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REVIEW ARTICLE

Clinical Features of AL Amyloidosis Presenting with 'Raccoon Eyes': A Case Report and Literature Review

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Abstract

Objective: This study presents and examines the clinical profiles of 28 patients with immunoglobulin light chain (AL) Amyloidosis who exhibit the characteristic "raccoon eye" appearance. It seeks to delineate the typical clinical manifestations, diagnostic approaches, and therapeutic strategies associated with this condition, thereby aiming to augment the clinical awareness and treatment proficiency among physicians.

Methods: We present a case of "raccoon eye" in a 63-year-old male patient diagnosed with AL amyloidosis and detail his clinical presentation. Furthermore, we conducted a comprehensive literature review of related case reports in the PubMed database and emphasized the clinical features and treatment outcomes associated with AL amyloidosis featuring this rare form of periorbital purpura.

Results: We identified 27 cases of AL amyloidosis characterized by "raccoon eye" from the PubMed database, and including our reported case, a total of 28 patients were analyzed. Among them, 13 were male (46.4%) and 15 were female (53.6%), with a male-to-female ratio of 0.87:1. The average age for males was 66.31 ± 7.239 years, and for females, it was 66.00 ± 10.282 years. In these 28 patients, the majority exhibited renal and cardiac involvement. Renal involvement manifested as proteinuria or impaired renal function, while cardiac involvement was primarily characterized by left ventricular hypertrophy and early elevation of NT-proBNP levels. Additionally, some patients experienced involvement of the liver, lungs, nervous system, and macroglossia. AL amyloidosis can also present with nonspecific symptoms, mainly fatigue and unconscious weight loss. Six patients suffered from the disease within months after the appearance of the "raccoon eye" sign.

Conclusion: When the typical symptom of "raccoon eye" appears in patients, clinicians should be alert to the possibility of AL amyloidosis and promptly establish a diagnosis and initiate treatment.

Introduction

"Raccoon eyes" denotes periorbital purpura resulting from the Valsalva maneuver or minor trauma. While it is seen in a limited number of patients, it represents a highly distinctive feature of immunoglobulin

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light chain (AL) Amyloidosis [1]. However, once this sign appears, patients have a high mortality rate and poor prognosis. Hence, this study documents a case of AL amyloidosis manifesting with "raccoon eyes" and leverages this case to conduct a comprehensive review of the literature, with the goal of elevating clinicians' awareness and proficiency in diagnosing and managing immunoglobulin light chain amyloidosis that presents with "raccoon eyes".

Amyloidosis is a category of disorders marked by the accumulation of insoluble, misfolded proteins within tissues [2]. This process involves the misfiling of either native or mutant proteins, leading to their aggregation as insoluble fibrils in the extracellular spaces of various organs [3]. The four predominant types of amyloid include immunoglobulin light chain (AL), Amyloid A (AA), Transthyretin (ATTR), and Amyloid Beta peptide (AB) [4]. Light chain amyloidosis, namely AL amyloidosis, is the most frequently occurring type of systemic amyloidosis [2].

AL amyloidosis impairs organ function, leading to multi-organ dysfunction, organ failure, and death within 6 months of diagnosis in 24-37% of patients, predominantly affecting individuals over 65 years old with a mean age at diagnosis of 63 years [5]. As a consequence of the lack of specificity of the early clinical manifestations, a delayed diagnosis and treatment often ensues, when treatment is often ineffective.

The clinical spectrum of AL amyloidosis is characterized by a heterogeneous array of symptoms that hinge upon the specific organs affected, with a notable lack of specificity. The kidney and heart are the most commonly affected organs [6]. Renal involvement is observed in approximately 70% of patients [6], manifesting as asymptomatic proteinuria or nephrotic syndrome. Cardiac involvement is present in about 60% of patients, typically characterized by thickening of the interventricular septum and ventricular wall. This can lead to systolic or diastolic dysfunction and heart failure, with some patients experiencing syncope or sudden death. Although rare, angina pectoris or myocardial infarction may also occur. Approximately 25% of patients exhibit neuropathy, with peripheral neuropathy affecting about 20% of them, commonly presenting as numbness, paresthesia, and pain in the extremities. Gastrointestinal tract involvement is uncommon in AL amyloidosis. Hepatomegaly may be present in some patients, while splenomegaly may also occur, though the incidence of these manifestations is uncertain. Amyloid protein infiltration into skeletal muscle can cause visible enlargement, and a scalloped tongue edge, due to a giant tongue or tooth indentation, is a characteristic finding. Cutaneous involvement can manifest as periorbital purpura, known as "raccoon eye," which is precipitated by valsalva maneuvers or minor trauma and is a highly distinctive, though infrequently observed, sign of AL amyloidosis (spontaneous periorbital purpura is virtually unique to this disease) [1]. Other signs of cutaneous involvement include waxy thickening, subcutaneous ecchymosis, and the formation of subcutaneous nodules or plaques.

