Transient Heterotopic Calcification and Unexpected Hypercalcemia after Treatment of Septic Shock

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Abstract

Transient heterotopic calcification with unexpected hypercalcemia after septic shock is a very rare phenomenon. We encountered a complicated case in which heterotopic calcification occurred in the liver, bilateral iliopsoas and pubococcygeal muscles after treatment of septic shock and multiple organ failure. Hypercalcemia was not present when the heterotopic calcification was detected by plain CT scans. Physicians who observe acute and progressive heterotopic calcification during sepsis treatment need to recognize the risk of hypercalcemia even if it is not present before the detection of heterotopic calcification. This case provides useful information regarding the critical aspects of heterotopic calcification after sepsis treatment.

Key words: heterotopic calcification, sepsis, hypercalcemia

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Introduction

Transient heterotopic calcification after septic shock and multiple organ failure (MOF) is a very rare phenomenon. We observed a case of heterotopic calcification after septic shock in the liver, bilateral iliopsoas and pubococcygeal muscles. Two months later, transient hypercalcemia occurred during the patient's stay in the intensive care unit. The hypercalcemia was not present at the time the heterotopic calcification was detected by plain CT scans. The signs and symptoms of hypercalcemia are usually limited, but acute and rapid increases in calcium levels in critical patients will develop into severe conditions such as critical arrhythmias, kidney stones and other symptoms. We herein describe a very rare case of transient heterotopic calcification after septic shock with a concurrent unexpected hypercalcemia. This case provides useful information regarding the critical aspects of heterotopic calcification after sepsis treatment.

Case Report

A man in his 30s was admitted to our hospital with vomiting, abdominal pain and diarrhea, which continued for three days. He had a history of epilepsy from childhood and

was taking the anti-epileptic agents phenobarbital and phenytoin. His blood pressure on arrival was 56/38 mmHg, pulse was 169 beats/min and body temperature was 40.0°C. A physical examination revealed he had diffuse abdominal distention without guarding or rebound tenderness. The results of an arterial blood gas analysis were as follows: pH 7.356, PaCO₂ 19.0 mmHg, PaO₂ 85.7 mmHg (F_iO₂=1.0), base excess -14.2 mmol/L, HCO₃⁻ 10.4 mmol/L and lactate 6.1 mmol/L. Laboratory data on admission are shown in Table 1. The patient was intubated and placed on a mechanical ventilator because of hypotension and respiratory failure with metabolic acidosis. Chest radiography indicated acute respiratory distress syndrome (ARDS). He developed MOF due to hypoxia, ARDS, liver dysfunction, acute renal injury and rhabdomyolysis after admission. Laboratory data indicated high total bilirubin (T-Bil, maximum value 3.07 mg/dL on the ninth day and 0.44 mg/dL at three weeks after admission), aspartate aminotransferase (AST, maximum value 1,622 U/L on the second day and 37 U/L at three weeks after admission), alanine aminotransferase (ALT, maximum value 883 U/L on the second day and 47 U/L at three weeks after admission), creatine kinase (CK, maximum value 42,699 U/L on the seventh day and 179 U/L at three weeks after admission) and blood myoglobin (maximum value 30,600 ng/mL on the second day). Abdominal

radiography and computed tomography (CT) showed marked small bowel dilatation. Strangulation ileus was excluded based on physical findings, laboratory data and diagnostic imaging. At this point, there was no evidence of heterotopic calcification on CT (Fig. 1A). The abdominal distention rapidly resolved after the insertion of a nasal decompression tube. The diagnosis was septic shock with MOF after small bowel obstruction. He was administered antibiotics (tazobactam/piperacillin; 2.25 g three times daily). A sputum culture detected methicillin-sensitive *Staphylococcus aureus* and *Klebsiella pneumoniae* bacteria, even though no bacteria were identified from a blood culture taken during admission.

Table 1. Laboratory Data on Admission.

