Renal Replacement Therapy

CASE REPORT

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A case of fulminant cryofibrinogenemia with rapid renal dysfunction and toe necrosis

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Abstract

Background There are few reports of kidney disease caused by cryofibrinogen (CF). There are still many unknowns regarding its diagnosis, treatment, and prognosis.

Case presentation A woman in her 70s experienced gross hematuria without any triggers; no urinary abnormalities had been previously detected. At the same time, the urine protein level was 5 g; therefore, a renal biopsy was performed. Light microscopy revealed a membranoproliferative glomerulonephritis-like pattern. And the electron microscopic findings were extremely characteristic and specific. Development of ischemic lesions was observed in the lower legs. A skin biopsy performed at the sites of toe necrosis showed fibrinoid necrotizing vasculitis and thrombi in the blood vessels. Eventually, the patient was diagnosed with cryofibrinogenemia (CF-emia) by mass spectrometry. The effect of steroids was limited. Subsequently, the patient's renal function rapidly deteriorated, and toe necrosis progressed. The patient died after initiation of hemodialysis.

Conclusion Although CF-emia is an unknown disease and has been infrequently reported, no reported cases exhibited rapid worsening of toe necrosis and renal function during the same period. Therefore, this case can be said to be the first case of fulminant cryofibrinogenemia. Due to the development of nephropathy, which is likely to be a factor for poor prognosis, establishment of therapeutic strategies is urgently required.

Keywords Cryofibrinogen, Cryofibrinogenemia, Liquid chromatography tandem mass spectrometry, Electronic microscope

Background

Cryofibrinogen (CF) is a cryoprotein that precipitates at cold temperatures and redissolves by warming. It was first characterized by Korst and Kratochvil [1]. Cryofibrinogenemia (CF-emia) refers to the presence of proteins that precipitate in plasma at low temperatures, including CF, fibrin, fibrin fragments X and Y, fibronectin, albumin, factor VIII, small amounts of immunoglobulins, and other plasma proteins [2, 3]. Cryoprecipitates in the plasma consist of fibrinogen, fibrin, fibronectin, factor VIII, and small amounts of plasma proteins, whereas those in the serum mainly consist of cryoglobulin. Thus, CF and cryoglobulin can be differentiated by the precipitation of plasma and serum proteins at low temperatures.

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CF-emia manifests primarily or secondarily to factors such as autoimmune disease, malignant tumors, infection, and thromboembolism. CF-emia is considered to be a rare disease, and its accurate prevalence is unknown. However, there have been a number of reports in recent years that suggest the prevalence is higher than previously expected [4], while others indicate that it has a prevalence of 3% in hospitalized patients [3].

The clinical manifestations of CF-emia vary from an asymptomatic state to thromboembolism. In general, symptoms such as purpura, livedo reticularis, Raynaud's phenomenon, ulcers, and gangrene appear, mainly manifesting in the skin [5, 6]. Although symptoms may also manifest in the kidney, only nine cases of CF-associated nephropathy have been reported to date [6–13]. In general, the lesions are often localized to the skin, and CF-emia is sometimes recognized as being a mild disease. However, we encountered a patient with fulminant CF-associated nephropathy who experienced rapid progression of the disease and died. We report herein this case along with the characteristic electron microscopic findings.

Case presentation

The patient was a previously healthy 70-year-old woman with the chief concern of gross hematuria. One year earlier, she had elevated urine protein levels for the first time on a regular medical checkup; however, the results for occult blood in urine were negative. Four months before visiting our hospital, the patient noticed gross hematuria without any triggers and underwent detailed examination at the department of urology. However, because no abnormalities were found, the patient was referred to our department. The patient had no history of either skin ulceration or skin disease. The patient's laboratory findings at the initial visit to our hospital are shown in Table 1. Gross hematuria was detected, and the urine total protein to creatinine (Cr) ratio was 7.8 g/gCr. Although no abnormalities in the renal function were found, the patient manifested nephrotic syndrome. No abnormalities were found for complements or electrophoresis, and the patient also tested negative for cryoglobulin. There was no evidence of malignant tumors within the screened area.

The renal light microscopic findings are presented in Fig. 1. The glomeruli were swollen and lobulated with diffuse global mesangial matrix expansion and cell proliferation. Intraductal cell proliferation of lymphocytes and neutrophils was enhanced, and periodic acid Schiff (PAS)-positive thrombus-like masses were observed in the loop. Tubulointerstitial fibrosis and tubular atrophy affected approximately 10% of the observed area, and mild lymphocytic infiltration was observed around sclerotic glomeruli. A lesion of small vasculitis with fibrin deposition was observed in an arteriole. Immunostaining revealed no significant positive staining with frozen samples, whereas paraffin sections revealed only weak deposition of IgG, and complement C1q and λ chains in hyaline thrombi (Fig. 2). The electron microscopic findings were extremely specific and characteristic, showing a

Table 1 Laboratory data at first admission

WBC	7200	/μl	CRP	0.29	mg/dl	PT-INR	1.04	
RBC	333	$\times 10^4$/μl	IgG	782	mg/dl	APTT	23.2	sec
Hb	9.5	g/dl	IgA	290	mg/dl	Fibrinogen	475	mg/dl
Ht	28.3	%	IgM	71	mg/dl	D-dimer	1.47	μg/dl
Plt	19.1	$\times 10^4$/μl	IgG4	49.2	mg/dl			
TP	6.0	g/dl	C3	88	mg/dl	Urinalysis		
Alb	3.2	g/dl	C4	31	mg/dl	Protein	3+	
AST	24	IU/l	CH50	55.4	mg/dl	Blood	3+	
ALT	16	IU/l	PR3–ANCA	–		Urine	sediment	
LDH	281	IU/l	MPO–ANCA	–		Red Blood Cell	>100	/HPT
γ GTP	18	IU/l	ANA	<40×		White Blood Cell	20–29	/HPT
UN	17	mg/dl	Bence JP	–		Granule cast	+	
Cr	0.78	mg/dl	Cryoglobulin	–		Gross Hematuria		
UA	5.6	mg/dl	FLC K/λ	1.121				
Na	138	mEq/l	ASO	<20	IU/ml	U–TP/Cr	7.8	g/g/Cr
K	3.5	mEq/l				U–β 2MG	4907	μg/g/gCr
TCho	262	mg/dl				NAG	23.7	U/gCr
TG	165	mg/dl						
HbA1c	6.4	%						

