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Case Report

CASE REPORT

Sudden unexpected death caused by infantile acute lymphoblastic leukaemia

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Abstract

A 7-week-old girl with a normal birth history suddenly developed respiratory distress while feeding. Cardiopulmonary resuscitation was initiated at home after she had a cardiac arrest and was continued in the emergency room but all efforts at resuscitation proved unsuccessful and she died 2 h after presentation. Investigations performed in the emergency room revealed that she had a significantly high white blood cell count and severe anaemia. The cause of death was identified as *KMT2A*-rearranged infantile acute lymphoblastic leukaemia based on cytogenetic tests. She had no abnormalities at the 4-week check-up; however, she developed a skin nodule on her abdomen thereafter, and the family did not consult a doctor for fear of contracting COVID-19. Early detection and diagnosis could have changed the prognosis of the patient. The present case highlights the negative impact of the reduction of outpatient consultations during the COVID-19 pandemic.

INTRODUCTION

Sudden unexpected death is defined as death in a person who was normal until evolution of acute symptoms and signs. Reports of sudden unexpected death due to neoplastic disease in infancy and childhood (SUDNIC) are extremely rare, only two cases of infantile acute leukaemia have been reported [1, 2]. Diagnosis of childhood leukaemia has been reportedly delated due to health delivery changes during the COVID-19 pandemic [6, 7].

We report a case of SUDNIC in a 7-week-old girl caused by *KMT2A*-rearranged infantile acute lymphoblastic leukaemia (ALL). This raises concerns that the fear of contracting COVID-19 from hospitals may lead to preventable deaths.

CASE REPORT

A 7-week-old girl who was born full term with appropriate weight was brought to our hospital. She had no family history to note and her mother had no complications or infections during

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pregnancy. Although mild liver enlargement was observed on foetal ultrasound, no further investigations were performed. Results of screening tests for congenital metabolic disorders and the automatic auditory brainstem response were normal. No abnormal findings were detected at her 4-week check-up. A few days after the check-up, her parents noticed a skin nodule and abdominal distension prompting intent for a doctor's visit. However, they decided to wait and observe, considering the risk of COVID-19 and the nationwide state of emergency in Japan at the time. No other symptoms such as fever or sweating were observed thereafter. On the day of admission, she has sudden gasping breaths while feeding at home. As respiratory arrest progressed, her father started cardiopulmonary resuscitation (CPR), taking turns with the emergency service crew a few minutes shortly upon their arrival. Intubation and intraosseous infusion were performed in the ambulance on the way to our hospital. Upon arrival, vital signs were as follows: axillary temperature 33.9°C, no spontaneous respiration, and no spontaneous heart rate. Electrocardiography revealed asystole. She was noted to have pale skin, abdominal distension, with marked hepatosplenomegaly. A 1.5 × 2.0 cm white nodule below the left rib arch as well as generalized petechiae were noted on physical examination (Fig. 1a-1). Laboratory results revealed the following: white blood cell count, 1 204 000/μL with 95.0% blasts; haemoglobin, 2.2 g/dL; platelet count, 23 000/μL; aspartate aminotransferase, 1720 U/L; alanine transaminase, 687 U/L; lactate dehydrogenase, 6265 U/L; uric acid, 11.9 mg/dL; creatinine, 0.42 mg/dL; potassium, 8.8 mEq/L; and inorganic phosphate, 17.2 mg/dL. The nasal swab was negative for SARS-CoV-2 on reverse transcription polymerase chain reaction test. In the emergency room, CPR was continued and a total of 13 doses of intravenous adrenaline were administered, however, all efforts at resuscitation proved unsuccessful. Although full resuscitation was attempted, the patient did not respond and eventually died 2 h after admission. An autopsy was performed with informed consent from her parents and revealed enlargement of the liver, kidneys, pancreas, spleen, and mesenteric and peri-aortic lymph nodes (Fig. 1b). Histological investigation revealed diffuse infiltration of small atypical lymphocytes in the parenchyma of the stomach, intestinal tract, liver, kidney, pancreas, spleen and uterus, and vessel lumina of the heart, lungs, thymus, thyroid, adrenal glands, ovaries, and skin including the nodule on the left upper abdomen (Fig. 1a-2). Her bone marrow was fully occupied with CD10-negative/CD19-positive blasts (Fig. 1c), and cytogenetic tests showed 46,XX,t(11;19)(q23.3;p13.3)[19/20] and 1.3×10^4 copies/μgRNA of *KMT2A-MLLT1* fusion transcripts.