Materials and Methods

Research subjects

This study includes a total of 28 patients, comprising 27 cases of immunoglobulin light chain (AL) Amyloidosis characterized by "raccoon eyes," as reported in the existing literature, along with one newly identified case from our institution.

We report the case of a 63-year-old man admitted to our hospital with a one-year history of proteinuria and a 10-day history of nausea accompanied by periorbital purpura. On admission, physical examination revealed a blood pressure of 110/80 mmHg, periorbital purpura around the right eye (Figure 1), and a systolic murmur audible over the aortic valve area. Laboratory investigations showed hypoalbuminemia (albumin 29 g/L), elevated serum creatinine (160 μmol/L), significant proteinuria with a 24-hour urinary protein excretion of 6.02 g, elevated B-type Natriuretic Peptide (BNP) at 909.62 pg/mL, and high-sensitivity cardiac troponin I at 0.025 μg/L. Serum and urine immunofixation electrophoresis and other assessments revealed no significant abnormalities.

Electrocardiography demonstrated sinus rhythm, signs indicative of an old inferior myocardial infarction, and ST-T segment changes. Transthoracic echocardiography revealed biatrial enlargement, left ventricular myocardial thickening, reduced left ventricular systolic function with a Fractional Shortening (FS) of 21% and an Ejection Fraction (EF) of 41%, as well as a small pericardial effusion. Renal ultrasonography showed the right kidney measuring 9.5 × 3.9 cm and the left kidney 9.7 × 4.2 cm, with increased cortical echogenicity and indistinct corticomedullary differentiation.

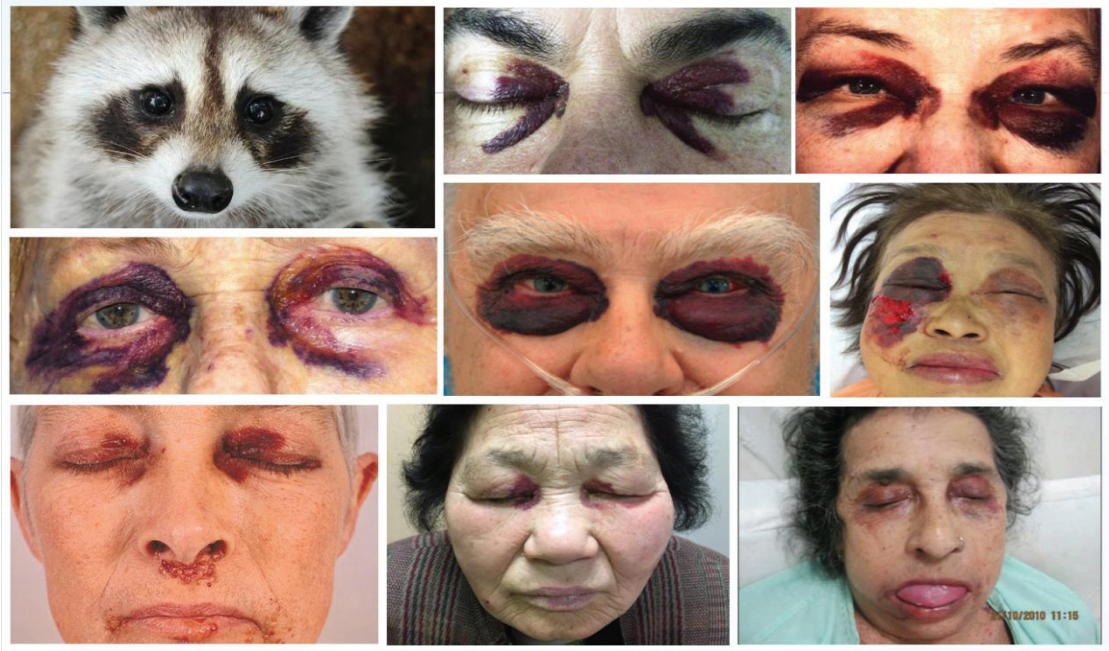

Figure 1 Palpebral and periorbital purpura on the right eye.