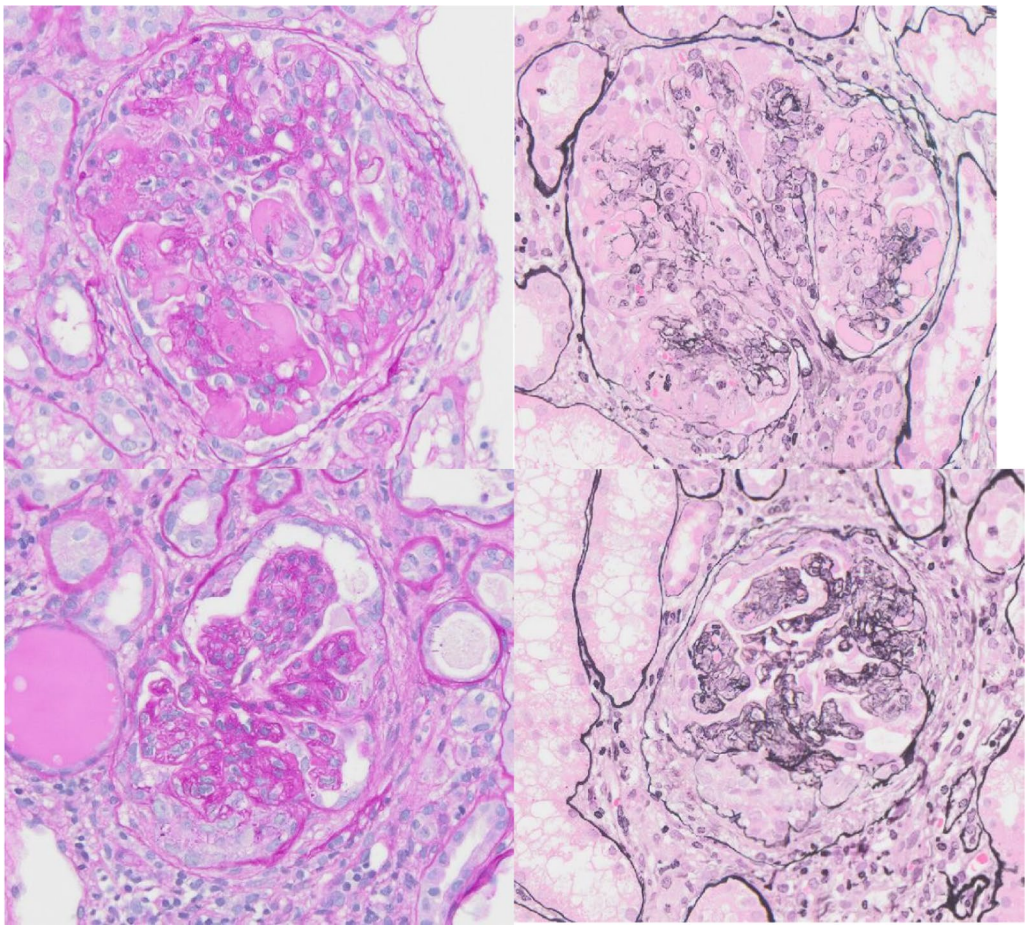

Fig. 1 Light microscopy findings

large amount of electron-dense deposits (EDD) under the endothelium with a thick basal membrane. The EDD had an organoid structure, in which hollow tubular structures formed bundles. The diameter of the tubular structures ranged from 50–70 nm, with some being slightly thicker (140 nm). Some spiral tubular structures measured approximately 1.2 μm and were arranged in a regular periodic transverse pattern were also observed. The foot process had disappeared, and the endothelial cells were swollen (Fig. 3, 4).

To detect cryoprecipitates, 10 ml of the blood collected from the patient was put into a blood collection tube without anticoagulants and into another tube containing ethylenediaminetetraacetic acid. After collection, the blood samples were kept at 37 °C, then centrifuged at 2000 revolutions for 30 min in a centrifuge warmed to 37 °C. After centrifugation, the supernatant was cooled at 4 °C for 48 h. No precipitation was observed in the serum; however, precipitation was detected in the plasma (Fig. 5). Thus, the presence of CF was suspected. Electron microscopy of the precipitates in the plasma showed double-layered structures with a diameter of approximately 70 nm. Because they showed a transverse pattern along the long axis, these structures were similar to the subendothelial EDD (Fig. 6).

Furthermore, liquid chromatography tandem mass spectrometry (LC–MS/MS) was performed to make a definitive diagnosis. The glomerular protein was extracted from paraffin sections by laser capture microdissection, and then LC–MS/MS was performed. The levels of fibrinogens (α, β, and γ), fibronectin, complements (C3, C7, and C9), and α-2 macroglobulin were significantly higher than those in the control cases. Although the levels of IgG1, IgG2, IgA1, IgM, light chain kappa, and light chain lambda were mildly elevated, they seemed to reflect the plasma components (Fig. 7). Based on these results, CF-associated nephropathy was diagnosed.

