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Case Report

Myocardial calcification in a patient with B-lymphoblastic leukemia accompanied by tumor lysis syndrome

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ABSTRACT

Myocardial calcification, a rare disease that leads to chronic or acute heart failure and with a poor prognosis, occurs in patients with abnormal calcium-phosphorus metabolism. The association between myocardial calcification and tumor lysis syndrome has not been reported to date. A 50-year-old man with hyperthermia and general malaise presented to our hospital and was clinically diagnosed with B-lymphoblastic leukemia (B-ALL) and febrile neutropenia accompanied by septic shock. Prednisolone was administered for tumor reduction. Two to three hours later, electrocardiography demonstrated ST elevation in V4–6, and blood tests showed elevated levels of cardiac enzymes. Transthoracic echocardiogram revealed diffuse severe hypokinesis with decreased left ventricular ejection fraction. Additionally, blood tests showed that serum phosphorus level increased to 8.0 mg/dl, which was likely due to tumor lysis syndrome. Circulatory and respiratory failure due to left heart failure progressed, and he died 3 days after administration of prednisolone. Pathological autopsy revealed diffuse proliferation of atypical B-lymphoblasts in the bone marrow, which led to the pathological diagnosis of B-ALL, accompanied by necrosis. On the cut surface of the heart, the left ventricle was dilated, and patchy yellowish-brown areas were present in the epicardial-side of the myocardium and spread through the circumferential wall of the left ventricle and interventricular septum. Microscopically, myocardial fibers were granularly basophilic in that area and were revealed as calcium deposits by Von Kossa staining. He was diagnosed with myocardial calcification. The drastic increase in the serum phosphorus level caused by tumor lysis syndrome seemed to be associated with myocardial calcification.

1. Introduction

Myocardial calcification is a rare disease that leads to chronic or acute heart failure and has poor prognosis [1,2]. Myocardial calcification is categorized into three different subtypes: dystrophic, metastatic, and idiopathic calcification [2,3]. In metastatic myocardial calcification, patients present an abnormal calcium-phosphorus metabolism resulting from a wide range of diseases [2,4–6]. Most cases of myocardial calcification in leukemia or lymphoma patients occur in those with adult T-cell leukemia/lymphoma which is often accompanied by hypercalcemia [5,6]. Only two cases of myocardial calcification in patients with B-lymphoblastic leukemia/lymphoma (B-ALL) have been reported; these patients also experienced septic shock [7,8]. To our knowledge, myocardial calcification associated with tumor lysis syndrome has never been described. Here, we present an autopsy case of B-ALL with tumor lysis syndrome after induction of steroid therapy accompanied by myocardial calcification that resulted in heart failure.

2. Case report

A 50-year-old man presented to our hospital with hyperthermia and general malaise. He had no history of cardiovascular or hematologic diseases. Moreover, no history of vitamin D use, kidney disease, or parathyroid disease was known. Peripheral blood tests performed in our hospital 6 months before revealed no abnormalities. He experienced severe nosebleed a month prior to his visit

Abbreviations: B-ALL, B-lymphoblastic leukemia; ECG, electrocardiography; TTE, transthoracic echocardiogram.

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and developed progressive shortness of breath during physical activity for 2 weeks. On the day before the visit, the patient complained of a sore throat, lightheadedness and shivering. At the visit, his vital signs were indicative of shock, as follows: body temperature, 40.1°Celsius; respiratory rate, 26 breaths/min; pulse rate, 116 beats/min; and blood pressure, 88/44 mmHg. A general physical examination revealed conjunctival anemia, oral mucosal hemorrhage, and subcutaneous bleeding. Peripheral blood tests showed a decrease in hemoglobin level, neutrophil, and platelet counts, and an elevated blast ratio, lactate level, and C-reactive protein level (Table 1). A smear test revealed that the blasts were negative for peroxidase. Flow cytometry demonstrated that blasts were positive for CD19, CD20, CD34, and terminal deoxynucleotidyl transferase (TdT) and were negative for CD3, CD5, CD7, and CD33. Multiplex reverse transcription-polymerase chain reaction for quantification of minor BCR-ABL1 fusion gene transcripts showed mn-bcl/abl, 1.9×10^6 copies/μgRNA (reference range: <50 copies/μgRNA). Therefore, he was clinically diagnosed with B-ALL. Peripheral blood culture showed positivity for group C β-streptococcus. He was also diagnosed with febrile neutropenia accompanied by septic shock and was emergently admitted. At admission, the electrolyte balance was almost within normal limits (Table 1). Electrocardiography (ECG) showed a normal sinus rhythm, and a transthoracic echocardiogram (TTE) did not detect any abnormalities in cardiac wall motion. The patient was treated with prednisolone (60 mg/day) and rasburicase (7.5 mg/day) for B-ALL, and with meropenem (3 g/day), filgrastim (150 μg), noradrenaline (0.5 μg/kg/min), and vasopressin (1 U/h) for septic shock. Red blood cells (4 U), platelets (20 U) and fresh frozen plasma (2 U) were transfused for nosebleed.