To further clarify the etiological diagnosis, a percutaneous renal biopsy was performed under ultrasound guidance after excluding contraindications. Histopathological examination of the kidney revealed positive Congo red staining, and under polarized light, apple-green birefringent deposits were observed in the vascular walls and mesangial areas. Considering the patient's clinical manifestations and laboratory findings, a diagnosis of renal amyloidosis was established. Unfortunately, the patient experienced sudden cardiac death before the initiation of specific treatment for amyloidosis.

We verbally informed the patient of the intention to publish their case as a case report and sought their confirmation, and the patient gave their consent.

Literature Review and Analysis

A literature search was conducted in the PubMed database of the U.S. National Library of Medicine up to January 1, 2025, using the search terms [(raccoon eyes) AND (amyloidosis)] or [Amyloid Purpura], restricted to case reports in English. This search yielded 27 case reports of AL amyloidosis patients featuring the characteristic "raccoon eyes," encompassing a total of 27 patients [1,7-32]. For each case, the following variables were recorded: first author and publication year, patient age and sex, triggering factors for "raccoon eyes," involved organs, reported symptoms, treatment received, and patient outcome/prognosis. Including the patient reported in this paper, a total of 28 patients were analyzed (Table 1).

Results

The first case was reported in 1979 and published in the Journal of the American Medical Association (JAMA). The patient was a 75-year-old man who presented with dysphagia, fatigue, weakness, inappetentia, and a weight loss of 15 kg over four months. Physical examination revealed pitting edema of the ankles, muscle atrophy, and orthostatic hypotension. Electrophysiological studies demonstrated peripheral neuropathy. Gastroscopic examination showed absence of peristalsis in the gastric antrum. Urinalysis revealed 4+ proteinuria with hyaline and granular casts. Approximately 18 hours after a percutaneous renal biopsy, significant periorbital purpura was observed. The subsequent treatment and prognosis of this case were not reported [7]. From 2006 to 2024, additional 26 cases of AL amyloidosis characterized by the presence of "raccoon eyes" have been reported.

Demographics and General Characteristics

Including the case, we reported, among the 28 patients, there were 13 males (46.4%) and 15 females (53.6%), with a male-to-female ratio of 0.87:1. The

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Table 1: Summary of the clinical features of cases with raccoon eyes.

No./study	Gender/age	Characteristic of raccoon eye	Purpura in other areas	Organ involvement						Non-specific systemic symptoms	Comorbidity	Treatment	Outcome
				kidney	heart	lung	nervous system	liver	Macroglossia				
Milutinovich J, et al. [2]	M/75	Approximately 18 hours after a renal biopsy.	/	Rountine urinalysis: 4± protein with hyaline and granular casts. 24-hour urine protein level was 2.1g.	/	/	Peripheral neuropathy	/	/	dysphagia, fatigue, weakness, inappetentia, weight loss, pitting ankle edema, muscle wasting, orthostatic blood pressure drop,	Aperistalsis of the gastric antrum	NA	NA
Roge´rio Da Hora Passos. et al. [3]	F/51	Appeared spontaneously. 1 year before diagnosis.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lihi Eder, et al. [1]	F/73	Appeared spontaneously	/	mild impairment of renal function and nephritic range proteinuria	/	/	/	/	/	/	Multiple myeloma	Cy and dex	Died from pneumonia 6 months after the lesions first appeared.
LEE HJ, et al.[4]	M/63	Appeared spontaneously. Progressive enlargement of the perorbital brusing for 6 months.	/	2.9g proteinuria over 24h	/	/	/	/	/	general weakness	Multiple myeloma	Prednisone and melphalan	Skin lesions slightly improved.
Lestre S, et al. [5]	F/71	Appeared spontaneously. With 6 months of evolution.	Perioral region	Proteinuria	/	/	depressive syndrome with psychotic features	/	Macroglossia	chronic constipation, dysphagia	/	Prednisone and melphalan	Died 3 weeks after hospital discharge.
Nicholson JA, et al. [6]	M/71	Appeared spontaneously.	/	/	/	Lung biopsy showed infiltration with amyloid.	/	/	/	minor weight loss	Myeloma	Cyc, thalidomide and dex	Stable
George EC, et al.[7]	F/75	Appeared spontaneously.	/	Proteinuria (0.981 g/d)	Left ventricular (LV) hypertrophy	/	Peripheral neuropathy	/	Macroglossia	/	/	Untreated	Died of heart failure within a few weeks

