mechanical complications. Obstructive shock was excluded due to the absence of echocardiographic findings suggestive of cardiac tamponade or right ventricular pressure overload. Hypovolemic shock was ruled out given adequate volume resuscitation, the absence of ongoing fluid losses, and stable hemoglobin levels. Adrenal insufficiency was also excluded, as serum cortisol levels were within normal limits during hypotensive episodes, and there was no clinical response suggestive of adrenal crisis.

After several days of appropriate treatment, the patient's clinical condition improved. She was successfully weaned from mechanical ventilation and vasopressor support, and there were no further signs of tissue hypoperfusion. Repeated laboratory studies, including complete blood count, serum electrolytes, renal function, arterial blood gas analysis, serum lactate, and serum cortisol, were all within normal limits. Despite this overall clinical stabilization, she continued to have persistently low systolic blood pressure, ranging from 70 to 80 mmHg, without evidence of end-organ hypoperfusion.

Despite normalization of laboratory parameters and resolution of acute illness, the patient continued to exhibit persistent hypotension without signs of tissue hypoperfusion, suggesting a non-shock state mechanism. Autonomic dysfunction became a key diagnostic consideration. However, formal autonomic testing such as tilt-table testing, the Valsalva maneuver, or deep breathing tests was not performed. Therefore, autonomic dysfunction could not be de-

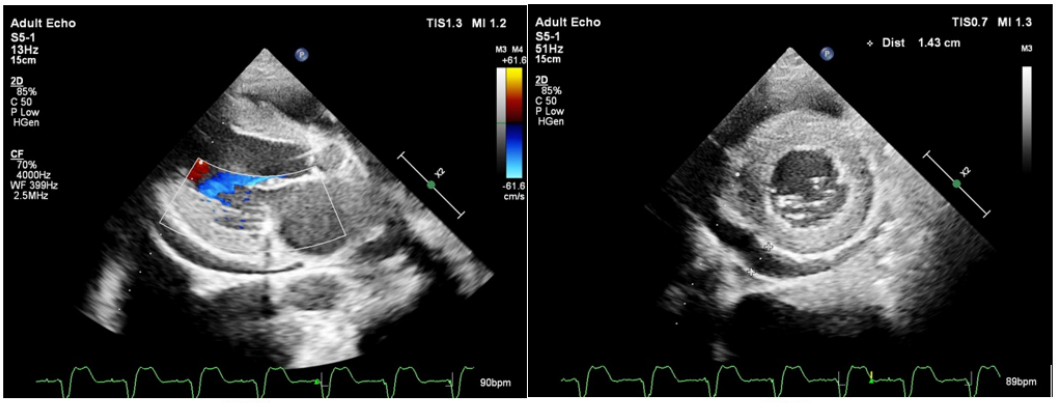


(1A)



(1B)

Figure 1. The cutaneous lesion showed periorbital ecchymosis with macroglossia.



(2A) (2B)

(2C) (2D)

Figure 2. Echocardiogram with parasternal long axis (2A), parasternal short axis (2B), E/A (2C), and medial e'(2D). The findings show myocardial thickening with speckled, left ventricular hypertrophy and grade II-diastolic dysfunction compatible with infiltrative cardiomyopathy.

finitively confirmed using standardized diagnostic criteria. Nevertheless, the diagnosis was supported by the clinical presentation of refractory hypotension and the absence of alternative explanations. Midodrine was administered as a therapeutic intervention for the management of refractory hypotension. Based on the characteristic physical findings of periorbital ecchymosis and macroglossia, dermatology and neurology consultations were obtained to evaluate the possibility of amyloidosis.

Laboratory finding

Decrease in gamma globulin in serum protein electrophoresis; serum free light chain showed lambda light chain monoclonal gammopathy: κ 64.13 mg/l (3.30-19.40 mg/l), λ 1427.23 mg/l (5.71-26.30 mg/l), κ/λ = 0.05 (0.26-1.65)

Abdominal fat pad biopsy

Focal amyloid deposits in the muscular wall of two blood vessels located in the subcutis, highlighted by Congo red, showed positive apple-green birefringence under polarized microscopic examination (Figure 3).

