

Case Report

Do Not Ignore Those Raccoon Eyes; They May Indicate Lethal AL Amyloidosis

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Keywords

Raccoon eyes · AL amyloidosis · Cardiac amyloidosis · Chemoimmunotherapy

Abstract

Light chain (AL) amyloidosis is a lethal form of systemic amyloidosis that arises from the clonal expansion of CD38+ plasma cells. Organ damage occurs when these plasma cells produce misfolded immunoglobulin light chains, which form amyloid fibrils and deposit in tissues. A minority of patients with AL amyloidosis show “raccoon eyes” caused by increased vascular fragility from accumulation of amyloid fibrils. Amyloidosis can be directly associated with bleeding diathesis due to factor X deficiency as factor X binds to amyloid fibrils primarily in the liver and spleen. A 65-year-old Caucasian male presented with random bruising in the upper chest and around the eyes for 1.5 years. Physical examination was unremarkable, except for neck bruising. Pertinent workup showed protein electrophoresis with a faint M spike, increased serum lambda light chains, a kappa to lambda ratio of 0.06, increased Bence-Jones proteins, reduced factor X activity, elevated NT-proBNP. The bone marrow biopsy was positive for Congo red stain for amyloid protein. Magnetic resonance imaging revealed diffuse enhancement of the right and left ventricle subendocardial late gadolinium, consistent with cardiac amyloidosis. The patient started systemic therapy with a regimen of daratumumab, cyclophosphamide, bortezomib, and dexamethasone. After one cycle of therapy, lambda light chains normalized with an improvement in bruising. Diagnostic delays for cardiac patients are concerning as the median survival rate among these patients, when not treated, is approximately 6 months after the onset of symptoms. Since timely treatment can prevent organ damage, clinicians should be aware of specific clinical signs such as raccoon eyes and the importance of systemic evaluation for a prompt diagnosis.

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Introduction

Systemic amyloidoses constitute disorders of diverse etiologies involving the synthesis and abnormal extracellular deposition of misfolded proteins in various organs with resultant damage [1]. Amyloidosis has 22 different types of localized forms and 18 types of systemic forms. The most common systemic forms are light chain (AL) amyloidosis and transthyretin amyloidosis [2]. Light chain (AL) amyloidosis is a rare, heterogeneous condition that affects approximately 8–12 new individuals per million person-years [3]. Light chain amyloidosis is a life-threatening and the most serious form of amyloidosis [4, 5]. It arises from clonal expansion of CD38+ plasma cells that produce misfolded immunoglobulin light chains, which form amyloid fibrils that are deposited in tissues. This process results in organ damage, most frequently to the heart and kidneys [6]. Amyloid involvement of the heart (cardiac amyloidosis) carries the worst prognosis of any involved organ [5].

The presentation of amyloidosis largely depends on the organs involved in the disease and is often vague and nonspecific and can be confused with several disorders, thus clouding the diagnosis of amyloidosis. Many of the symptoms like nephrotic range proteinuria, congestive cardiomyopathy, macroglossia, hematemesis, hematochezia, and autonomic or sensory neuropathy are the result of organ and tissue involvement by amyloidosis [7]. Although “raccoon eyes” are a well-known manifestation of amyloidosis, they are only present in a minority of patients. The prevalence of purpuras in patients with AL amyloidosis is estimated to be less than 15% [3]. Other possible causes of raccoon eyes are facial and skull trauma, neuro-interventional procedures, excessive coughing, sneezing, neuroblastoma, and lymphoma.