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Lavorato FG, et al. [8]	F/57	Appeared spontaneously. Bilateral eyelid hyperchromia for the last 15 years.	/	Bence-Jones proteinuria	/	/	bilateral carpal tunnel syndrome	/	/	cutaneous laxity, pain and paresthesia in a stocking-like pattern affecting the lower limbs	Multiple myeloma	NA	NA
Vera GP, et al. [11]	F/62	Appeared spontaneously.	/	/	Restrictive cardiomyopathy.	/	/	CT showed hepatomegaly	/	/	/	Dex and Bor	Died of liver and cardiac failure within 8 months
Colucci G, et al. [9]	M/58	Appeared spontaneously.	/	Proteinuria	Left ventricular hypertrophy	/	/	/	/	/	Hypertension and diverticulosis	Melphalan and HCT	Stable
Hosoi T, et al. [10]	M/76	Appeared spontaneously.	/	Bence-Jones proteinuria	left ventricular hypertrophy.	/	/	/	/	/	Hypertension, Multiple myeloma, bilateral external auditory canal obstruction	Several courses of chemotherapy	Died from progressive myeloma 2 years after.
Ryota I, et al. [12]	F/65	Appeared spontaneously.	/	impaired renal function	/	/	/	/	/	/	/	/	NA
Andrew K, et al. [13]	F/66	Appeared spontaneously.	inframammary region	Impaired renal function (creatinine 1.4 mg/dl)	Severe left ventricular hypertrophy	/	/	/	/	Substantial fatigue	sick sinus syndrome	CyBorD	Stable
Cecily JF, et al. [14]	M/51	Appeared spontaneously.	/	/	Confirmed on cardiac magnetic resonance	/	/	/	/	/	NA	HCT	NA
Hiroki M, et al. [15]	F/82	Appeared spontaneously.	/	/	/	/	/	/	Macroglossia	/	diabetes	NA	NA
Shuqin M, et al. [17]	F/64	After Valsalva.	/	Proteinuria (2.4g/d)and Impaired renal function	/	/	/	/	/	/	diabetes	CyBorD	Stable
Atanu C, et al. [16]	M/62	Appeared spontaneously	/	Proteinuria (5.4g/d)	Left ventricular hypertrophy	/	/	/	Macroglossia	/	NA	Bor, linalidomide and prednisolone.	Lost to follow-up.
Nguyen HT, et al. [18]	M/72	Appeared spontaneously	trunk and above the nipples	/	low amplitude QRS complexes, right bundle branch block (RBBB), concentric left ventricular hypertrophy, biatrial dilation, mild pericardial effusion close to the right atrium, a preserved ejection fraction	/	/	/	Macroglossia	/	ACS	losartan 12.5 mg o.d., bisoprolol 1.25 mg o.d., furosemide 20 mg o.d., isosorbide mononitrate 60 mg o.d.	Died 5 days after discharge

