MASSIVE MYOCARDIAL CALCIFICATION OF RIGHT
AND LEFT VENTRICLES FOLLOWING ACUTE
MYOCARDITIS COMPLICATED WITH
RHABDOMYOLYSIS-INDUCED
ACUTE RENAL FAILURE

ATSUSHI WADA, M.D., TOMOAKI NAKATA, M.D.
KAZUHUMI TSUCHIHASHI, M.D., SHINYA Aoyama, M.D.
MASAAKI NARBA, M.D., HIROMI MURAKAMI, M.D.
KAZUAKI SHIMAMOTO, M.D. AND OSAKU IIMURA, M.D.

A 26-year-old man was admitted with a high fever, oliguria, skeletal muscle weakness, and cardiogenic shock which led to a diagnosis of acute myocarditis and acute rhabdomyolysis. During treatment with hemodialysis and calcium supplementation, because of severe hypocalcemia, a massive calcification of both right and left ventricular myocardium gradually became apparent with repeated computed tomographic (CT) examinations. Technetium-99m scannings more clearly delineated the markedly accumulated calcium in the myocardium, while significant activity was not detected in other soft tissues. Histopathological examinations by myocardial biopsy revealed a large amount of fibrosis and calcium deposits, and serial CT scans showed a gradual regression of the calcium deposition, suggesting that this rare form of massive dystrophic calcification may parallel changes in the severity of myocarditis, and may be associated with abnormalities in calcium metabolism secondary to rhabdomyolysis-induced acute renal failure.

(Jpn Circ J 1993; 57: 567–572)

MYOCARDIAL calcification has been observed microscopically in necrotic tissue following experimental viral myocarditis1–4 and acute myocarditis in human newborns and infants5–8. Metastatic calcification in soft tissues (including skeletal muscle) associated with acute or chronic renal failure and acute rhabdomyolysis has also been reported9–14. Although the manifestations of acute myocarditis vary widely in humans, it is unusual for marked dystrophic cardiac calcification to develop in an adult patient. We describe an adult patient who survived acute myocarditis and rhabdomyolysis-induced acute renal failure, with accompanying massive calcification of both ventricular walls suggestive of a "plaster cast", as shown by technetium-99m scintigrapies and repeated computed tomographic (CT) examinations.

CASE REPORT

A 26-year-old man was admitted with a high fever, nausea, muscle weakness of the lower limbs, general malaise, and oppressive

Key words:
Acute myocarditis
Acute rhabdomyolysis
Cardiac calcification
Technetium-99m scintigraphy

(Received August 29, 1992; accepted October 29, 1992)
The Second Department of Internal Medicine, Sapporo Medical College, S-1, W-16, Chuo-ku, Sapporo 060, Japan
Mailing address: Tomoaki Nakata, M.D., PhD, The Second Department of Internal Medicine, Sapporo Medical College, S-1, W-16, Chuo-ku, Sapporo 060, Japan

Japanese Circulation Journal Vol.57, June 1993 567
anterior chest pain. The patient had no history of cardiac, renal, or other disorders. Three days previously, he had complained of shaking chill and a high fever (39.5°C). Despite treatment with an antipyretic drug, general malaise and oliguria were manifested, and he continued to experience a high fever. Because his condition deteriorated and electrocardiographic abnormality and laboratory data strongly suggested myocardial damage, he was transferred to our hospital. On admission, blood pressure was low (55/44 mmHg) and peripheral pulses were not palpable. His heart rate was 88 min, heart sounds were scarcely audible, and third and fourth sounds were present. He had no crackle, but did have moderate hepato-megaly, definitely diminished deep-tendon reflexes, and muscular pain in both legs. Chvostek's sign was also present. Laboratory examinations revealed leukocytosis (11,600/mm³), renal and liver dysfunction (serum creatinine 5.3 mg/dl and GPT 5,420 IU/l), and severe muscle injury (LDH 19,300 IU/l, CK 4,970 IU/l, serum myoglobin 22,915 ng/ml, and urinary myoglobin 174 ng/ml). Severe metabolic acidosis (pH 7.07 and HCO₃⁻ 3.8 mEq/l) and profound hypocalcemia (6.0 mg/dl) were observed, but serum phosphorus did not exceed 7.0 mg/dl. Parathyroid hormone concentration was slightly increased at 1.5 pg/ml. His chest radiograph showed cardiac enlargement and pulmonary edema. His electrocardiogram showed a complete atrioventricular block, severe right axis deviation, ST-segment depression in leads II, III, aVF, V₄₋₆, ST-segment elevation in leads V₁₋₃, and a markedly prolonged corrected QT interval (0.53 sec). A few days later, the atrioventricular block returned to sinus rhythm and ST-segment abnormalities gradually normalized for several weeks. Two-dimensional echocardiography revealed edematous ventricular walls, markedly enlarged right heart chambers, and generally reduced wall motions of the right and left ventricles. From these findings, we made the diagnosis of acute heart failure due to acute myocarditis and acute renal failure due to acute rhabdomyolysis. However, no significant increase in viral titers was detected during the clinical course.