Case Presentation

A 66-year-old Caucasian male came to our clinic after noticing random purpuras and ecchymoses mainly on the upper chest and periorbital ecchymoses for one and a half years. The patient reported that he would find these randomly upon awakening. He also reported ecchymoses with minimal trauma. These were reported to be approximately a dime in size. He also reported dry lips and easy bruising of the lips simply by biting. He further added that his dentist had noticed erythematous mucosa after a dental cleaning. He denied having any issues with clotting after simple cuts. There was no reported history of nose or mouth bleeds. He denied melena, hematochezia, prior history of bleeding, and joint swelling. He had an inguinal hernia repair in his youth that was uneventful. He reported eating a healthy diet and denied using any alternative supplements. He had no recent infections or reported any recent use of antibiotics. Past medical history included seasonal allergies and hyperlipidemia. There was no history of blood transfusion. Home medications included vitamin D, Allegra (fexofenadine) as needed, and atorvastatin. There was no anticoagulation or antiplatelet medication. He had no history of allergies to food or medications. There was no family history of bleeding disorders or other hematologic disorders. There was also no history of any kind of malignancy. He is a history professor and was working at the time of the visit. He reported playing tennis 3 times a week at the time he saw us. He reported drinking wine daily, approximately 2 glasses a day, which he had been doing for several years.

At the time of presentation, he had a temperature of 98.6°F, heart rate of 82 beats/min, SaO₂ of 98% on room air, respiratory rate of 16/min, and blood pressure of 127/62 mm Hg. Physical exam was remarkable for upper extremity purpuras on the extensor surfaces, purpuras around the collar line, and nasal scratches with bleeding on the left side. There was no hepatomegaly, splenomegaly, or adenopathy. The patient provided us with his picture of periorbital ecchymoses that he had sustained a few weeks ago (shown in Fig. 1).



Fig. 1. Periorbital bruising on the left eye.

Initial evaluation included complete blood count, TSH, fibrinogen, von Willebrand antigen, von Willebrand multimer, Von Willebrand factor (VWF, RCF), factor VIII activity, and factor XIII activity, all normal. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) were within normal limits. Further study revealed protein electrophoresis with an M spike of 0.15 g/dL, serum kappa light chain of 22 mg/L, serum lambda light chain level of 344 mg/dL with a kappa to lambda ratio of 0.06. Urine electrophoresis showed a monoclonal spike in the beta region. The monoclonal protein peak represented 33.8% of the total protein in urine. Urine immunofixation showed monoclonal free lambda light chains with Bence-Jones protein of 205 mg/day. Factor X activity was found to be reduced to 42%. Laboratory values have been summarized in Table 1. Bone marrow flow cytometry confirmed an abnormal lambda-positive plasma cell population, identified by bright expression of CD138/CD38, along with abnormal coexpression of CD56. Bone marrow biopsy showed a normocellular marrow with 10% plasma cells. The Congo red stain for amyloid was positive in the walls of a few small blood vessels and stromal connective tissue and showed apple-green birefringence (shown in Fig. 2a, b). Mass spectrometry (MS) was done; however, it did not identify an amyloid proteome. FISH analysis was performed with a plasma cell myeloma immunoglobulin heavy chain (IGH) complex probe panel to further define an IGH gene abnormality. A fusion signal pattern was detected with the 11;14 probe set, indicative of t(11;14), i.e., cyclin D1 (CCND1)/IGH fusion. The following translocations were not detected: t(4;14), t(14;16), t(14;20). It was only after the biopsy, almost 8 weeks after the first visit, that the patient reported exerted dyspnea along with fatigue and anxiety. He stated that with these symptoms, it had been difficult for him to continue teaching. Bruising on the upper body, especially the neck and upper back, was persistent. With symptoms of cardiac involvement, additional tests were ordered. Troponin T was <0.02 ng/mL (0–0.03 ng/mL), NT-proBNP was 1,503 pg/mL (0–124 pg/mL). A strain echocardiogram revealed left ventricular hypertrophy with an ejection fraction (EF) of 65–70%. CT chest/abdomen/pelvis showed chronic osseous changes without suspicious osseous lesions; no hepatosplenomegaly; minimal, slightly complex bilateral pleural effusions; and slightly heterogeneous thyroid gland with low-density nodules. The patient was referred to an outside center for a cardiac MRI. He had an excellent performance status but started to show signs of cardiac involvement. Implications of amyloidosis and organ