WBC ($4.0-8.0 \times 10^3/\mu\text{L}$)	14.4	Na (136-148 mmol/L)	128
RBC ($4.5-5.5 \times 10^6/\mu\text{L}$)	6.24	K (3.6-5.0 mmol/L)	4.5
Hgb. (14-17 g/dL)	20.1	Cl (98-109 mmol/L)	86
Hct (40-50 %)	54.5	Ca (8.8-10.8 mg/dL)	10.1
FDP ($<5\mu\text{g/mL}$)	38.3	P (2.4-4.5 mg/dL)	6.5
D-dimer ($<1\mu\text{g/mL}$)	15.4	Mg (1.7-2.3 mg/dL)	3.1
T-Bil (0.3-1.2 mg/dL)	0.65	CRP ($<0.2\text{ mg/dL}$)	25.42
D-Bil (0.05-0.4 mg/dL)	0.3	TP (6.5-8.0 g/dL)	8.0
AST (8-38 U/L)	24	Albumin (3.8-5.3 g/dL)	4.0
ALT (4-44 U/L)	20	Blood sugar (70-110 mg/dL)	236
LD (106-220 U/L)	287	Presepsin ($<500\text{pg/mL}$)	3520
ALP (117-335 U/L)	234	Procalcitonin ($<0.5\text{ng/mL}$)	48.34
G-GT (12-73 U/L)	169		
CK (54-253 U/L)	129		
UN (8-19 mg/dL)	87.8		
Creatinine (0.8-1.3 mg/dL)	7.38		

Continuous hemodiafiltration was also performed for two weeks for acute kidney injury (Fig. 2).

Although the patient's general condition gradually improved after treatment, approximately one month after admission we observed a recurrence of small bowel dilatation and diffuse abdominal distention. Both sputum and blood cultures detected methicillin-sensitive *S. aureus* and *K. pneumoniae* bacteria. Plain abdominal CT scans indicated re-dilatation of the small bowel and several calcified areas in the liver, bilateral iliopsoas muscles and pubococcygeal muscles (Fig. 1B, black arrows). A surgical intervention was performed for the small bowel obstruction and for a biopsy of the iliopsoas muscle. A histological examination of the iliopsoas muscle tissue revealed diffuse calcification in the muscle tissue accompanied by an infiltration of inflammatory cells (Fig. 3). The cause of the bowel obstruction was an internal hernia due to an adherent band formation.

The blood calcium levels (normal range: 8.8-10.8 mg/dL) were low from the second to the 40th day after admission ($6.6 \pm 0.53\text{ mg/dL}$, mean $\pm$ standard deviation; range 5.7-7.3 mg/dL). Hyperparathyroidism was not observed because the laboratory blood data for calcium metabolism on the 30th, 60th, 69th and 80th day after admission were within normal limits, with the exception of low 1,25-(OH)₂-Vitamin D. Renal function improved, although there were no laboratory data available regarding renal dysfunction (Table 2) during this period. We were not able to detect other causes of hypercalcemia such as cancer or drug side effects. Details on

A. On admission
Plain and enhanced CT

B. After sepsis treatment
Plain CT

C. Before hospital discharge
Plain and enhanced CT

Figure 1. Whole body CT scans of our patient. A: Initial plain and contrast enhanced CT scans on admission. There was no evidence of heterotopic calcification in the liver (upper), bilateral iliopsoas muscles (middle) and pubococcygeal muscles (lower). B: After sepsis treatment, plain CT scans (on the 30th day after admission) indicated high density areas (heterotopic calcification: black arrows) in the liver, bilateral iliopsoas and pubococcygeal muscles. The blood calcium level was still within the normal range at this point. C: Plain and contrast enhanced CT. Heterotopic calcification in the bilateral iliopsoas and pubococcygeal muscles were resolved as of the 110th day after admission, but the calcification in the liver remained unresolved.

Figure 2. Clinical course, treatment and progressive changes in laboratory data. The blood calcium level was within the normal range and gradually increased from the 36th day after admission and peaked on the 69th day. Surgical intervention and biopsy: A surgical intervention for bowel obstruction was performed along with a biopsy of the iliopsoas muscles. WBC: White blood cell (normal range: $4.0-8.0 \times 10^3/\mu\text{L}$), Ca: Calcium (normal range: 8.8-10.8 mg/dL), P: Phosphate (normal range: 2.4-4.5 mg/dL), CRP: C-reactive protein (normal range: <0.2 mg/dL), Creatinine: normal range: 0.8-1.3 mg/dL. The arrows indicate the days on which the plain or contrast enhanced CT and surgical intervention were performed. The patient experienced acute cholecystitis on the 73rd day after admission. The contents per 500 mL of acetated Ringer's solution were as follows: NaCl: 3.0 g, KCl: 0.15 g, $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$: 0.10 g, $\text{C}_2\text{H}_3\text{NaO}_2 \cdot 3\text{H}_2\text{O}$: 1.90 g. TAZ/PIPC: tazobactam/piperacillin; 2.25 g, three times daily. CAZ: ceftazidime; 1 g, two times daily. ABPC/ST: ampicillin/sulbactam; 3 g, three times daily. Meropenem: meropenem hydrate; 1 g, two times daily. Enteral nutrition: Tube feeding. Start of medication (orally, but stopped at recurrence of abdominal distention and re-started with enteral nutrition): 1: ambroxol hydrochloride; 45 mg/day, 2: carbocisteine; 1,500 mg/day, 3: itopride hydrochloride; 150 mg/day, 4: Tsumura Daikenchuto; 15.0 g/day, 5: levetiracetam; 1,000 mg/day.