Paula BE, et al. [19]	F/69	Appeared spontaneously. 18 months	/	Urine protein–creatinine ratio was elevated at 142 (ULN <15)	/	/	/	/	Macroglossia	/	hypertension, rheumatoid arthritis, multiple myeloma	CyBorD	NA
Chen-Xu M, et al. [20]	F/70	Appeared spontaneously	/	creatinine 111 lmol/l (45–84 lmol/l), chronic kidney disease	/	/	/	/	/	/	/	CyBorD	NA
Haász C, et al. [21]	M/66	Appeared spontaneously	buccal mucosa, in the axillary and inguinal areas	microscopic hematuria, and proteinuria	high-grade atrial fibrillation left ventricular hypertrophy, moderate mitral insufficiency, mild pulmonary hypertension, an enlarged heart in all directions, a sclerotic aorta	increased interstitial lung markings	a transient ischemic attack	/	Macroglossia	/	a medical history of bilateral carpal tunnel syndrome surgeries and a superficial parotidectomy due to a histologically confirmed Warthin tumor.	CyBorD	Stable
Latuour D, et al. [22]	F/82	Appeared spontaneously	buccal mucosa, eyelids, infra-mammary, and infra-abdominal skin	/	/	/	/	/	/	/	/	NA	NA
Surendra M, et al. [23]	M/66	Appeared spontaneously	Upper limbs, neck	/	Biatrial wall thickening and ventricular wall thickening.	/	/	/	/	Fatigue	Seasonal allergies	Dara-CyBorD	Stable
Shinichi S, et al. [24]	M/65	Appeared spontaneously	/	proteinuria	/	/	/	/	/	a poor appetite with weight loss	hypotension	/	NA
Miguel PM, et al. [26]	M/74	Appeared spontaneously	Neck and shoulders	/	/	/	/	/	/	asthenia, anorexia, weight loss	Multiple myeloma, polyarthritis	Conventional treatment for multiple myeloma.	Died from pneumonia 2 months later.
Nor FJ, et al. [25]	F/56	Appeared spontaneously	Chest and groin	/	/	/	/	/	Macroglossia	Weakness	myeloma rheumatoid arthritis	Dara and bor	Stable
Wang XF, et al. [27]	F/47	Appeared spontaneously	/	/	significant reduction in overall longitudinal strain of the left ventricle and visible apical exemption phenomenon	/	/	/	/	/	pleural effusion	daratumumab + bortezomib + cyclophosphamide + dexamethasone (D-VCD)	Stable
Ours	M/63	Appeared spontaneously	/	Proteinuria (6.02g/d) and impaired renal function	Left ventricular hypertrophy	/	/	/	/	Fatigue	Hypotension	Untreated	Sudden death after renal puncture

Cy: Cyclophosphamide; Dex: Dexamethasone; Bor: Bortezomib; Dara: Daratumumab; CyBorD: Clophosphamide Bortezomib and Dexamethasone; NA-Not Available

average age for male patients was 66.31 ± 7.239 years, and for female patients, it was 66.00 ± 10.282 years.

Characteristics of "Raccoon Eyes"

In the 28 patients, "raccoon eyes" were predominantly spontaneous rather than trauma-induced. Only one case [22] developed "raccoon eyes" after the patient was asked to hold their breath and perform the Valsalva maneuver during a renal biopsy. Another case [7] observed the onset of "raccoon eyes" 18 hours after renal biopsy. The duration of the "raccoon eyes" was reported in a limited number of cases, lasting for 6 months, 1 year, 1.5 years, 3 years and even 15 years. Additionally, purpura can also appear in other parts of the body, such as the upper limbs, neck, shoulders, chest, and inguinal regions.

Organ and tissue involvement

In terms of systemic involvement, the kidneys were the most commonly affected organs (17/28), presenting as proteinuria with or without renal insufficiency. Cardiac involvement was also common (12/28), mainly manifesting as left ventricular hypertrophy; moreover, several cases reported elevated NT-proBNP levels. Macroglossia (enlarged tongue) was observed in 8 patients [10,12,20,21,23,24,26,30], including one patient with intermittent tongue swelling causing difficulties when speaking. Neurological involvement was noted in five patients [7,10,12,13,26], including depressive syndrome, peripheral neuropathy, bilateral carpal tunnel syndrome and a transient ischemic attack. Liver involvement was observed in one patient [16]; Computed Tomography (CT) showed hepatomegaly and bilateral pleural effusions. This patient also had elevated gamma-glutamyl transferase and aspartate aminotransferase levels, while coagulation profiles and bilirubin levels were normal. Notably, two patients [11,26] exhibited pulmonary involvement, one presenting with exertional dyspnea; lung biopsy indicated amyloid infiltration, and the other indicating increased interstitial lung markings. Pulmonary involvement is very rare in AL amyloidosis, and many physicians may attribute dyspnea to heart failure, potentially overlooking lung involvement. In addition to organ involvement, AL amyloidosis may present with non-specific symptoms such as fatigue, anorexia, and weight loss. Among the 28 cases, 5 patients [7,9,18,29,30] presented with fatigue, and 4 patients [7,11,28,31] experienced unintentional weight loss.

