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Hemodialysis Patient with Diffuse Liver Calcification After Septic Shock

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Patient: Female, 82-year-old
Final Diagnosis: Diffuse liver calcification
Symptoms: Shock
Medication: —
Clinical Procedure: —
Specialty: Nephrology

Objective: Rare coexistence of disease or pathology

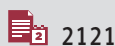
Background: Calcification in arteries is sometimes observed in patients undergoing hemodialysis; however, ectopic calcification in other organs is uncommon. In particular, diffuse liver calcification is very rare. We report a case of rapidly developing diffuse liver calcification in a patient undergoing hemodialysis.

Case Report: An 82-year-old woman started hemodialysis because of diabetic nephropathy, and her renal function worsened due to acute coronary syndrome. Percutaneous coronary intervention was conducted, and she was referred to our hospital. However, she subsequently contracted various infections, including a urinary tract infection and pneumonia. On day 43 of hospitalization, she developed septic shock and liver dysfunction due to catheter-induced infection. Although she did not have any medical history of liver disease, hypoperfusion of the liver resulted in liver dysfunction, and a computed tomography scan conducted 3 months later showed diffuse calcification in her liver. Despite recovering from septic shock, she ultimately died of multiple organ failure 21 months after admission to our hospital.

Conclusions: Diffuse liver calcification is extremely rare; however, it can be observed in patients undergoing hemodialysis who experience liver hypoperfusion. The precise mechanisms underlying this disorder remain unknown, but a critically ill status and specific characteristics of hemodialysis patients may play important roles in liver calcification.

Keywords: Calcification, Physiologic • Renal Dialysis • Renal Insufficiency • Sepsis

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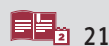
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Background

Calcification in arteries is not uncommon in patients undergoing hemodialysis and is accelerated by the systemic imbalance of minerals, including calcium and phosphate. Secondary hyperparathyroidism has a negative effect on this mineral bone disorder and increases the risks of cardiovascular diseases partly via arterial calcification [1,2]. Since the formation of vascular lesions takes a long time, the prevalence of arterial calcification in patients with a long history of hemodialysis is higher than that in patients without it [3].

By contrast, ectopic calcification in other organs, such as muscles, is rare, apart from systemic calciphylaxis [4,5]. Although there have been reported cases so far, diffuse liver calcification is an extremely rare disorder; however, we experienced the case of a patient who developed diffuse liver calcification over a short period. This patient experienced severe septic shock repeatedly, and her computed tomography (CT) scan revealed diffuse liver calcification. This case differed from calciphylaxis in terms of localization in the liver and rapid progression of calcification. Thus, this case and other cases should be differentiated from calciphylaxis. Moreover, showing the clinical features of past cases and this case can be advantageous to elucidate the mechanism in patients undergoing hemodialysis with diffuse liver calcification. Herein, we report this case with a review of the literature.

Case Report

An 82-year-old woman with type 2 diabetes mellitus, who had been receiving diabetes treatment for more than 10 years, normally maintained her renal function with a serum creatinine concentration of 3 mg/dL. She had hypertension, and none of her relatives had renal diseases. Further, she was diagnosed with acute coronary syndrome and had pulmonary congestion, and percutaneous coronary intervention was performed at a general hospital. Thereafter, hemodialysis was initiated because her serum creatinine concentration increased to 7 mg/dL, and she developed anuria. About 1 month later, she was referred to our hospital to continue treatment.

After admission to our hospital, she developed a urinary tract infection on day 10, and administration of 4.5 g of tazobactam piperacillin hydrate daily was initiated. In addition, she developed hypoxia on day 12. Her chest X-ray examination showed increased pleural effusion, and pneumonia was noted in the lower right lung field. From day 14, fasting and intravenous hyperalimentation were started. Although her fever abated and X-ray examination showed improvement after day 18, she suddenly developed a fever (temperature, 38°C) on day 23, and a catheter-related infection was suspected. The central venous catheter was

removed, and 0.5 g of vancomycin was administered after each hemodialysis session. Furthermore, her urine culture was positive for *Enterococcus faecium* and *Klebsiella oxytoca*, and 250 mg of levofloxacin was orally administered from day 30. Thereafter, her systolic blood pressure decreased to approximately 70 mmHg, and doripenem infusion was initiated to treat septic shock. Following this treatment, her symptoms significantly improved, and doripenem and vancomycin were discontinued on day 35.