Prednisolone was administered for tumor reduction and 2 to 3 h later, the patient complained of chest tightness. ECG demonstrated ST elevation (3 mm) in V4–6. Blood tests revealed elevated levels of creatine kinase-MB and troponin I (Table 1). TTE demonstrated diffuse severe hypokinesis with a low left ventricular ejection fraction of 32%. ST-segment elevation myocardial infarction was clinically suspected at this time; however, administration of isosorbide dinitrate (3 ml/h) did not improve the ST elevation on ECG. Because of hemodynamic instability and clinical suspicion of disseminated intravascular coagulation from his laboratory data, emergency coronary angiography could not be performed, and dopamine (5 μg/kg/min), dobutamine (5 μg/kg/min), and thrombomodulin (9600 U/day) were administered. Additionally, blood tests showed elevated levels of serum potassium and phosphorus (Table 1), which led to the clinical diagnosis of tumor lysis syndrome [9]. In spite of tumor lysis syndrome, peripheral blood tests did not show an increase in uric acid (Table 1), presumably due to treatment with rasburicase. Five hours after the ST-segment elevation, circulatory and respiratory failure progressed, which further developed into acute renal failure and acute hepatic insufficiency. Although he was treated with continuous venovenous hemodiafiltration and non-invasive positive pressure ventilation, the patient died 3 days after beginning these treatments. The patient was examined post-mortem through a pathological autopsy at our hospital under family's consent.

The autopsy revealed an atypical and diffuse lymphoid cells proliferation in the bone marrow, which was accompanied by necrosis (Fig. 1A). Atypical lymphoid cells had a monotonous, medium-sized nucleus with an irregular shape and the nuclear cytoplasmic ratio was high (Fig. 1B). Immunohistochemistry showed positivity for CD79a, PAX5, and CD10 (Fig. 1C, D), as well as a partial, weak positivity for TdT. Considering clinical and molecular findings, the underlying lymphoproliferative disease was diagnosed as B-ALL with t(9;22)(q34.1;q11.2), BCR-ABL1; the diagnosis was in accordance with the revised 4th edition of The World Health Organization classification for tumors of hematopoietic and lymphoid tissues [10]. The lymphoblasts infiltrated multiple organs (i.e. systemic lymph nodes such as the axillary, inguinal, paraaortic, hepatic hilar, and mesenteric lymph nodes; liver; spleen; tonsils; lungs; kidneys; adrenal glands; epicardium; appendix; and testes). On the cut surface of the heart, the left ventricle was dilated, indicating left heart failure, and patchy yellowish-brown areas were macroscopically spread throughout the epicardial-side of the myocardium and through the circumferential wall of the left ventricle and interventricular septum (Fig. 2). Microscopically, basophilic granules were deposited on the cardiomyocytes in the same area (Fig. 3A and C). The nuclei of these granularly basophilic cardiomyocytes were not well observed (Fig. 3B). Von Kossa staining revealed the granular materials to be calcium deposits (Fig. 3C). The cardiomyocytes with calcium deposits were extensively detected, in patches, on the epicardial-side of cardiomyocytes in the left ventricle and interventricular septum, similar to the macroscopic observation. Cardiomyocytes around the degenerated cells were almost conserved (Fig. 3B). Coronary artery stenosis or thrombosis was not detected. The acute left ventricular failure seemed to be due to myocardial calcification. Small calcified foci were also detected in the renal medulla exclusively. Uric acid crystals were not detected within the lumen of the distal renal tubules, as far as detectable with formalin fixation. Dissection around the trachea and thyroid gland did not reveal enlarged parathyroid tissue. And, sections of tissue from the dissection