After treatment was initiated with prednisolone (PSL) at a dose of 0.8 mg/kg, the patient's Cr level, which was elevated up to 1.2 mg/dl at treatment initiation, rapidly decreased to the original level. Gross hematuria disappeared, and the patient was discharged

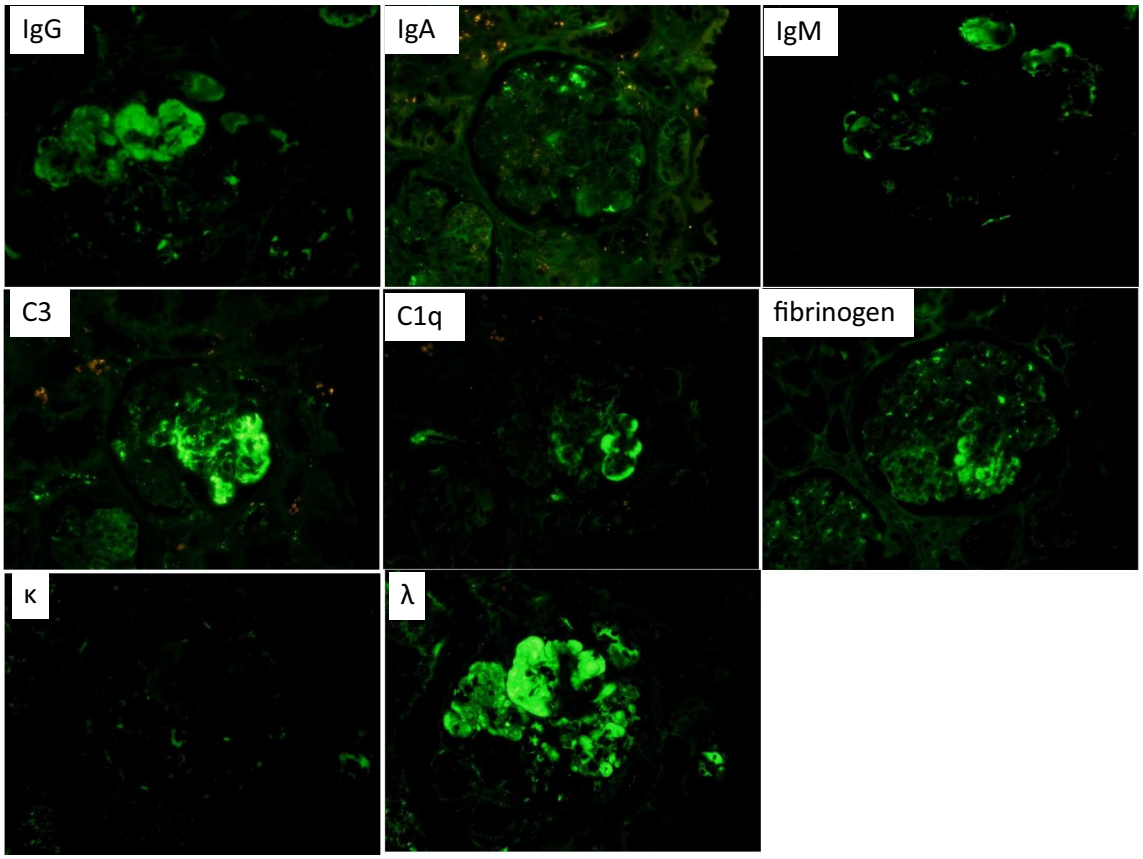

Fig. 2 Immunofluorescence staining of paraffin sections; IgG+, C3+, C1q+, and λ+

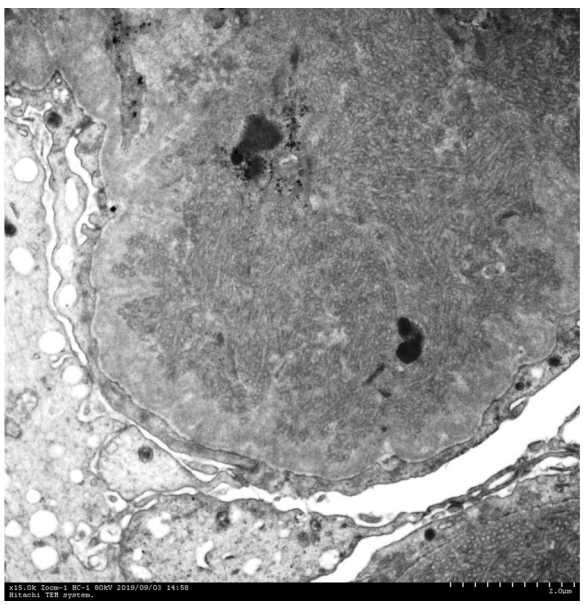

Fig. 3 Low magnification scanning electron microscope micrographs

from our hospital. The dose of PSL was tapered to 0.5 mg/kg during the winter season. The patient's renal function deteriorated again with a Cr level of 1.2, and when gross hematuria relapsed, she was subsequently readmitted to our hospital. In our region, which is located in the temperate zone, winter is relatively mild with an average temperature of approximately 7 °C. Because the patient simultaneously noted pain in the soles of the feet, we judged that the disease activity had not been sufficiently suppressed. After pulse therapy with methylprednisolone, cyclosporin A (CyA) was additionally administered at a dose of 100 mg; however, black necrosis developed in the toes several days later. Skin biopsy of these affected sites revealed neutrophil infiltration, nuclear fragmentation, and red blood cell leakage around capillary and small vessels in the dermis, as well as fibrin deposition in the vessel walls and vessels (Fig. 8). These findings indicated fibrinoid necrotizing vasculitis. Despite the initiation of anticoagulant therapy, the patient's urine output rapidly decreased, and renal function deteriorated; hence, hemodialysis was initiated. Toe necrosis progressed along with deterioration of renal function