Nonetheless, she again developed a fever (39°C) on day 38, and her systolic blood pressure dropped to 50 mmHg. Her serum C-reactive protein (CRP) level increased to 15 mg/dL, and her platelet count was 55 000/mm³ at that time. Due to shock, continuous venous dopamine was needed to maintain systemic blood flow. On day 43, her blood tests showed the following: aspartate aminotransferase (AST), 1832 U/L; alanine aminotransferase (ALT), 725 U/L; lactate dehydrogenase (LDH), 1348 U/L; alkaline phosphatase (ALP), 883 U/L; γ -glutamyl transpeptidase (γ -GTP), 98 U/L; procalcitonin increased to 37.8 ng/mL; and platelet count decreased to 17 000/mm³, suggesting the development of disseminated intravascular coagulation syndrome. Regarding chronic kidney disease-mineral bone disorders (CKD-MBD) parameters, serum-corrected calcium and serum phosphate levels were 8.8 mg/dL and 7.3 mg/dL, respectively, on day 43. Since the central venous catheter culture was positive for methicillin-resistant *Staphylococcus epidermidis* (MRSE), vancomycin infusion was restarted, and the septic shock was suspected to have been caused by MRSE. Her blood pressure improved until day 45, and continuous intravenous dopamine was halted. Her blood tests on day 56 showed the following: AST, 63 U/L; ALT, 24 U/L; LDH, 272 U/L; ALP, 662 U/L; and γ -GTP, 73 U/L, which implied that the liver enzymes, apart from biliary enzymes, had decreased to near-normal levels. Regarding CKD-MBD, her serum-corrected calcium level was 9.6 mg/dL and serum phosphate level was 4.1 mg/dL on day 56, and intact parathyroid (iPTH) level was 11 pg/mL on day 66.

Although her symptoms were improved by vancomycin, she developed high fever again on day 75. The intravenous catheter was removed, and vancomycin was restarted at the same dose as before, considering the exacerbation of MRSE infection. However, her blood culture was positive for *Escherichia coli* and *Pseudomonas aeruginosa*. Therefore, we switched her medication from vancomycin to 1 g ceftazidime daily. After that, her fever improved, and her general condition was similarly stable; ceftazidime was stopped on day 90.

From day 112 to day 125, she had high fever (38.5°C). Teicoplanin (800 mg administered as a loading dose then 200 mg every 48-72 h to maintain a suitable concentration) and ceftazidime were administered despite her negative blood culture test result. Vancomycin could not be used because it caused skin eruption. Her blood test on day 131 revealed