Bone marrow biopsy

Occasional amyloid deposit in blood vessel wall (Congo red positive with apple-green birefringence under polarizing microscopy), slight hypercellularity due to scattered plasma cells with infrequent binucleate form; immunostaining showed monoclonal lambda with plasma cell population; consistent with primary AL amyloidosis

After stabilization of blood pressure with midodrine, a CT scan of the chest and upper abdomen was performed for malignancy staging, which revealed axillary nodal metastasis. A treatment plan was discussed with the patient, including surgery for esophageal cancer and chemotherapy for amyloidosis. However, the patient requested palliative care, and additional cardiac investigations, including cardiac MRI and cardiac biopsy, were not performed to confirm the presence of cardiac or the other organs' involvement.

DISCUSSION

In this case, the patient was an elderly female, over 73 years old, with a history of complete heart block and heart failure with mid-range ejection fraction. During this hospitalization, the patient was diagnosed with esophageal cancer and unexplained hypotension with autonomic dysfunction, ultimately leading to a diagnosis of amyloidosis.

This patient may need to be differentiated as having AL or ATTR amyloidosis, given the likely history of cardiac involvement. Alternatively, AA amyloidosis should be considered due to the history of esophageal cancer, which may indicate chronic inflammation. Further investigations were conducted, including serum protein electrophoresis, serum free light chain testing, abdominal fat pad biopsy, and bone marrow biopsy.

The fat pad biopsy revealed characteristic amyloid deposits confirmed by Congo red staining. The deposits exhibited apple-green birefringence under polarized light, confirming the diagnosis of amyloidosis, while the bone marrow biopsy result confirmed a diagnosis of AL amyloidosis. Despite the patient having esophageal cancer, the development of AL amyloidosis remains possible.

AL amyloidosis results from the excessive production of free light chains by an abnormal plasma cell clone, which accumulate throughout the body, causing systemic involvement and leading to various clinical manifestations. Amyloidosis is a disease that affects multiple organ systems that commonly affects the kidneys, liver, gastrointestinal tract, heart, and autonomic nervous system. Among these, autonomic dysfunction is a significant yet often underrecognized feature [5].

In AL amyloidosis, the deposition of amyloid fibrils can impair normal autonomic nervous system function, resulting in autonomic neuropathy, which typically presents as orthostatic hypotension. Orthostatic hypotension can be especially difficult to manage because it often occurs alongside cardiac and renal involvement, which worsens

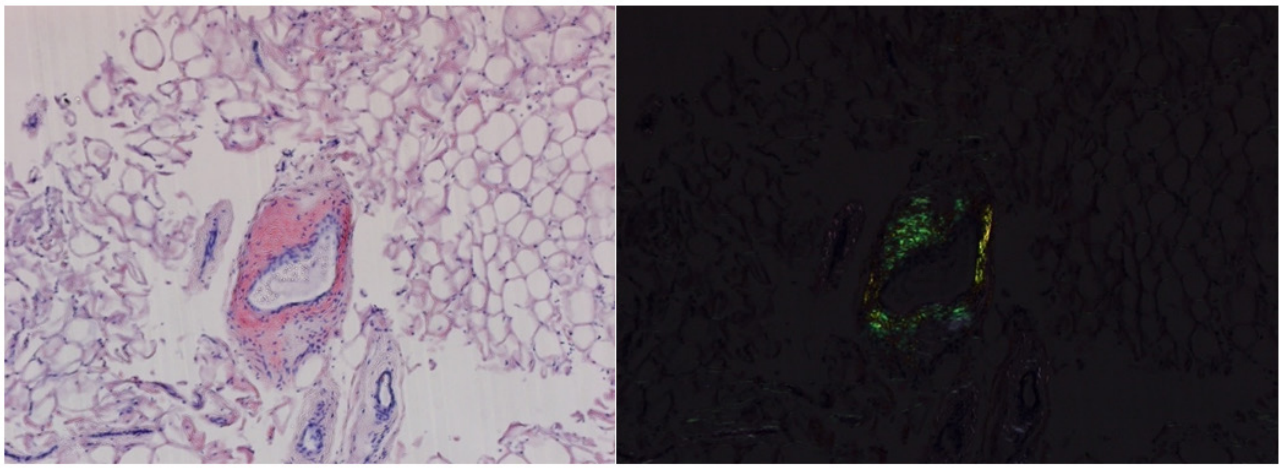


Figure 3. Abdominal fat pad biopsy revealed amyloid type changes of subcutaneous fat immunohistochemistry; bright greenish color after staining with Congo red can be seen under polarized light.