The patient was intensively treated with catecholamines, hemofiltration, and hemodialysis. A high dose of calcium gluconate was also intravenously infused because of severe hypocalcemia (960 mg/day during the initial 7 days) which caused tetany and prolonged the QT interval. The patient gradually improved. Thirty days later, renal and liver function normalized completely and serious dysrhythmias and atrioventricular block disappeared, although a severe left axis deviation and a complete right bundle branch block with an inverted T wave in leads, I, aVL, V₁₋₄ remained. Left and right ventricular ejection fractions determined by radionuclide ventriculography were 32% and 8%, respectively, and cardiac enlargement and generally hypokinetic wall motion were still observed on repeated echocardiograms. Massive technetium-99m-labeled MDP accumulation (Fig. 1A), was observed in both cardiac chambers but not in
skeletal muscles or other soft tissues, and $^{99m}$Tc-pyrophosphate scintigraphy more clearly showed intense activities in both ventricles (Fig. 1B–1D). CT studies performed serially for 18 months revealed calcium deposition and subsequent mobilization in the heart after acute myocarditis (i.e., the density of cardiac muscle progressively increased and extensive and dense calcifications appeared in both ventricles after 1 month; the calcium deposits then gradually regressed [Fig. 2]). Histopathological examination of biopsied specimens from the right ventricle obtained 3 months after the onset (Fig. 3) disclosed widespread fibrosis and large amounts of calcium deposits. Eighteen months later, the patient is still alive and tolerates an ordinary working day and daily life well, despite an impaired cardiac function.
DISCUSSION

Dystrophic calcification can be observed microscopically in necrotic myocardial tissue obtained from experimental and clinical preparations. In addition, calcification of skeletal muscle and other soft tissues is not an uncommon complication of rhabdomyolysis-induced renal failure, and can be demonstrated by technetium-99m scanning$^{11-14}$ The most unusual finding in this case was the apparent manifestation of massive dystrophic calcification of both ventricular myocardium, suggestive of a "plaster cast" in cardiac imaging in an adult patient with rhabdomyolysis-induced acute renal failure. Technetium-99m scintigraphy appears to be very useful when scanning the entire body for calcium deposition, as demonstrated in the present case. The patient's clinical history, physical findings, and clinical examinations did not reveal any trauma, ischemic conditions associated with increased muscle oxygen consumption (heat stroke, severe exercise, or seizures) or decreased muscle energy production electrolyte imbalance or genetic disorders), or previous disorders, including cardiac, renal, metabolic hormonal, or vascular disease, malignancies, or intoxications of alcohol or other chemicals, except infectious conditions (a high fever and shaking chill). These findings suggest that some type of infection (probably viral) produced acute rhabdomyolysis and myocarditis resulting in acute renal failure and massive myocardial damage, despite the lack of increased viral titer or other etiological evidence.

The cardiac calcification in the present case is apparently different from metastatic calcium deposition, which can often be found in soft tissues, including the heart, during long-term hemodialysis$^{9-15}$

There are other possible mechanisms of myocardial calcification. First, as suggested by the clinical and histopathological findings, large amounts of damaged cardiac tissue in the right and left hearts may be associated with marked calcium deposition. Cardiac calcification has been demonstrated histologically in acute viral myocarditis, especially in that caused by Coxsackie virus group B infection in young children$^5-8$ and in experimental murine myocarditis!$^{14}$ However, when compared to the frequency and magnitude of calcification in experimental viral myocarditis, massive dystrophic calcification is uncommon in humans. There are only 2 reports of microscopic myocardial calcification in human infants infected with Coxsackie virus$^6,7$. Although the mechanism of myocardial calcification following acute viral myocarditis is not clear, it has been suggested that acute myocarditis due to viral infection can provoke more serious myocardial injury, in which calcium deposition is more likely$^{14}$. Although, in the present case, no evidence of acute "viral" infection was obtained, the occurrence of an earlier severe acute myocarditis was strongly suggested by the clinical and histological findings.