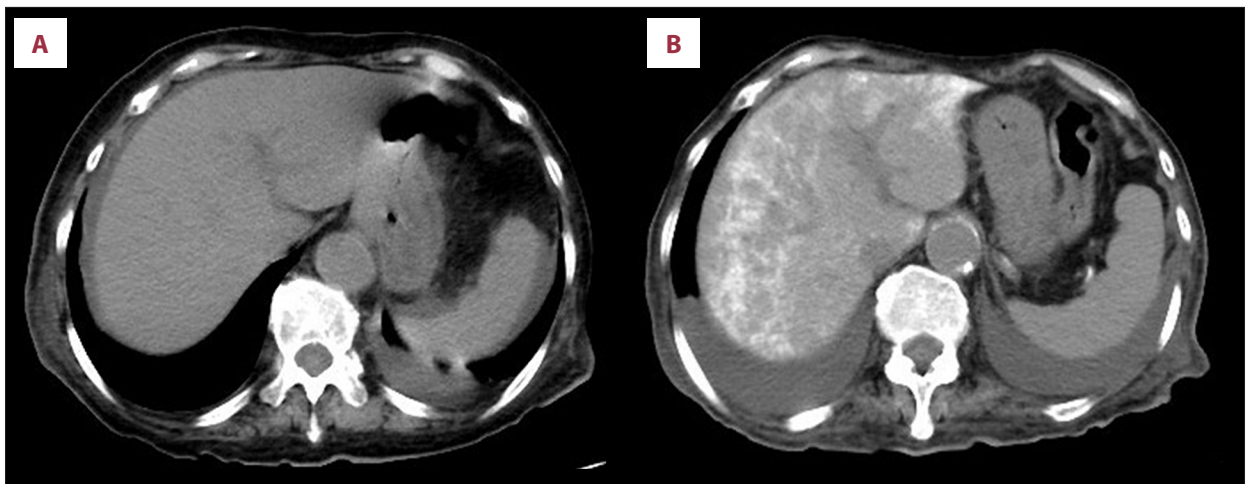


Figure 1. (A) Abdominal computed tomography (CT) scan on day 45. There is no calcification in the liver. (B) Abdominal CT scan on day 140. Diffuse liver calcification is observed in the liver, and small patchy aortic calcification is similarly observed in her aorta.

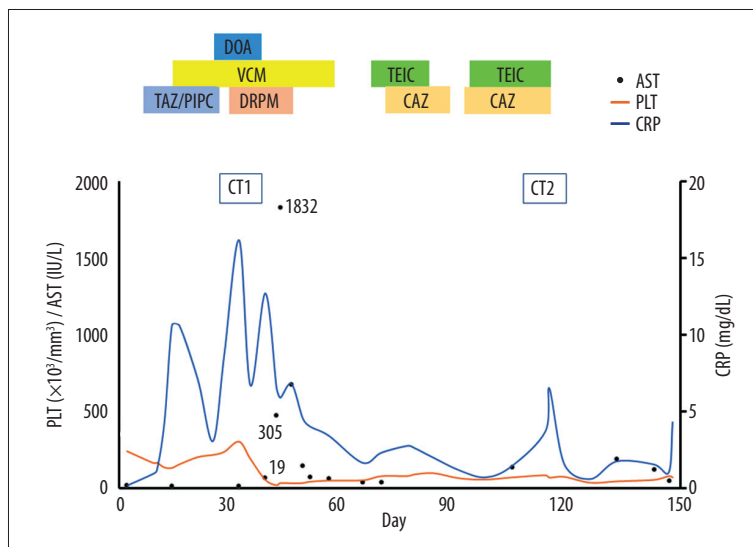


Figure 2. Summary of the clinical course from day 1 to day 150. DOA – dopamine; VCM – vancomycin; TEIC – teicoplanin; TAZ/PIPC – tazobactam piperacillin hydrate; DRPM – doripenem; CAZ – ceftazidime; CT – computed tomography; PLT – platelet; AST – aspartate aminotransferase; CRP – C-reactive protein.

mild liver dysfunction: AST, 192 U/L; ALT, 132 U/L; LDH, 246 U/L; ALP, 922 U/L; and γ -GTP, 87 U/L. Regarding CKD-MBD parameters, her serum-corrected calcium level was 9.0 mg/dL, serum phosphate level was 6.1 mg/dL, and iPTH level was 52 pg/mL on day 131. Although there were no abnormal liver findings on day 45 (Figure 1A), a second abdominal CT scan on day 136, approximately 3 months later, revealed faint and unclear high absorption areas in both lobes of the liver, indicating marked calcification (Figure 1B). In addition, her aorta showed slight calcification, which was not observed on day 45 (Figure 1B). Her overall clinical course until day 150 is summarized in Figure 2.