Table 1. Pertinent laboratory values along with the reference ranges

Laboratory	Value	References
WBC count	7.7 L	4.0–11.0 × 10 ³ /μL
Hemoglobin	14.0 L	13.0–17.0 g/dL
Platelet count	283.0 K/μL	150–400 × 10 ³ /μL
PT	10.9 s	9.1–12 s
aPTT	27 s	23–31 s
Fibrinogen	324 mg/dL	198–513 mg/dL
Von Willebrand antigen, %	179	52–214
Von Willebrand multimer	Normal multimeric distribution	
VWF (RCF), %	181	51–215
Factor VIII activity, %	179	56–191
Factor XIII	No lysis	No lysis
Factor X activity, %	42	81–157
Free kappa light chains	22.03 mg/L	3.30–19.40 mg/L
Free lambda light chains	298.86 mg/L	5.71–26.30 mg/L
Free kappa/lambda ratio	0.07	0.26–1.65
Urine IFE kappa	51.73 mg/L	0.00–32.90 mg/L
Urine IFE lambda	260.87 mg/L	0.00–3.79 mg/L
Urine Bence-Jones protein 24 h	205 mg/day	?150 mg/day
Troponin T	<0.02 ng/mL	0–0.03 ng/mL
proBNP	1,503 pg/mL	0–124 pg/mL

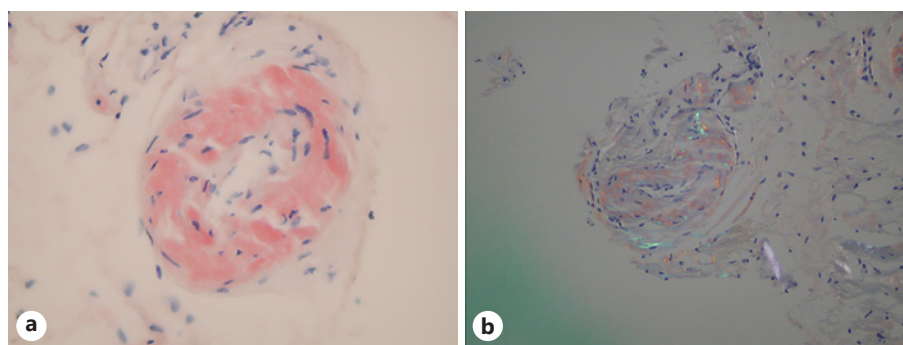


Fig. 2. **a** Blood vessel stained with Congo red under regular light. **b** Apple-green birefringence under polarized light.

involvement were discussed with him at length. Several treatment options including side effects were reviewed. Finally, he started the Dara-CyBorD regimen (daratumumab with cyclophosphamide, bortezomib, and dexamethasone). Herpes zoster prophylaxis with valacyclovir was also started. The patient was seen by a cardiologist and underwent a cardiac magnetic resonance imaging that showed findings consistent with cardiac amyloidosis that included concentric thickening of the left ventricle, thickening of the atrial wall, abnormal nullification of the blood pool relative to the myocardium, and diffuse subendocardial late gadolinium enhancement of the right and left ventricle, predominantly at the base (shown in Fig. 3a, b).