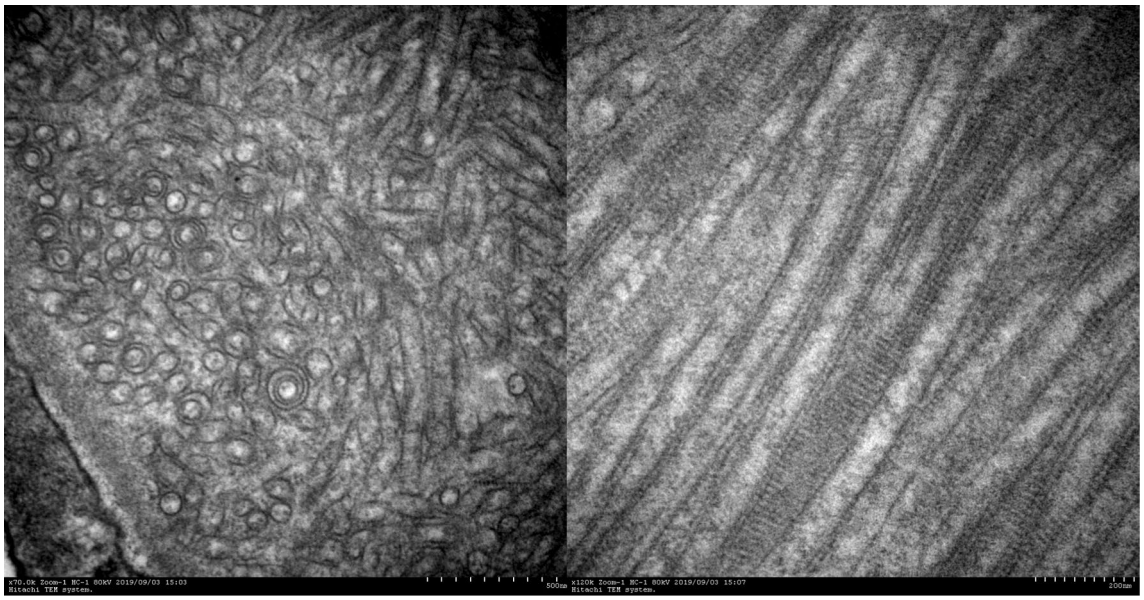

Fig. 4 Electron microscopic findings; some structures have diameters of 90–140 nm. Bundles of deposits with cavities and annular structures are seen with striped pattern

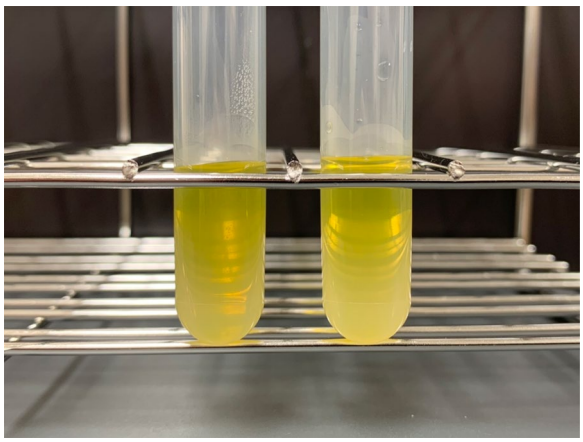

Fig. 5 The cryoprecipitate in plasma at 4 ℃. After centrifugation at 37 ℃, the supernatant was cooled at 4℃ for 48 h. Left: plasma precipitation (–); right: plasma precipitation (+)

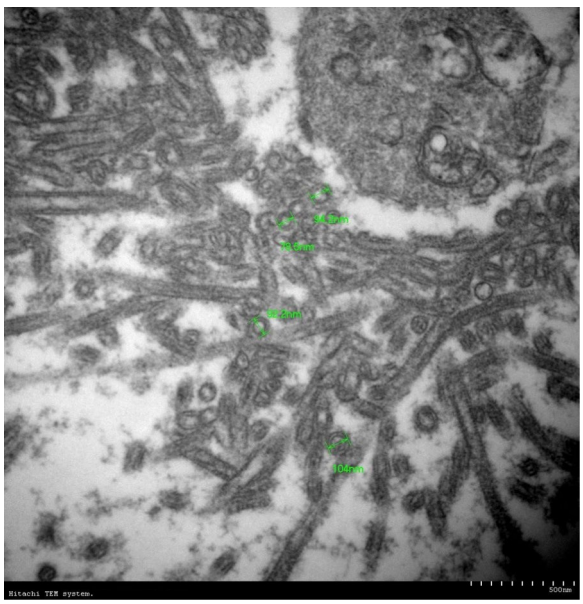

Fig. 6 Plasma electron micrograph

and continued to worsen after the initiation of hemodialysis. Images showing its progression are presented in Fig. 9. Because no blood flow was observed from the vicinity of the ankle joint on magnetic resonance angiography of the lower limb arteries or angiography of the lower limbs, bilateral below-knee amputation was scheduled. However, the patient developed septic shock before surgery and died despite the intensive care. The overall clinical course is shown in Fig. 10 and 11.

Discussion

We present the first case of fulminant cryofibrinogen (CF)-associated nephropathy worldwide.