Although her liver function returned to normal, with enzyme levels maintained almost in the normal range, the patient repeatedly developed aspiration pneumonia, and *P. aeruginosa*, extended-spectrum β -lactamases (ESBL)-positive *K. oxytoca*

and ESBL-positive *E. coli* were detected. Similarly, she developed central venous catheter-related infections and sepsis. Meanwhile, her liver calcification did not improve during the rest of her clinical course. The calcium concentration of the dialysate at our facility is 1.375 mmol/L (2.75 mEq/L), and she underwent consecutive dialysis sessions at this concentration. She was not prescribed vitamin D analogs or calcium bicarbonate throughout her clinical course because her CKD-MBD parameters could be controlled without medication. Unfortunately, she died on day 635 due to multiple organ failure.

Discussion

Herein, we present the case of a hemodialysis patient with diffuse liver calcification. Because she repeatedly went into septic shock, ischemic liver perfusion and tissue injury seemed

Table 1. Previously reported cases of patients undergoing hemodialysis with diffuse liver calcification.

Case	Age	Sex	Causes of renal failure	Dialysis vintage	Clinical background	AST	ALT	ALP
1	41	M	CGN	9 years	Septic shock	6465	735	220
2	47	M	BNS	1 week	Cardiac arrest	>10000	>10000	NA
3	31	F	Ns	3 years	Cardiogenic shock	9232	3520	NA
4	60	F	MPA	3 months	Hemorrhagic shock	NA	NA	NA
5	74	F	CGN	5 months	Hemorrhagic shock	11020	4711	NA
6	66	M	UNK	2 days	AMI	2797	935	565
This case	82	F	DMN	4 months	Septic shock	1832	725	883

Case	LDH	CK	cCa	P	PTH	Outcome	Ref
1	11600	679	8.8	9.5	130	Death	[9]
2	NA	NA	8.5	18.5	NA	Recovered	[10]
3	8230	86	7.9	11.6	NA	Death	[11]
4	NA	NA	8.8	3.3	NA	Death	[12]
5	NA	NA	NA	NA	NA	Death	[13]
6	396	NA	7.9	6.4	NA	Recovered	[14]
This case	1348	101	8.8	7.3	NA	Death	

AST – aspartate aminotransferase; ALT – alanine aminotransferase; ALP – alkaline phosphatase; LDH – lactate dehydrogenase; CK – creatine kinase; cCa – corrected calcium; P – phosphorus; PTH – parathyroid hormone; Ref – reference; M – Male; F – Female; CGN – chronic glomerular nephritis; BNS – benign nephrosclerosis; Ns – nephrosis; MPA – microscopic polyangiitis; UNK – unknown; AMI – acute myocardial infarction; DMN – diabetic nephropathy; NA – not available.

to have played a key role in the pathophysiology of liver calcification. In contrast, CKD-MBD parameters seemed to have little effect on the liver calcification.

Calcification is sometimes observed in various parts of the body, including the arteries, corneas, conjunctiva, periarterial tissue, skin, subcutaneous tissue, lungs, stomach, heart, and kidneys [6]. Arterial calcification is among the complications that most affect the prognosis of patients undergoing hemodialysis. Vascular calcification can be attributed to high serum Ca×P products, secondary hyperparathyroidism, lower serum Mg concentration, metabolic acidosis, and local tissue injuries. Apart from arterial calcification, uremic tumoral calcification and multiple organ calcification caused by systemic calciphylaxis have been observed among patients receiving dialysis [5,7]. Although the mechanisms underlying these disorders can differ, it takes a long time to develop calcification, irrespective of the etiology.

Liver tissue calcification is extremely rare, especially in patients undergoing hemodialysis. Generally, liver calcification is caused by granulomatous lesions, infections, echinococcosis, or malignancies [8]. Almost all reported cases showed local

calcification along with vessel or interstitial calcification, and diffuse liver calcification was extremely rare [8]. In our search of medical databases, including MEDLINE and Google Scholar, we found only 6 previously reported cases [9-14] (Table 1). The prognosis of these patients tended to be poor, and all of these cases, as well as our case, were supposedly caused by liver ischemia due to systemic shock; this is called ischemic hepatitis or shock liver [15]. Regarding liver function, survivors in the previous cases and the present case showed the recovery of normal liver function because the liver is a tolerant organ with regenerative activity. The causes of this disorder vary and include heart failure, infection, and hypovolemic shock, and an acute liver injury is caused by insufficient oxygen delivery to the liver [15]. Some of these cases showed high Ca×P products, which might accelerate calcification; however, not all cases had poor control of mineral bone disorders. Regarding our patient, her serum phosphate level was high; however, the Ca×P products level was moderate. In addition, her serum iPTH level was low.