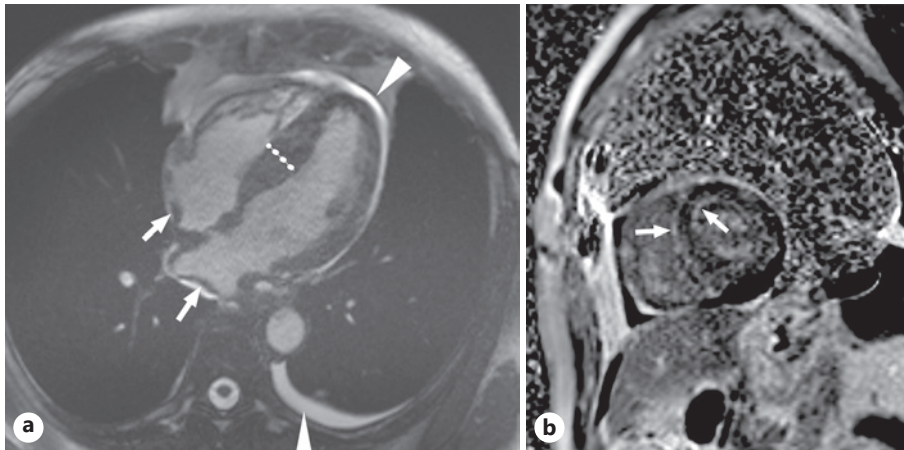


Fig. 3. a, b Cardiac MRI. **a** Cardiac MRI (4ch SSFP): 4 chamber steady-state free precession image in end diastole shows biatrial wall thickening (white arrows) and ventricular wall thickening (dotted line). Additionally, there is a small pericardial effusion and pleural effusion (white arrowheads) which are commonly seen in amyloidosis. **b** Cardiac MRI (SAx LGE Blood null PSIR): short axis delayed post-contrast blood null phase-sensitive inversion recovery images show diffuse subendocardial late gadolinium enhancement of the left and right ventricles (white arrows).

Biventricular systolic function was normal with a left ventricular EF of 58% and a right ventricular EF of 58%. He has tolerated 4 cycles of chemoimmunotherapy. He has responded very well to chemoimmunotherapy with normalization of free kappa light chains 6.61 mg/L, free lambda light chains 8.50 mg/L, and a free kappa/lambda ratio of 0.78. NT-proBNP was reduced to 1,156 pg/mL. He continues to receive systemic therapy in conjunction with cardiology follow-up.

Discussion

Raccoon eyes occur due to increased vascular fragility caused by the accumulation of amyloid fibrils. Amyloidosis can be directly associated with bleeding diathesis due to factor X deficiency since factor X binds to amyloid fibrils primarily in the liver and spleen. In patients with AL amyloidosis, acquired hemostatic abnormalities, including coagulation factor deficiency, hyperfibrinolysis, and platelet dysfunction are important pathogenetic factors [8].

Our patient had only purpuras of the neck and upper extremities and shared with us pictures of the periorbital ecchymosis he had in the past. Careful history taking is crucial in patients with purpuras. It is important to rule out common bleeding disorders. Von Willebrand disease is the most common inherited bleeding disorder and is characterized by abnormally low levels of VWF and excessive mucocutaneous bleeding [9]. The clinician can begin with an assessment of VWF: antigen level, VWF ristocetin cofactor activity (VWF: RCo), VWF multimers, and factor VIII activity for the detection of von Willebrand disease. All of these tests were normal in our patient. Mixing studies are used to distinguish among possible causes of prolonged aPTT or PT [10]. Since our patient had normal PT and aPTT, the mixing study was not performed. Factor XIII activity was evaluated to rule out any rare bleeding disorder. Factor X activity was found to be mildly low. This improved to 53% from 42% (normal 81–157%) after 4 cycles of chemoimmunotherapy. The most clinically significant coagulopathy in amyloidosis is factor X deficiency as it causes the most frequent manifestations of bleeding. The incidence of acquired factor X deficiency associated with systemic AL amyloidosis varies from 8.7% to 14% [11]. A review of complications of percutaneous renal biopsy from three

teaching hospitals in the UK over a 25-year period showed that the risk of bleeding was not higher among patients with amyloidosis than among those with other pathologies [12]. In a study carried out at the Mayo Clinic in 101 patients, the risk of bleeding during kidney biopsy did not increase in patients with systemic amyloidosis in the absence of hemostatic disorder and/or uncontrolled hypertension [13]. In another study by Eiro et al. [14], hypertension, puncture frequency, and amyloidosis were significant risk factors for bleeding complications in percutaneous renal biopsy. Most investigators agree that aggressive treatment of patients with systemic amyloidosis can lead to an improvement in amyloid-related factor X deficiency and thus an improvement in the tendency to bleed [8]. This requires an early histological diagnosis, and therefore we proceeded with a bone marrow biopsy. Our patient was normotensive and did not take blood thinners. In addition to a mild factor X deficiency, other factors (VIII and XIII) along with the coagulation panel (PT, PTT) were normal. These might be the reasons why he did not have obvious bleeding complications. Factor X in the form of fresh frozen plasma and prothrombin complex concentrates (PCCs) can be administered as needed for severe bleeding and trauma, as well as before major surgical procedures. PCCs are useful when sustained hemostasis is necessary and would require large volumes of plasma infusions [15]. Clinicians should keep in mind the possible risk of developing PCC-induced thrombosis [16]. Close hemodynamic monitoring during and after the procedure, follow-up of CBC, and appropriate imaging as needed could be helpful in detecting and preventing bleeding complications. Amyloidosis can also lead to erythroblastopenia. Gunes et al. [17] have defined clinical associations of acquired erythroblastopenia in a retrospective study analyzing bone marrow samples. Erythroblastopenia is a condition characterized by a reduction in erythroid precursors in the bone marrow together with low peripheral blood reticulocyte counts [18]. Although the most common causes of erythroblastopenia are myelodysplastic syndrome and pure red cell idiopathic aplasia, they have also described secondary amyloidosis as associated with erythroblastopenia [17].