Table 1
Peripheral blood test data at admission and at the time of ST elevation in echocardiogram

	Reference range [unit]	Admission (before steroid induction)	ST elevation (after steroid induction)
White blood cell counts	3.1–9.5 [10^3/μl]	4.4	10.4
Blasts ratio	0 [%]	78	N/A
Neutrophils counts	1200–8000 [/μl]	22	87
Red blood cell counts	4.01–5.40 [10^6/μl]	1.41	2.75
Hemoglobin	13.5–16.9 [g/dl]	4.2	8.5
Platelet counts	15.1–34.9 [10^4/μl]	0.2	6.1
Uric acid	3.7–7.0 [mg/dl]	7.9	4.8
Lactate dehydrogenase	120–245 [/μl]	3010	5660
Lactate	4.0–16.0 [mg/dl]	82.0	N/A
C-reactive protein	<0.3 [mg/dl]	11.7	22.3
Creatine kinase-MB	<3.7 [ng/ml]	0.5	16.6
Troponin I	<26.2 [pg/ml]	81.6	4532.3
Natrium	136–145 [mmol/l]	139	140
Potassium	3.6–4.8 [mmol/l]	3.6	5.3
Calcium (corrected by albumin)	8.8–10.1 [mg/dl]	8.7	8.2
Phosphorus	2.2–4.6 [mg/dl]	3.3	8.0

N/A; not available.