Additionally, our patient was not administered any vitamin D analogs throughout the clinical course, and calcium carbonate was not prescribed because her CKD-MBD parameters

could be controlled without medications. Exogenous calcium intake should be considered; however, her intravenous hyperalimentation or tube feeding contained only a small amount of calcium. In addition, the dialysate calcium level at our facility is within the range recommended by the 2017 Kidney Disease Improving Global Outcome CKD-MBD guidelines [16]. From this perspective, CKD-MBD parameters did not seem to play an important role in our patient's developing liver calcification. In contrast, CKD-MBD might play a role in developing aortic calcification, as observed in the present case. A previous study suggested that ischemia of hepatocytes induces permeability of the cell membrane and causes calcium ions to flow into the hepatocytes, resulting in the activation of phospholipase. According to this hypothesis, absorption of phospholipids on the cellular membrane induces new calcium ion channels. After the restoration of blood flow, a large amount of calcium is absorbed into cells, which causes the disruption of mitochondria and enzyme and protein synthesis, finally leading to cell death [17].

Contrary to arterial calcification, diffuse liver calcification in the previously reported cases and the present case developed in a short period. Apart from cases 1 and 3, the previously reported cases and our case involved patients undergoing hemodialysis with a dialysis history of less than 6 months. We speculated that serum fetuin-A may be associated with liver calcification in patients who have been on hemodialysis for a shorter duration. Fetuin-A is known to prevent calcification; however, the serum fetuin level at the point of initiation of hemodialysis was proven to be low [18]. While continuing hemodialysis, the serum fetuin-A level gradually increased, suggesting that calcification may not be adequately prevented in patients who have just initiated hemodialysis. Moreover, serum parathyroid hormone levels are supposed to be higher at the initiation of hemodialysis [19], which might be associated with rapid liver calcification among patients who have just started hemodialysis.

Regarding fetuin-A, septic shock reduces serum fetuin-A level because inflammatory cytokines suppress the secretion of fetuin-A [20]. By contrast, the administration of fetuin-A significantly improved the survival rate in a septic animal model via high mobility group box protein 1 [21], suggesting that

fetuin-A plays a key role in septic shock. Nevertheless, further molecular mechanisms need to be elucidated to clarify the progression of calcification.

This report has several limitations. First, liver biopsy was not performed owing to the poor general condition of the patient; moreover, an autopsy was not conducted. Therefore, details of microscopic change were not elucidated in this case. This is one of the most important limitations of this report. Second, the levels of liver enzymes increased in this case; however, not only ischemia but also antibiotics might be responsible for the liver dysfunction. Third, we did not perform an abdominal CT scan between days 45 and 136, that is, for approximately 3 months. Therefore, the precise speed at which the liver calcification developed remains unknown. Finally, the result of blood examinations was limited in this case, and her serum fetuin-A and serum 25-hydroxyvitamin D levels were not evaluated throughout the period.

We only speculate that lower serum fetuin-A level accelerates diffuse liver calcification; however, there was no evidence to support our hypothesis. Thus, the relationship between ectopic calcification and septic shock should be elucidated based on molecular biology techniques, including in animal models, in the future.

Conclusions

We report a rare case of a hemodialysis patient who repeatedly contracted urinary tract infection and pneumonia, resulting in septic shock. After her recovery from ischemia of hepatocyte, her liver showed diffuse calcification. Mineral imbalance and liver hypoperfusion could cause diffuse liver calcification in patients undergoing hemodialysis. Hence, we should pay careful attention to liver hypoperfusion in these patients to prevent lethal outcomes.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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