We cannot emphasize the necessity of reviewing systems as it helps identify the symptoms of organ involvement. McCausland et al. [3] describe in their article the challenging journey to the diagnosis of light chain amyloidosis. Fatigue, the most common symptom, was reported by 80% of all patients interviewed, and nonspecific symptoms as such could be attributed to more common chronic diseases and aging populations. According to this article, the interviewees of the patients reported an average of 3 years of diagnostic delay, and 28% of the patients saw 6 doctors before diagnosis [3]. Furthermore, patients with cardiac involvement were found to have a delayed diagnosis compared to those with renal involvement. Diagnostic delays in cardiac patients are concerning as the median survival rate among these patients, when not treated, is approximately 6 months after the onset of symptoms [3]. Therefore, physicians should use various laboratory tests and imaging modalities early to reach a diagnosis. As we were ruling out bleeding disorders and unsure of the underlying hematologic malignancy, we did not send for cardiac tests immediately on the first visit. He had reported playing tennis and continuing to teach when he was seen on the first couple of visits. Within 8 weeks of the first presentation, a bone marrow biopsy resulted in amyloidosis. All of these were outpatient visits. Once we had the biopsy results, the cardiac tests were sent. It was also only after the biopsy results, he had reported shortness of breath along with anxiety. Elevated BNP and troponins can be found in those with cardiac involvement. The echocardiogram is the initial diagnostic test of choice, and the first finding is relative apical sparing of longitudinal strain [2]. Other findings include symmetric or asymmetric ventricular hypertrophy, reduced EF <50%, restrictive diastolic pattern, and pericardial effusion [19]. Cardiac magnetic resonance imaging is the test of choice for diagnosing cardiac amyloidosis with a characteristic appearance of late gadolinium enhancement across the entire subendocardial circumference [2]. An endomyocardial biopsy is considered a gold standard for the diagnosis of cardiac amyloidosis. As the

underlying management would not change, an endomyocardial biopsy was not pursued in our case.

Important workups for amyloidosis include monoclonal protein testing, serum kappa and lambda light chain quantification and their ratio, serum protein immunofixation, and urine protein immunofixation. Bone marrow core biopsy is an essential component in the evaluation of any patient with suspected amyloidosis. Congo red tissue staining is used to diagnose amyloid deposits in tissues to confirm amyloidosis, while positive materials show apple-green birefringence under polarized light using the microscopy technique [20]. The use of flow cytometry is evolving in the identification of clonal plasma cells and the detection of specific phenotype profiles for the diagnosis, monitoring, and prognosis of AL amyloidosis [21]. MS is a recently developed technique used to sort a sample according to the ratio of mass to charge [22]. It has been explored in the evaluation of free light chains both in the setting of AL amyloidosis and other plasma cell dyscrasias [23]. It shows high diagnostic sensitivity and specificity and helps crucially identify monoclonal light chains in patients with a complete serological response but with persistent minimal residual disease [22]. MS can reveal new amyloid-forming proteins, for example, identification of leukocyte cell-derived chemotaxin-2 (LECT2) as a frequent cause of liver amyloidosis [24]. With significant technical advantages over immunohistochemistry, MS has been proposed as the new gold standard for amyloid typing based on promising reports of diagnostic precision [25]. In a study by Vrana et al. [26], the MS-based proteomic analysis of subcutaneous fat aspiration samples provided unprecedented sensitivity and specificity for the diagnosis and typing of amyloidosis, including rare hereditary and iatrogenic variants. Pathogenic alterations in TTR peptide sequences can be identified by MS-based proteomic analysis in hereditary transthyretin amyloidosis [26]. Maria M. Picken has discussed in her article some limitations of MS: (a) low-abundance proteins/peptides might be difficult to detect because their signals might be overshadowed by data from more abundant proteins; (b) the protein fragments obtained after enzymatic digestion must be of a size suitable for MS [27]. As protein identification by MS relies on database matching, mutated peptides will not be detected using this strategy [25]. Sharing from our experience, inadequate samples might be another limitation.