Secondly, abnormalities in calcium metabolism associated with rhabdomyolysis-induced acute renal failure may be responsible for the findings of marked hypocalcemia and cardiac calcification$^{11,16}$. It has been reported that hypocalcemia is caused by decreased 1,25-(OH)$_2$D$_3$ synthesis and skeletal resistance to the calcemic action of parathyroid hormone in the oliguric phase of
rhabdomyolysis-induced acute renal failure.\textsuperscript{16} However, it is not clear that the severe hypocalcaemia without marked hyperphosphatemia observed in the present case can be explained by such a mechanism alone. It has been reported that rhabdomyolysis per se can precipitate hypocalcaemia, independently of the presence of acute renal failure or hyperphosphatemia and that hypocalcaemia is more pronounced in combined acute renal failure and rhabdomyolysis than is either of them alone.\textsuperscript{11,17} This is probably because calcium deposition in rhabdomyolytic muscle can constitute an additional factor in the genesis of more severe hypocalcaemia.\textsuperscript{12,14,17} During the polyuric (recovery) phase of acute renal failure, an increased production of 1,25-(OH)\textsubscript{2}D\textsubscript{3}, hyperparathyroidism secondary to hypocalcaemia, and an improved response to parathyroid hormone can elevate serum calcium and phosphorus which may lead to myocardial calcification. However, in the present case, a hypercalcemic state did not develop, even during the polyuric phase, and serum phosphorus did not exceed 7.0 mg/dl throughout the clinical course. Furthermore, cardiac calcification in this case was detected by CT scans during an oliguric phase of rhabdomyolysis-induced acute renal failure, as has been previously reported.\textsuperscript{11} These findings suggest that renal and hormonal involvements may have been partially responsible for the genesis of marked hypocalcaemia and myocardial calcification.

The clinical implications of massive dystrophic cardiac calcification are not clear. Although massive cardiac calcification appears to be associated with severe dysfunction of both ventricles, calcium deposition per se may reflect only the degree of myocardial injury. However, we speculate that massive calcification may reduce cardiac compliance and affect the healing process. Serial CT scans showed a gradual regression of myocardial calcification during an 18 month follow-up period. We are interested in determining whether complete resolution of the calcium deposition and improvement of cardiac function will be forthcoming.

Acknowledgements

We acknowledge the editorial assistance of Dr. Naomi M. Anderson, Calgary, Canada.

Japanese Circulation Journal Vol. 57, June 1993

REFERENCES

1. SCHMIDT ECH: Virus myocarditis. Pathologic and experimental studies. \textit{Am J Path} 1948; \textbf{24}: 97—117

2. WILSON FM, MIRANDA OR, CHASON JL, LERNER AM: Residual pathologic changes following murine Coxsackie A and B myocarditis. \textit{Am J Path} 1969; \textbf{55}: 253—265


5. BATES Jr. HR: Coxsackie virus B3 calcific pancarditis and hydrops fetalis. \textit{Am J Obstet Gynecol} 1970; \textbf{106}: 629—630


7. GOREN A, KAPLAN M, GLASER J, ISACSOHN M: Chronic neonatal coxsackie myocarditis. \textit{Arch Dis Child} 1989; \textbf{64}: 404—406


9. KUZELA DC, HUFFER WE, CONGER JD, WINTER SD, HAMMOND WS: Soft tissue calcification in a chronic dialysis patient. \textit{Am J Pathol} 1977; \textbf{86}: 403—424


15. KAWAI S, FUKUDA K, OKADA R, HARUHARA S, WATANABE K, ONO S, SEKI-GUCHI H, SANJYO T, SOMA Y: An autopsied case of interstitial myocarditis with myocardial mineralization, accompanied by high titer of rubel-