Figure 3. Hematoxylin and Eosin staining of the muscles with diffuse calcification. Typical calcification lesions with inflammatory cells are identified. The scale is indicated in the image.

the administered drugs are shown in Fig. 2. During this period, he was administered antibiotics (ampicillin/sulbactam; 3.0 g three times daily) to treat a central venous catheter-related bloodstream infection. *Bacillus cereus* was determined to be the infecting bacterium based on blood culture results (Fig. 2). Afterwards, the blood calcium levels gradually but transiently increased (maximum blood calcium level was 14.9 mg/dL) with normal blood sodium, potassium and phosphate levels for the patient's clinical course. The blood calcium level returned to within the normal range following crystalloid infusion. The patient experienced acute cholecystitis with biliary sludge, but no gallstones according to CT after his clinical course (73rd day after admission). The muscle calcifications were resolved on the 110th day after admission, but calcification of the liver remained. Plain and contrast enhanced CT scans did not show any evidence of abscess formation in the liver or muscles (Fig. 1C). The patient recovered fully without complications and returned to

Table 2. Laboratory Blood Data for Calcium Metabolism.

Days after admission	1 day	15 days	20 days	30 days	60 days	69 days	72 days	80 days
Blood Ca (8.8-10.8 mg/dL)	10.1	6.7	7.1	6.5	12.6	14.0	12.0	8.3
Blood Creatinine (0.8-1.3 mg/dL)	7.38	4.93	3.81	0.71	0.46	0.52	0.51	0.39
Urine Ca (10-30 mg/dL)	-	1.8	1.8	2.8	-	16.5	11.4	4.5
PTH-intact (10-65 pg/mL)	-	-	-	62	-	10	-	25
PTH-rP (< 1.1 pmol/L)	-	-	-	1.0	1.0	1.0	-	1.0
Calcitonin (15-86 pg/mL)	-	-	-	57	23	-	-	66
1,25-(OH) ₂ -Vitamin D (20-60 pg/mL)	-	-	-	16.2	10.7	-	-	30.1

Ca: Calcium, PTH-intact: Parathyroid hormone, intact (blood sample), PTH-rP: Parathyroid hormone-related Peptide (blood sample)

Blanks were no clinical data.

the outpatient clinic.

Discussion

We herein report a very rare case of transient heterotopic calcification in various tissues after septic shock. Furthermore, there are no previously reported cases of transient heterotopic calcification with progressively changing blood calcium levels. Our patient developed septic shock with hypoxia, ARDS, liver dysfunction, rhabdomyolysis and acute renal injury after admission. After sepsis treatment, he was affected by transient and delayed hypercalcemia, although the blood calcium level was within the normal range when heterotopic calcifications were detected by plain CT scans. The pathophysiology of heterotopic calcification after severe sepsis and MOF and the relationship of heterotopic calcification with hypercalcemia remain unclear. However, the calcification process in damaged tissue has been reported for several conditions (1-4), including myocardial calcification (5-8) after sepsis. Sepsis, trauma, cancer or an imbalance in calcium metabolism are considered to be the triggering factors for these heterotopic calcification phenomena (8, 9). Because our patient followed the pattern of sepsis deteriorating to MOF (e.g., liver dysfunction and rhabdomyolysis) and the calcifications were located in the liver and muscles, we propose that the calcium depositions formed in post-septic damaged tissue.

Long-term systemic inflammatory stimuli may have affected signaling agents, such as those for the bone morphogenetic protein (BMP), which might also link the heterotopic calcification and bone formation process with the induction of mesenchymal cells in the various tissues to differentiate into osteoblasts or chondroblasts (10). Myositis ossificans is another critical differential diagnosis and occurs with the formation of heterotopic bone in various tissues (9, 10) after sepsis has been reported (9). Interestingly, in our case, a lesion was observed in the liver, which was previously unreported. A possible mechanism of heterotopic calcification in the various tissues may be related to BMP signals from tissue damage caused by long-term inflammatory stimuli, since the expression of BMPs has been detected in various organs such as the thymus, bone marrow,

spleen, brain, spinal cord, heart, skeletal muscle, kidney, lung, pancreas, prostate and the liver (11).