Treatment and prognosis

Among the 28 patients, 10 cases did not mention the prognosis, and 1 patient was lost to follow-up. Of the remaining 17 patients, 8 patients either did not receive treatment or died shortly after initiating treatment. 9 patients achieved disease stabilization after receiving treatment targeting amyloidosis or multiple myeloma, although their long-term prognosis was not detailed.

Discussion

This integrated analysis of 28 cases underscores that “raccoon eyes,” though rare, constitute a critical clinical indicator of underlying AL amyloidosis. The present case exemplifies both the diagnostic challenge and the profound clinical significance of this sign. Our patient exhibited classic features such as renal and cardiac involvement, yet diagnosis was delayed until the emergence of periorbital purpura, shortly followed by sudden cardiac death. This tragic outcome highlights the aggressive nature of AL amyloidosis and reinforces that “raccoon eyes” often appear in the context of advanced, life-threatening disease.

The pathophysiology of “raccoon eyes” involves amyloid infiltration of dermal blood vessels and periorbital tissues, resulting in increased vascular fragility. Minor elevations in venous pressure, such as those induced by vomiting (as observed in our patient), the Valsalva maneuver, or even postural changes, can precipitate this striking purpura [1]. Its appearance should therefore serve as an urgent clue to systemic amyloid deposition. Notably, in our case, the sign emerged not after trauma, but spontaneously following episodes of vomiting, correlating with elevated intra-thoracic and intra-abdominal pressure which is a mechanism consistent with previous reports [7,22].

A central insight from this review is that the “raccoon eye” sign frequently coincides with multi-organ involvement, particularly renal and cardiac-a pattern clearly illustrated by our case. The patient had documented proteinuria for one year prior to admission, yet the diagnosis of amyloidosis was not pursued until catastrophic cardiac involvement became apparent. This reflects a common diagnostic pitfall: the non-specific early presentation of AL amyloidosis. Importantly, biochemical markers such as NT-proBNP possess high sensitivity for detecting

cardiac amyloidosis even before overt heart failure develops [33,34]. Their underutilization in ambulatory settings, as may occurred here, represents a missed opportunity for earlier diagnosis.

Once "raccoon eyes" appear, clinical urgency escalates. Several cases in this review, including our own, suggest a grim short-term prognosis, with death occurring within months of this sign emerging [1,5,15,17,21,28]. Therefore, its recognition should immediately trigger a systematic diagnostic workup. This includes serum and urine immunofixation electrophoresis, serum free light chain assay, cardiac biomarkers (NT-proBNP and troponin), echocardiography, and confirmatory tissue biopsy-adhering to established international diagnostic criteria [35,36]. Early and accurate diagnosis is the cornerstone of management, as it enables initiation of therapy aimed at suppressing the underlying plasma cell clone, such with bortezomib-based regimens or daratumumab combinations, which have shown efficacy in stabilizing disease [37].

Several limitations inherent in this review must be acknowledged. As a synthesis of case reports, it is susceptible to publication bias and incomplete data reporting, particularly regarding treatment responses and long-term outcomes. The true prevalence of "raccoon eyes" in AL amyloidosis and its precise prognostic value remain to be defined through prospective studies.

In conclusion, the "raccoon eye" sign is a red flag for AL amyloidosis. Clinicians must recognize its grave implications. Its appearance, especially in the context of unexplained renal or cardiac abnormalities, should prompt an immediate and comprehensive evaluation to confirm or rule out systemic amyloidosis. Enhanced vigilance can facilitate earlier diagnosis, timely therapeutic intervention, and potentially improved outcomes in this devastating disease [38,39].

Conclusion

The "raccoon eye" sign is a highly specific though infrequent marker of AL amyloidosis. Clinicians must recognize its diagnostic significance. Its appearance, whether spontaneous or after minor strain, should trigger an immediate and comprehensive evaluation for systemic amyloidosis. Heightened vigilance and early diagnosis are essential to guide timely therapy and improve the prognosis of this serious disease.

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Conflict of Interest Statement

There is no conflict of interest.

Ethics Statement

The study was approved by the Local Ethics Commitee (CHEC 2020-171).

Consent

The patient's daughter consented to publication.

Data Availability Statement

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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