the related hemodynamic abnormalities [6]. The management of AL amyloidosis includes the medical optimization of affected organs, along with chemotherapy aimed at eliminating the plasma cells responsible for the production of abnormal free light chains in the body [7]. Initial treatment of hypotension in autonomic neuropathy should prioritize discontinuation of exacerbating medications, when feasible, in addition to wearing properly fitted elastic compression stockings to assist in maintaining blood pressure [8]. For patients with hypotension that is not sufficiently managed through non-pharmacologic measures, the oral sympathomimetic midodrine may be considered [9]. Another option is droxidopa, which is a more recent sympathomimetic agent approved for the management of symptomatic orthostatic hypotension [10] Alternatively, pyridostigmine may have a role in the management of orthostatic hypotension; however, it is less effective than midodrine [11]. Fludrocortisone has been utilized to treat orthostatic hypotension; however, its use may worsen volume overload, especially in patients with coexisting renal disease or cardiomyopathy [12].

Effective management of hypotension is crucial not only for improving patient comfort but also for facilitating the delivery of plasma cell-directed therapies essential for treating the underlying AL amyloidosis. The interplay between hypotension and organ involvement complicates treatment strategies, requiring a careful balance between managing symptoms and addressing the disease's progression [13].

Because of being elderly and diagnosed with advanced-stage metastatic esophageal cancer, the long-term management plan focused on supportive care. The patient opted to decline definitive treatment, expressing concerns about her potential inability to tolerate the associated side effects.

A strength of this case report is the histopathological confirmation of AL amyloidosis through abdominal fat pad and bone marrow biopsy, providing diagnostic certainty. Additionally, this case illustrates a rare but clinically important presentation of amyloidosis-related autonomic dysfunction manifesting as refractory hypotension.

However, several limitations must be acknowledged. Formal autonomic function testing was not performed, limiting definitive confirmation of autonomic neuropathy. Advanced cardiac imaging, such as cardiac magnetic resonance imaging or endomyocardial biopsy, was not pursued due to the patient's preference for palliative care. Furthermore, the coexistence of advanced esophageal malignancy limited therapeutic options and influenced clinical decision-making.

CONCLUSION

Refractory hypotension in patients with systemic AL amyloidosis represents a complex diagnostic and therapeutic challenge. This case emphasizes that persistent hypotension should prompt reconsideration of septic shock, particularly when standard diagnostic criteria are not fulfilled. Autonomic dysfunction should be strongly considered in amyloidosis patients with unexplained hypotension after exclusion of common shock etiologies, even in the absence of formal autonomic testing.

Primary takeaway message

In patients with biopsy-proven amyloidosis and persistent hypotension without evidence of ongoing shock, autonomic dysfunction should be recognized as a potential underlying mechanism, allowing for more appropriate management and avoidance of unnecessary escalation of shock therapies. Early recognition of this condition may facilitate targeted supportive treatment, improve hemodynamic stability, and support informed decision-making aligned with patient goals of care.

ABBREVIATIONS

mg/dL: milligrams/deciliter; cells/μL: cells/microliter; mL/min/1.73 m^2: milliliter/minute/1.73square meter; mm: millimeters; cm/s: centimeters/second; κ: kappa; λ: lambda; mmHg: millimeter of mercury; CT: computed tomography; BUN: blood urea nitrogen; Lat S Vel: tricuspid valve lateral systolic velocity; TAPSE: tricuspid annular plane systolic excursion

ETHICS

The patient clinical and demographic data were collected in accordance with the guidelines set forth by the Siriraj Institutional Review Board of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. The patient profiled in this report gave written informed consent to be studied and reported upon in this case report.

CONSENT FOR PUBLICATION

Informed consent to publish identifying data was obtained from the study participant and that this consent was informed.

ACKNOWLEDGEMENT

The authors gratefully acknowledge the patient profiled in this report for formally permitting us to report details relating to his case.

AUTHORS' CONTRIBUTIONS

(I) Conceptualization: Surat Tongyoo; (II) Data curation: Kamonchanok Boonsri; (III) Writing – original draft: Kamonchanok Boonsri; (IV) Writing – review & editing: Kamonchanok Boonsri, Surat Tongyoo.

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