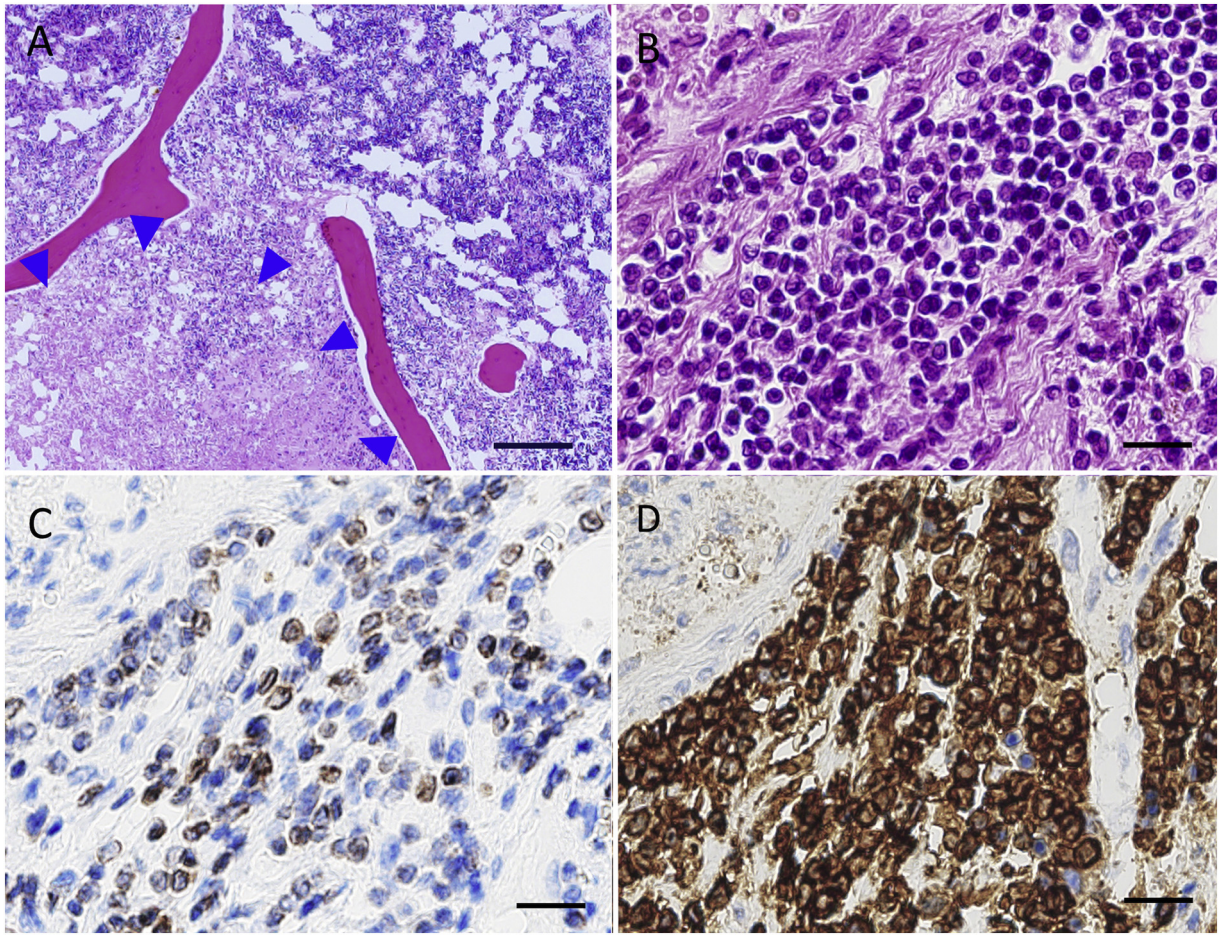

Fig. 1. Pathology of the bone marrow. (A) Atypical lymphoid cells diffusely proliferated in the bone marrow, accompanied by necrosis (arrowheads) (scale bar: 200 μm). (B) Atypical lymphoid cells had a monotonous, medium-sized nucleus with an irregular shape (scale bar: 50 μm). (C, D) Immunohistochemistry revealed that atypical lymphoid cells were positive for CD79a (C) and CD10 (D) (scale bar: 50 μm).

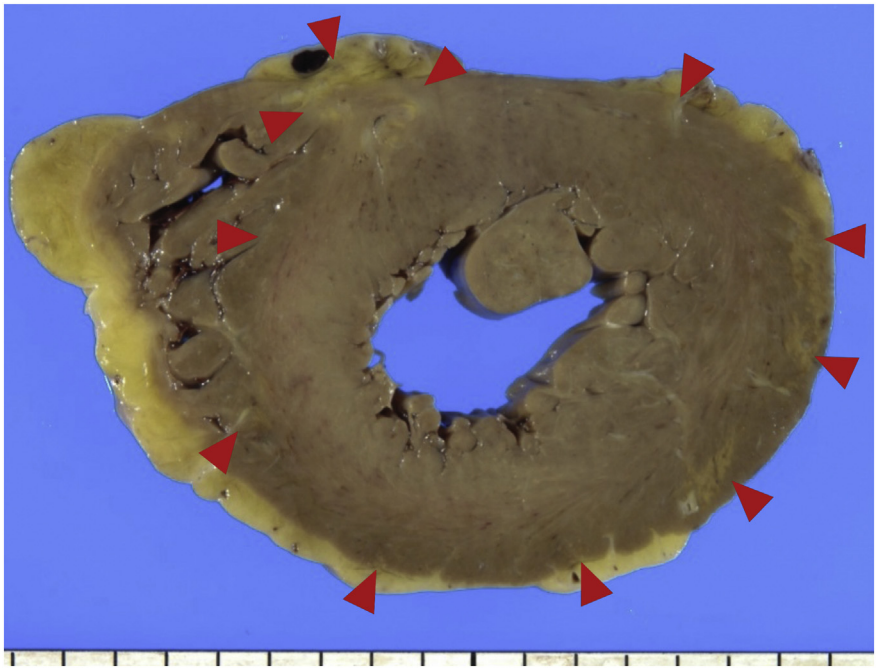

Fig. 2. Gross findings of the heart. On the cut surface of the heart after formalin fixation, the left ventricle was dilated, and patchy yellowish-brown areas were in the epicardial-side of the myocardium and through the circumferential wall of the left ventricle (arrowheads).