The etiology for calcification of various tissues and unexpected hypercalcemia after septic shock and MOF has not been identified. Other possible factors for this phenomenon, such as immobilization (12), drug side effects and parathyroid hyperactivity, might have contributed to the development of hypercalcemia. Because we did not find any previous reports of hypercalcemia being associated with the side effects of the drugs administered to treat the sepsis observed in our case, the exact pathogenetic mechanism remains unclear.

Our patient also experienced complications of acute cholecystitis with biliary sludge after hypercalcemia was detected. A case of acute cholecystitis induced by antibiotics has been reported (13, 14). Our patient was also administered antibiotics just before being diagnosed with acute cholecystitis. It is unclear whether the acute cholecystitis was related to the post-septic transient hypercalcemia, although biliary sludge commonly comprises cholesterol crystals and calcium salts. Patients with mild hypercalcemia might not have any symptoms. If the hypercalcemia is more serious, critically ill patients carry a serious risk of complications that can lead to potentially life-threatening events such as arrhythmia or coma. Our case suggests that physicians should be alert for signs of heterotopic calcification of various tissues and an occult unexpected hypercalcemia during the treatment of septic shock; the recognition of heterotopic calcification in various tissues is difficult in the clinical setting.

This is a very rare case of unexpected hypercalcemia after heterotopic tissue calcification in a critically ill patient. While there is a critical risk of unexpected hypercalcemia after treatment of septic shock and MOF, physicians who observe acute and progressive heterotopic calcification during sepsis treatment must recognize the potential risk of unexpected hypercalcemia, even if hypercalcemia is not present before heterotopic calcification is detected. Although the tissue calcifications were resolving, the relationship between hypercalcemia and the tissue calcification resolution process remains unclear.

Written informed consent to publish this case report was obtained from the patient before he was discharged from the hospital.

The authors state that they have no Conflict of Interest (COI).

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References

1. McClure J, Pieterse AS, Pounder DJ, Smith PS. Myocardial fibre calcification. *J Clin Pathol* **34**: 1167-1174, 1981.
2. Sencimen M, Gulses A, Ogretir O, Gunhan O, Ozkaynak O, Okcu KM. Dystrophic calcifications arising in the masseter muscle: a case report. *Quintessence Int* **41**: 295-297, 2010.
3. Tong KA, Christiansen EL, Heisler W, Hinshaw DB Jr, Hasso AN. Asymptomatic myositis ossificans of the medial pterygoid muscles: a case report. *J Orofac Pain Spring* **8**: 223-226, 1994.
4. Okada A, Hatori M, Hosaka M, Watanuki M, Itoi E. Calcific myonecrosis and the role of imaging in the diagnosis: a case report. *Ups J Med Sci* **114**: 178-183, 2009.
5. Schellhammer F, Ansén S, Arnold G, Brochhagen HG, Lackner K. Myocardial calcification following septic shock. *Cardiology* **98**: 102-103, 2002.
6. Lapatto-Reiniluoto O, Vaalamo M, Takkunen O, Mänttari M. Left ventricular calcification following resuscitation. *J Intern Med* **248**: 85-87, 2000.
7. Austin CO, Kramer D, Canabal J, Krishna M, Mergo P, Shapiro BP. A heart of stone: a case of acute development of cardiac calcification and hemodynamic collapse. *J Cardiovasc Comput Tomogr* **7**: 66-68, 2013.
8. Rossi MA, Santos CS. Sepsis-related microvascular myocardial damage with giant cell inflammation and calcification. *Virchows Arch* **443**: 87-92, 2003.
9. Jiang Q, Chen MJ, Yang C, et al. Post-infectious myositis ossificans in medial, lateral pterygoid muscles: a case report and review of the literature. *Oncol Lett* **9**: 920-926, 2015.
10. Yu PB, Deng DY, Lai CS, et al. BMP type I receptor inhibition reduces heterotopic ossification. *Nat Med* **14**: 1363-1369, 2008.
11. Bragdon B, Moseychuk O, Saldanha S, King D, Julian J, Nohe A. Bone morphogenetic proteins: a critical review. *Cell Signal* **23**: 609-620, 2011.
12. Forster J, Querusio L, Burchard KW, Gann DS. Hypercalcemia in critically ill surgical patients. *Ann Surg* **202**: 512-518, 1985.
13. Choi YY, Jung YH, Choi SM, Lee CS, Kim D, Hur KY. Gallbladder pseudolithiasis caused by ceftriaxone in young adult. *J Korean Surg Soc* **81**: 423-426, 2011.
14. Schaad UB, Wedgwood-Krucko J, Tschaeppler H. Reversible ceftriaxone-associated biliary pseudolithiasis in children. *Lancet* **17**: 1411-1413, 1988.