The diseases known to cause precipitation of blood proteins at low temperatures include cryoglobulinemia and CF-emia. In the former, the precipitates consist of immunoglobulins, which appear because of immunological abnormalities. In the latter, the precipitates consist

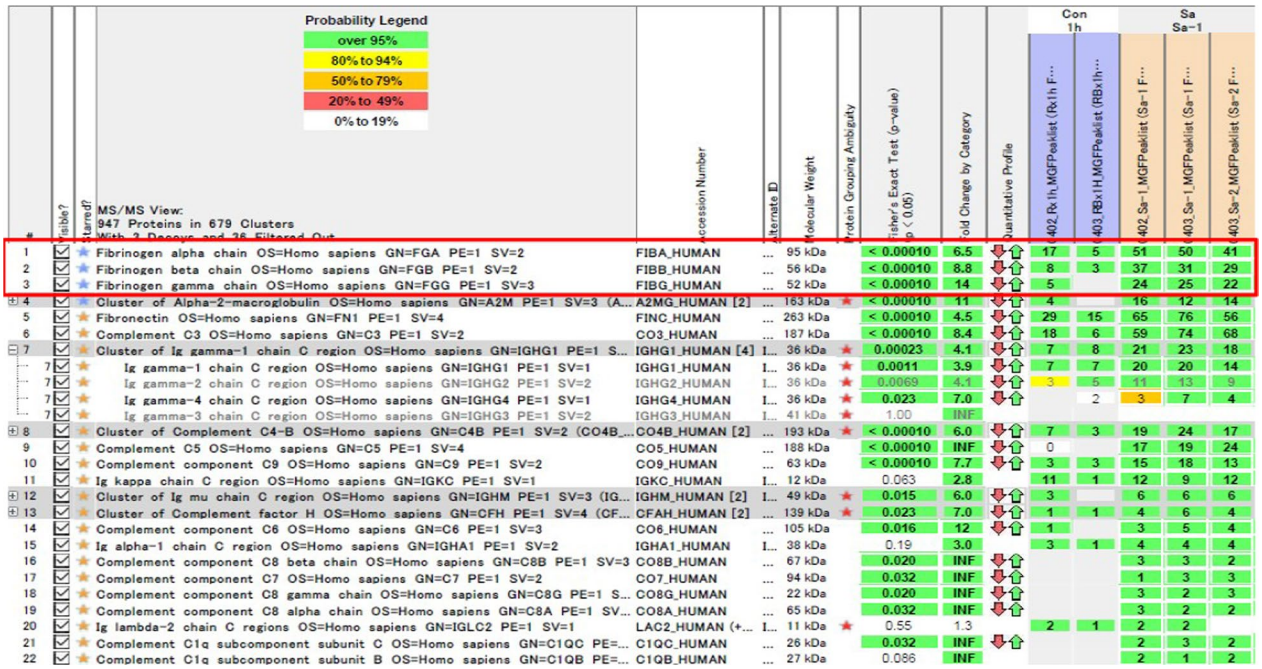

Fig. 7 Liquid chromatography tandem mass spectrometry (LC–MS/MS); fibrinogen α, β, and γ were significantly increased compared with control

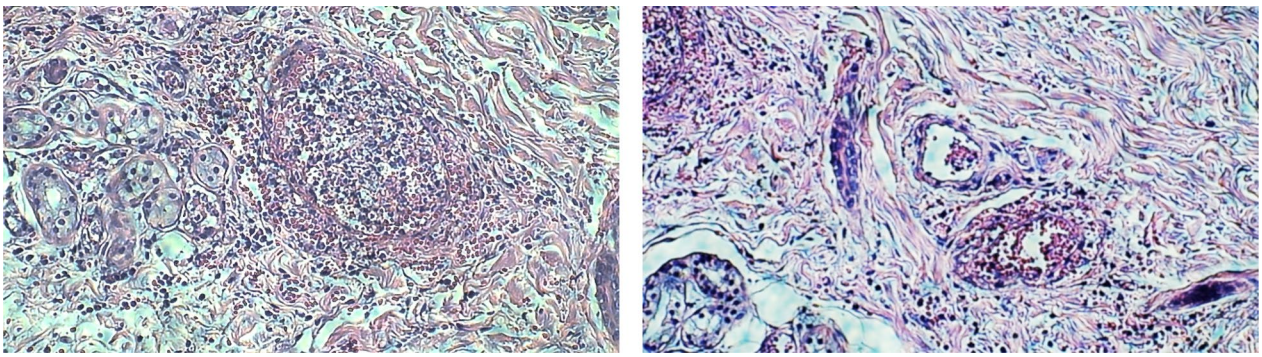

Fig. 8 Skin biopsy findings

of CF, which appears because of a blood coagulation disorder. Because blood proteins precipitate at low temperatures, both diseases cause vascular disorder, circulatory disturbance, cold hypersensitivity, bleeding, ulcers, gangrene, and other symptoms. CF is a cryoprotein that coagulates at cold temperatures and is produced in the process of conversion from fibrinogen, a blood-clotting factor, to fibrin. It is also generated as an intermediate when fibrinogen is added to fibrin by thrombin, which is a protease. Overproduction of CF leads to natural generation of a thrombus due to intravascular hypercoagulation [1–3, 14].

CF-emia has long been recognized as a causative factor in skin disease, with sporadic reports primarily in the field of dermatology [15]. However, its actual prevalence is believed to be even higher, with one report suggesting a 3% prevalence rate among hospitalized patients [3]. CF-emia is known to be either primary or secondary. This patient had no underlying disease and is considered to have had primary CF-emia. However, the possibility of an underlying autoimmune disease cannot be excluded because the patient initially responded partially to steroids. Since CF-emia is also thought to be caused by an immunological mechanism, no definitive conclusion can be drawn.