The goal of systemic therapy in AL amyloidosis is the elimination of clonal plasma cells, similar to other plasma cell dyscrasias such as multiple myeloma (MM) and monoclonal gammopathy of clinical significance such as monoclonal gammopathy of renal significance and sporadic late-onset nemaline myopathy with monoclonal protein. Various studies have emphasized the importance of antiplasma cell-directed therapy in various subtypes of monoclonal gammopathy of clinical significance [28, 29]. As AL amyloidosis involves clonal expansion of CD38+ plasma cells, daratumumab, a human CD38-targeting antibody, is used. Our patient had t(11,14) translocation detected by FISH. Translocation (11;14) which combines the IGH locus with the oncogene cyclin D1 is observed in approximately 40–60% of patients with AL amyloidosis and is associated with adverse outcomes [30]. Patients with AL amyloidosis who had t(11;14) tended to have a shorter overall survival, regardless of the presence or absence of concurrent MM, in a study by Kobayashi et al. [31]. Given the high expression of B-cell lymphoma 2 (BCL2) in patients with t(11;14), both preclinical and clinical evidence suggest susceptibility of MM with t(11;14) to venetoclax, an oral BCL2 inhibitor [32]. Patients with AL amyloidosis who harbor t(11;14) have inferior outcomes with respect to overall survival, hematologic and cardiac response when treated with bortezomib-based regimens as first-line therapy [33]. More studies will be needed to explore whether the use of BCL2 inhibitors can improve the prognosis of patients with MM alone, amyloidosis alone, or both with t(11;14). Daratumumab may be another therapeutic agent to overcome the adverse effect of t(11;14) in the treatment of AL amyloidosis [33]. Among patients with newly diagnosed AL amyloidosis, the addition of daratumumab to bortezomib, cyclophosphamide, and dexamethasone was

associated with higher frequencies of complete hematologic response and survival free of major organ deterioration or hematologic progression [6].

Conclusion

Since untreated amyloidosis has progressive and fatal consequences that can ultimately lead to death, an early and precise diagnosis is crucial to prevent further organ damage. With several advancements in treatment, overall survival has greatly improved. The presence of raccoon eyes should make clinicians highly suspicious for amyloidosis and other hematologic malignancies, and a systemic evaluation for early diagnosis must be pursued. Internists and primary care doctors should provide urgent oncological referral upon encountering cases like this.

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Statement of Ethics

Written informed consent for publication of this case report and any accompanying images was obtained from the patient. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors state they have no conflict of interest. This case was presented in ACP 2022 Mulholland-Mohler Residents Meeting in Maryland by Surendra Sapkota on 5th May, 2022, for oral clinical vignette category and was awarded the first place among speakers from 11 different internal medicine programs in Maryland. The case was entitled “Don’t ignore those raccoon eyes.”

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Author Contributions

Bhargavi Pulluri and Sapna Kuehl contributed to conceptualization of the case and critically reviewed and updated the manuscript. Surendra Sapkota wrote the initial manuscript. The final manuscript was drafted by Surendra Sapkota and approved by Bhargavi Pulluri and Sapna Kuehl.

Data Availability Statement

All data relevant to the case are available as part of the article, and no additional source data are required. Further inquiries can be directed to the corresponding author.

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