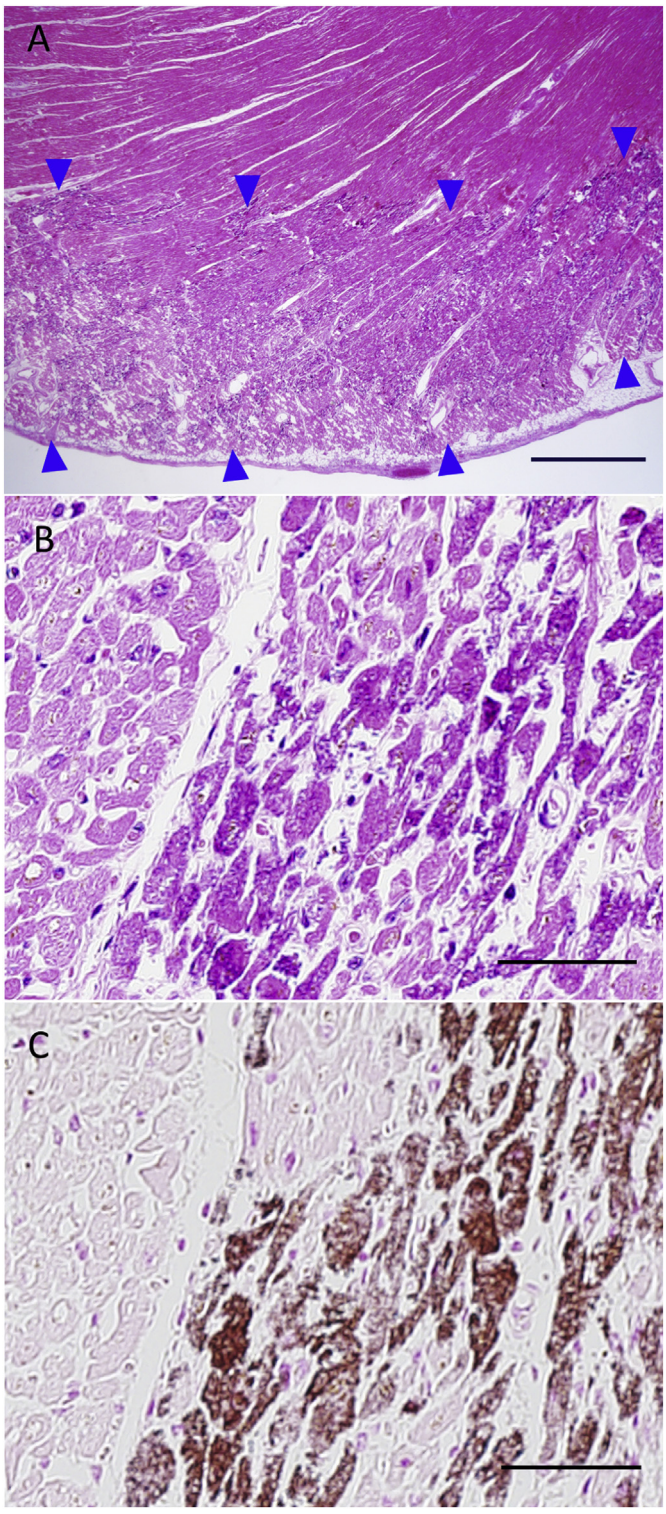

Fig. 3. Pathology of the heart (anterior wall of the left ventricle). (A) Microscopically, cardiomyocytes in the macroscopically yellowish-brown area were granularly basophilic (arrowheads) (scale bar: 2 mm). (B) The nuclei in the granularly basophilic cardiomyocytes were not well observed. Cardiomyocytes around the degenerated cells were almost conserved (scale bar: 100 μm). (C) Von Kossa staining revealed calcium deposits in these cardiomyocytes (at the same part as B; scale bar: 100 μm).

microscopically showed some parathyroid tissue without evidence of hyperplasia.

Gram-positive cocci similar to those found on peripheral blood culture at the time of admission were detected in the left tonsil, which was suggested to be a focus of infection. Autopsy also revealed pulmonary congestion, centrilobular necrosis of the liver, and acute tubular necrosis of the kidneys. We, therefore, concluded that septic shock and acute left heart failure due to myocardial calcification in association with B-ALL and tumor lysis syndrome were the major causes of systemic circulatory failure, leading to multiple organ failure and death.

3. Discussion

This report presents a rare case of myocardial calcification with B-ALL accompanied by tumor lysis syndrome. Myocardial calcification acutely developed and was accompanied by a drastic increase in the serum phosphorus level in association with tumor lysis syndrome, leading to acute left heart failure. In our case, myocardial infarction was clinically suspected; however, an autopsy did not detect coronary artery stenosis or thrombotic microangiopathy. The necrotic cardiomyocytes with calcium deposits were located in the epicardial side of the left ventricle and interventricular septum. These pathological findings were inconsistent with those generally associated with acute myocardial infarction.