Surprisingly, a study highlighting an association with collagen disease revealed that 60% of hospitalized patients with rheumatism and systemic sclerosis

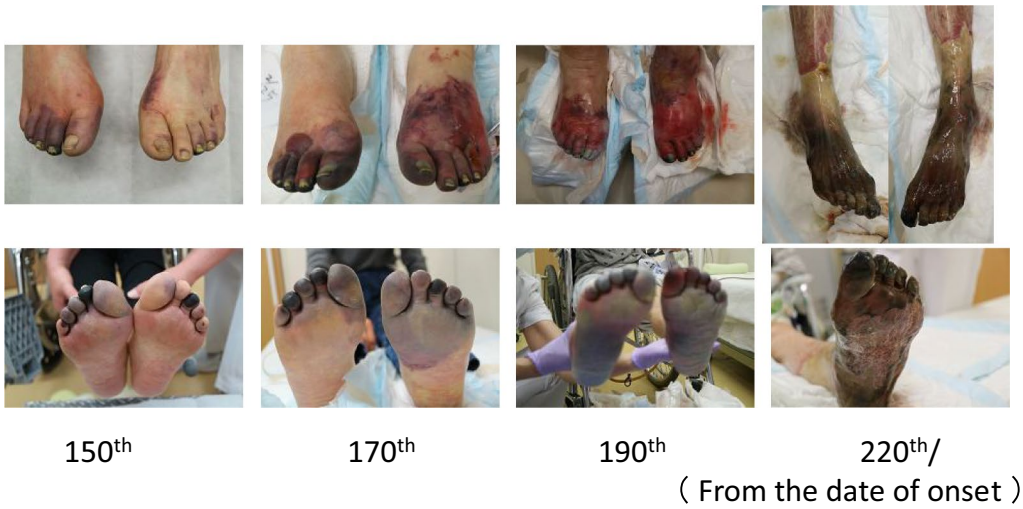

Fig. 9 Changes in toe ischemia

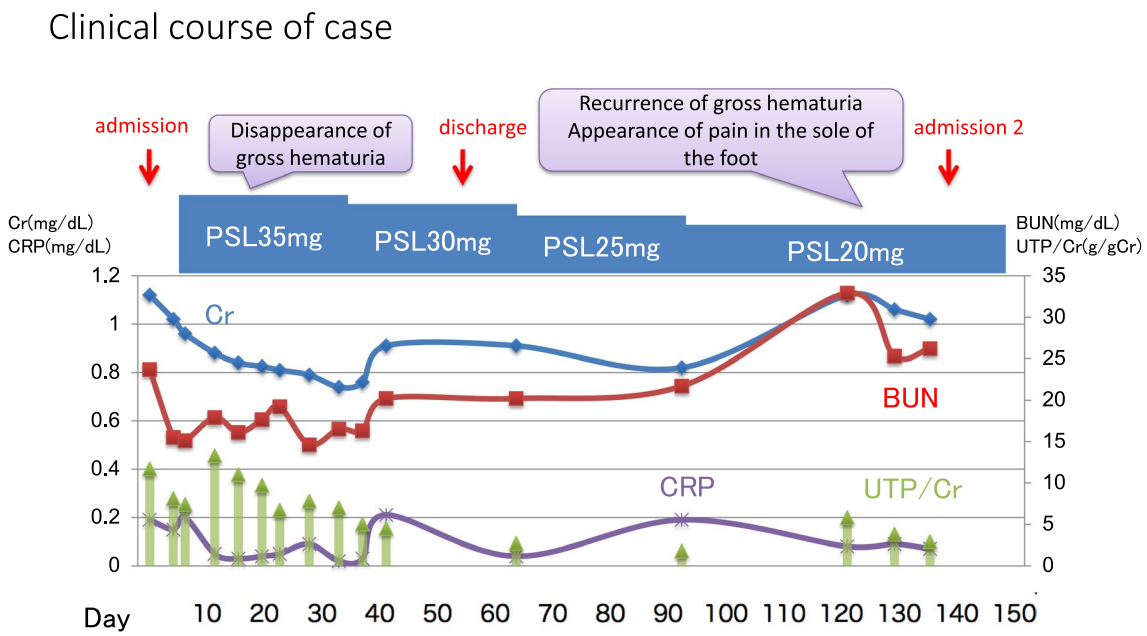

Fig. 10 Clinical course of case

had CF-emia [4]. Conversely, this suggests that CF-emia rarely progresses to clinical symptoms, with most cases remaining asymptomatic or presenting with mild manifestations.

CF-associated nephropathy is an extremely rare disease, with only about ten reported cases, including our own, in the medical literature. Table 2 shows a summary of all these reported cases. Given the limited number of reported cases, both prognosis and therapeutic methods remain largely unknown. However, the development of CF-associated nephropathy may be associated with a poor renal prognosis, as evidenced by the initiation of dialysis in four of the eleven cases, with persistent renal dysfunction observed in many cases.

The pathogenesis of nephropathy arising from CF-emia remains elusive, despite its impact on a subset of patients. However, renal and skin pathological findings, including those observed in our case, suggest that vascular lesions and thrombosis may play a pivotal role in disease pathogenesis.

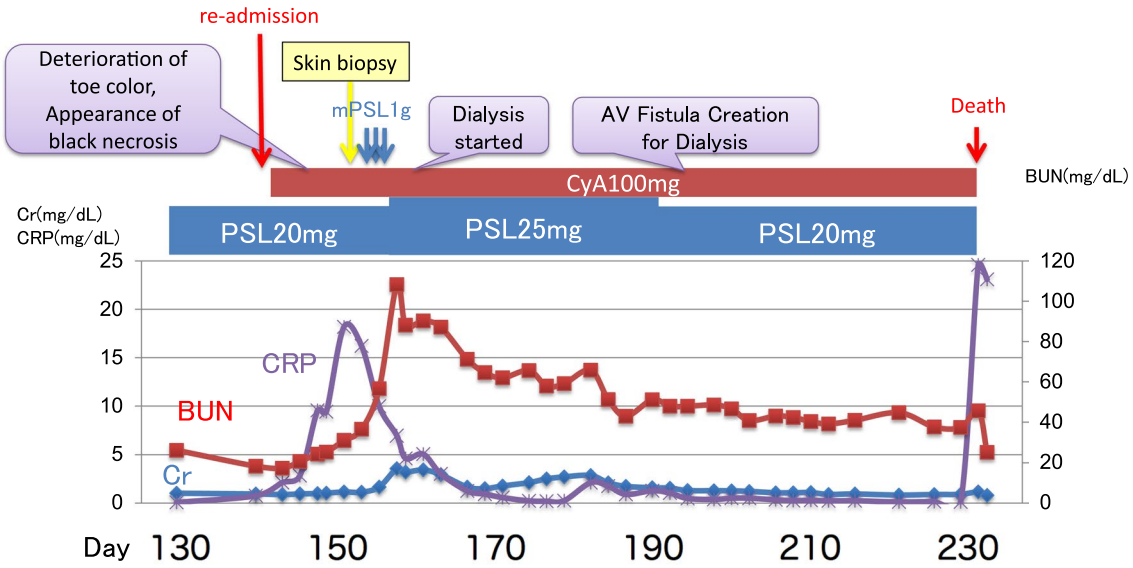

Fig. 11 Clinical course of case after readmission

Table 2 Literature review of clinical characteristics of the cryofibrinogen-associated glomerulonephritis patients

Age	Sex	sCr	Proteinuria	Hematuria	Skin lesions, renal	Prognosis	Treatment	Reference
41	F	Failure	NR	NR	Thrombogenic vascular reaction	NR	PEx	6
70	M	Insufficiency	NR	NR	+	NR	NR	6
66	M	1.4	> 7 g	8–10/F	Erythema, ulcers	NR (Final Cr1.4?)	PSL 5 mg, warfarin	7
66	M	NR	NR	NR	Purpuric rash, ulcers	HD	PSL 10 mg, aspirin	8
70	M	2.2	> 8 g	30–49/F	None	Improve (Cr3.6 → 1.7)	PSL, CY	8
60	M	3.53	7.6	3 +	None	Cr3.53 → 4.14	PSL, heparine	9
78	M	3.51	4.5	5–9/F	None	HD, Sudden Death	None	10
72	M	0.9 → 1.41	5.4	5–9/F	Noe	Death (gastric cancer)	DOAC	11
41	F	(GFR = 33)	10.6	NR	Purpura	Improve	Chemotherapy (myeloma resume)	13
74	M	1.2 → 3.9	5.15	+	None	HD	PSL (1 mg/kg/day)	12
70s	F	0.9	7.8	Gross	Purpura + vasculopathy	HD, death	PSL, CyA, heparin	Our case

Cr creatinine, *NR* not reported, *Pex* plasma exchange, *PSL* prednisolone, *HD* hemodialysis, *CY* cyclophosphamide, *CyA* cyclosporin A

The scarcity of reports on CF-associated nephropathy suggests potential underdiagnosis due to the challenges associated with definitive diagnosis of this disease.

In addition, owing to the difficulty in diagnosis, this disease may have been overlooked in some cases. In most previous reports of CF-associated nephropathy, a definitive diagnosis was made with the help of LC–MS/MS. As with our case, facilities that can perform LC–MS/MS are limited, and this process is time-consuming and expensive. We believe that the characteristic electron microscopic findings in our case were helpful for diagnosis. The findings presented here regarding the tubular structures are similar to those reported by Sethi et al. [8]. The tubular structure is often observed in patients with CF-associated nephropathy. The image of a regular periodic transverse pattern along with a spiral pattern is very impressive, and a similar case has only been reported by Sethi et al. That is [8], glandular structures with a regular periodic transverse pattern were observed. Similar tubular structures were also observed in our case. Even if it were the same as the report by Sethi Sr et al., it is only two out of ten reported cases, and it is still unclear whether this finding is typical or not. It is also unclear whether the disease shows fulminant findings. However, this is a very characteristic finding, if such findings are detected, the presence of CF should be considered. Moreover, detection of similar tubular structures in the plasma by electron microscopy should be attempted.

While CF-associated nephropathy poses a risk factor for renal failure, as described above, only two deaths have been documented due to sudden death or cerebral hemorrhage. Consequently, the prognosis is not extremely poor. However, our patient's trajectory was notably fulminant. Both skin lesions and renal function deteriorated, ultimately leading to her demise because of the resistance to various treatments.

In CF-emia, particularly the variant with skin lesions as the primary feature, coagulation disorder is often the primary feature. Our case followed a fulminant course that had not previously been reported. In our case, because fibrinoid necrotizing vasculitis was detected from necrotic skin tissues along with renal lesions, severe systemic vasculitis might have been induced in addition to coagulation disorder. Intense vasculitis and intravascular coagulation appear to have caused systemic thrombosis resulting in death.

For the treatment of CF-associated nephropathy, immunosuppressive therapy is generally attempted. Because this therapy has been effective for skin manifestations in some patients with CF-emia, we assume that its application to nephropathy is basically correct. In our case, gross hematuria was temporarily improved by the administration of steroids; however, the treatment was not effective overall. The same applies to cyclosporine A (CyA), an immunosuppressant.

Immunosuppressive therapy represents a common approach for managing CF-associated nephropathy. Previously reported cases have predominantly received immunosuppressive therapy, notably steroids, with some cases showing improvement. Given the observed treatment responses for skin manifestations of CF-emia, immunosuppressive therapy remains a basic therapeutic method. In our case, steroid administration transiently improved gross hematuria; however, overall treatment efficacy was limited, including with CyA, an immunosuppressant.

A recent report from the Netherlands suggested treatment success following a myeloma-based approach, proposing an association between M-proteinemia and CF-emia. However, neither M-proteinemia nor similar associations were detected in our case or previously reported nephropathy cases, suggesting its non-essential role. Meanwhile, given the prevalence of CF-emia among patients with collagen disease or blood disorders, treatment tailored to underlying diseases warrants consideration.