Myocardial calcification is categorized into three different subtypes: dystrophic, metastatic, and idiopathic calcification [2,3]. Dystrophic calcification results from tissue damage caused by various cardiac diseases (e.g. sepsis [11,12], myocardial infarction [13,14], and ventricular aneurysm [15]), and such calcium deposition in the damaged cardiomyocytes develop over days or months [2]. Metastatic calcification results from abnormal calcium-phosphorus metabolism, which is secondary to end-stage renal disease [2,16,17], hyperparathyreosis [18], and malignancies, such as adult T-cell leukemia/lymphoma [5,6]. Unsaturated minerals in blood precipitate as calcium deposits on cardiomyocytes [19]. Myocardial calcification without dystrophic or metastatic cause is classified as idiopathic calcification [3,20]. In our case, ST elevation on ECG and elevated levels of cardiac enzymes occurred only a few hours after the administration of steroids, which was considered to be caused by myocardial calcification in association with tumor lysis syndrome, which was classified as metastatic calcification.

Myocardial tissue damage due to septic shock did not seem to be a major cause of myocardial calcification in this case. Past studies revealed that patients experiencing septic shock also developed left ventricular systolic dysfunction due to myocardial calcification [11,12]. Although the precise mechanisms of myocardial calcification remain unclear, past reports indicated catecholamine to have a critical role in the pathology of myocardial necrosis and calcium deposition in cardiomyocytes [21,22]. Excessive endogenous and exogenous catecholamine injures the cardiomyocytic membrane, increasing the membrane permeability and influx of calcium into cardiomyocytes [11,21,22]. This calcium influx causes myocardial fiber hypercontraction and cardiomyocytic necrosis, leading to secondary calcium deposition [11,21,22]. In our case, cardiomyocytes without calcium deposits did not show necrosis, which was not consistent with the secondary calcium deposition following myocardial necrosis in association with septic shock. Additionally, myocardial calcification and left ventricular systolic dysfunction progressed more drastically in our case than in previously reported cases of myocardial calcification due to septic shock [11]. These pathological findings and acute clinical course did not support that myocardial tissue damage due to septic shock was the cause of myocardial calcification.

The drastic increase of the serum phosphorus level in our case seemed to be associated with myocardial calcification. Metastatic calcification results from abnormal calcium-phosphorus metabolism [2,19]. Continuous hypercalcemia or hyperphosphatemia increases the multiplication product of calcium and phosphorus ions, leading to plasma saturation and metastatic tissue

calcification [19]. These myocardial calcium deposits have been supposed to cause myocardial damage [2,23]. In addition, a study revealed that administration of steroids and sodium phosphate caused local cardiomyocytic necrosis with calcium deposition [23]. In our case, the serum phosphorus level increased from 3.3 to 8.0 mg/dl after the administration of prednisolone. This sudden increase in levels may be associated with acute calcium deposition in the heart, leading to cardiomyocytic necrosis, which can histologically be confirmed by disappearance of the nucleus. Additionally, calcification also occurred in the kidney. This finding seemed to also support that hyperphosphatemia in association with tumor lysis syndrome was the main cause of calcification.

Presently, the accurate clinical diagnosis of myocardial calcification is still challenging. In our case, ST elevation on ECG, increasing levels of creatine kinase-MB and troponin I, diffuse severe hypokinesis with a low ejection fraction on TTE were consistent with myocardial infarction. Past cases of myocardial calcification due to septic shock also demonstrated similar conditions that mimicked myocardial infarction [8,12]. The similar clinical course and laboratory findings between myocardial calcification and myocardial infarction appear to reflect myocardial necrosis. These similarities also make accurate diagnosis of myocardial calcification difficult. Myocardial calcification might be better listed as a differential diagnosis when patients with abnormal calcium-phosphorus metabolism, such as tumor lysis syndrome (like in this case), develop acute heart failure with ST elevation on ECG and elevated levels of cardiac enzymes (i.e. myocardial infarction-like state).

In conclusion, we present a rare case of myocardial calcification with B-ALL accompanied by tumor lysis syndrome. The drastic increase in serum phosphorus level accompanied by tumor lysis syndrome in this case seems to be associated with myocardial calcification.

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