The high levels of CF in plasma, as observed in our case, indicates the potential effectiveness of apheresis techniques such as plasmapheresis. Based on the advances in structural studies using cryogel, it has been proven that CF can be removed by plasmapheresis (PEx). Although Nash et al. reported the first case treated with plasmapheresis, comprehensive descriptions of its effects and outcomes were lacking.

The condition of the disease progressed acutely and rapidly in our patient. Blood pressure decreased, dialysis and extracorporeal circulation became difficult, and PEx could not be performed. PEx might have changed the condition of the disease in the early stages.

In alternative apheresis modalities other than plasmapheresis, low-density lipoprotein cholesterol is adsorbed by dextran sulfate fixed on adsorptive cellulose beads, while fibrinogen is adsorbed by L-tryptophan. Given these mechanisms, it is reasonable to hypothesize that CF is also adsorbed. Thus, apheresis employing an adsorptive blood purifier holds promise, theoretically. CF-emia-associated nephropathy remains an enigmatic disease, necessitating multidisciplinary treatment approaches, particularly in the fulminant variant, similar to that observed in our case.

Conclusion

This is the first report of fulminant CF-emia with rapid renal dysfunction and toe necrosis. The development of CF-associated nephropathy is a threat with respect to renal prognosis. It is important to note that this disease is not localized to the skin, but is systemic, and also presents as a fulminant variant. The future accumulation of cases and findings is awaited.

Abbreviations

CF	Cryofibrinogen
CF-emia	Cryofibrinogenemia
EDD	Electron-dense deposits
PAS	Proliferation and periodic acid Schiff
Cr	Creatinine
PSL	Prednisolone
CyA	Cyclosporin A
LC–MS/MS	Liquid chromatography-tandem mass spectrometry
NR	Not reported
PEx	Plasma exchange
HD	Hemodialysis
CY	Cyclophosphamide

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Author contributions

S.H. is responsible for the manuscript. S.K., K.O., Y.Y., M.K., and Y.K. were in charge of actual diagnosis and treatment. T.K., H.S., and K.H. made a pathological diagnosis. K.D., K.T., and H.K. performed LC–MS/MS. I.E. helped detect cryoprecipitates. A.S. gave guidance with an overview of the whole case. All authors read and approved the final manuscript.

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Availability of data and materials

The data and materials were all included in the manuscript.

Declarations

Ethics approval and consent to participate
Written informed consent was obtained from the patient's bereaved families after a detailed explanation of the objectives of the study.

Consent for publication
Written informed consent was obtained from the patient's family for publication of this case report and the accompanying images.

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

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References

1. Korst DR, Kratochvil CH. Cryofibrinogen in a case of lung neoplasm associated with thrombophlebitis migrans. Blood. 1955;10:945–53.
2. Stathakis NE, Karamanolis D, Koukoulis G, Tsianos E. Characterization of cryofibrinogen isolated from patients plasma. Haemostasis. 1981;10:195–202.
3. Smith SB, Arkin C. Cryofibrinogenaemia: incidence, clinical correlations, and a review of the literature. Am J Clin Pathol. 1972;58:524–30.
4. Natali P, Debbia D, Cucinelli M, Trenti T, Amati G, Spinella A, Giuggioli D, Mascia M, Sandri G. Analysis of cryoproteins with a focus on cryofibrinogen: a study on 103 patients. Clin Chem Lab Med. 2022;60:1796–803.
5. Amdo TD, Welker JA. An approach to the diagnosis and treatment of cryofibrinogenaemia. Am J Med. 2004;116:332–7.
6. Nash JW, Ross P Jr, Neil-Crowson A, Taylor J, Morales JE, Yunger TM, et al. The histopathologic spectrum of cryofibrinogenemia in four anatomic sites. Skin, lung, muscle, and kidney. Am J Clin Pathol. 2003;119:114–22.
7. Singh A, Gaber LW. Nephrotic syndrome and chronic renal insuf- ficiency associated with essential cryofibrinogenemia. Nephrol Dial Transplant. 2007;22:1772–5.
8. Sethi S, Yachoui R, Murray DL, Radhakrishnan J, Alexander MP. Cryofibrinogen-associated glomerulonephritis. Am J Kidney Dis. 2017;69:302–8.
9. Sudo M, Sakamaki Y, Hosojima M, Yamamoto S, Ito Y, Imai N, et al. Cryofibrinogen-associated glomerulonephritis diagnosed by mass spectrometry and immunoelectron microscopy. Human Pathol Case Reports. 2019;15:83–7.
10. Ibuki E, Shiraishi A, Sofue T, Kushida Y, Kadota K, Honda K, et al. Characteristic electron-microscopic features of cryofibrino- gen-associated glomerulonephritis: a case report. BMC Nephrol. 2020;21:27.
11. Kakeshita K, Yamazaki H, Imamura T, Ando T, Kobayashi S, et al. Cryofibrinogen-associated glomerulonephritis accompanied by advanced gastric cancer. CEN Case Reports. 2021;10:527–36.
12. Kim M, Kim SS, Choi HI, Choi HS, Bae EH, Ma SK, Kim SW, Kim CS. Cryofibrinogen-associated membranoproliferative glomerulonephritis. Kidney Int. 2023;104:860.
13. Gant CM, Koelman CA, Nguyen TQ, Abrahams AC, Wetzels JF, Duineveld C, Jak M, Minnema MC, Klein SK, Jacobs JF, Bosma RJ. Cryoglobulinemic vasculitis in disguise: cryofibrinogenemia as variant of monoclonal gammopathy of renal significance. Am J Kidney Dis. 2023;S0272–6386(23):00825–9.
14. Michaud M, Pourrat J. Cryofibrinogenemia. Clin Rheumatol. 2013;3:142–8.
15. Grada A, Falanga V. Cryofibrinogenemia-induced cutaneous ulcers: a review and diagnostic criteria. Am J Clin Dermatol. 2017;18:97–104.

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