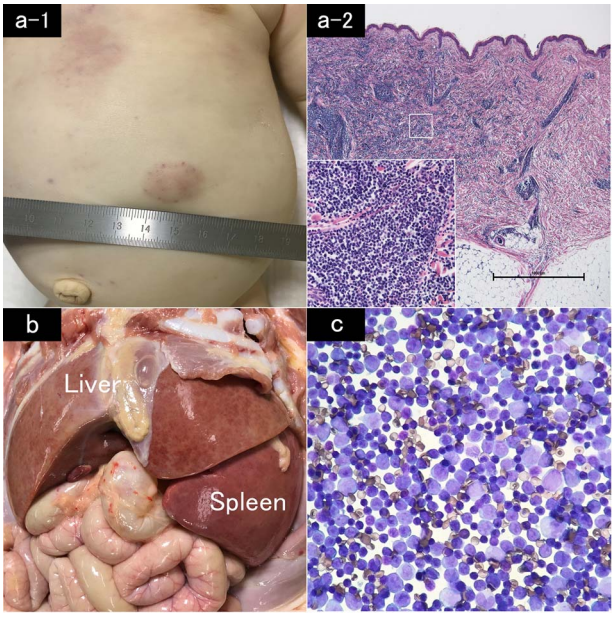

Figure 1: Imaging and pathological findings. White nodule on the upper left abdomen (**a-1**) and light microscopy findings of an autopsy sample of the skin nodule with infiltration of leukaemic blasts (**a-2**, scale bar = 1000 μm, inset 50 μm). Macroscopic autopsy findings of the enlarged liver and spleen (**b**). Bone marrow aspirates with full leukemic blasts (**c**, ×400).

DISCUSSION

The patient's death resulted from a rapid progression of *KMT2A*-rearranged infantile B-ALL, which was directly associated with severe anaemia, hypoxemia due to widespread intravascular infiltration of leukaemic blasts, affecting the lungs and hyperkalaemia due to tumour lysis syndrome.

SUDNIC is extremely rare, and there has been only two other instances of SUDNIC due to infantile acute leukaemia: one in a 1-month-old and another in a 4-month-old infant (Table 1) [1, 2]. Among the infantile ALL cases, rearrangement of the *KMT2A* gene is a hallmark feature noted in 80% of the cases, and the *KMT2A*-rearranged cases are the aggressive form [3]. Such are characterized by leucocytosis, marked hepatosplenomegaly, and extramedullary invasion including that in the skin.

Although the molecular biological aberrations of *KMT2A*-rearranged ALL occurs through multi-step genetic events in utero [3], the timing of onset and diagnosis varies. However, given the rapid course of this case, hepatomegaly noted in the foetal period and abdominal distension noted in the neonatal period may be signs of leukaemia. Skin infiltrations, namely 'leukaemia cutis', are observed in approximately 60% of infantile ALL cases diagnosed within the first 4 weeks of life [4, 5]. Leukaemia should be considered when refractory skin lesions are found in infants. In such a case, screening blood tests may lead to early detection. There have been reports of fatal cases with delayed leukaemia diagnosis due to the COVID-19 pandemic [6, 7]. In this case, the COVID-19 pandemic had negatively affected willingness to consult a doctor for the infant's skin nodule, resulting in poor linkage to paediatric health services.

There is no clear evidence that the timing of diagnosis decisively impacts the prognosis of children with ALL [8]. However, appropriate diagnosis and initiation of anti-leukaemic therapy are important initial steps for inducing remission. These opportunities were not offered to this case. The recently reported clinical trial in Japan, showed a 5-year event-free survival rate of 61.5% in *KMT2A*-rearranged infantile ALL cases diagnosed before 90 days of age, which is generally an aggressive and a poor-risk subgroup of infantile ALL [9]. We believe that at least a chance for remission could have been offered with prompt diagnosis. Considering the aggressive nature of *KMT2A*-rearranged infantile ALL, diagnostic delay should be avoided.

It is important for health care providers to pay attention to persistent symptoms and to be aware of the changes in healthcare delivery during the COVID-19 pandemic. The fear of contracting COVID-19 from hospitals could affect clinical courses of certain diseases. Moreover, information must be provided to families when necessary. This would foster vigilance, leading to early consultation and diagnosis. This case raises alarm for the paediatric health care system during the pandemic.

Table 1: SUDNIC due to infantile acute leukaemia

Case	Age	Sex	Clinical presentation	Autopsy findings	Confirmed diagnosis
1 (Reference 1)	1 month	Female	Lethargy and poor feeding 20 h prior to death. Diagnosed with upper respiratory tract infection; found unresponsive next morning; did not respond to resuscitation and died.	Distension of visceral and cerebral vessels owing to leukemic cells.	Acute lymphoblastic leukaemia (suggestive of pre–B-cell type)
2 (Reference 2)	4 months	Female	Poor feeding and irritability for 3 days. Presented to Accident & Emergency with fever, dyspnoea, bruising and oro-nasal bleeding; deteriorated rapidly and died on arrival at the hospital.	Widespread lymphadenopathy and hepatosplenomegaly	Acute leukaemia
3 (Present case)	7 weeks	Female	Previously well until sudden gasping breath was noted during feeding. Respiratory distress developed and went into cardiopulmonary arrest; died hours later at the hospital.	Enlargement of the liver, kidneys, pancreas, spleen, and mesenteric and peri-aortic lymph nodes	Acute lymphoblastic leukaemia (KMT2A-rearranged infantile ALL)

CONFLICT OF INTEREST

No conflicts of interest.

FUNDING

No sources of funding were used.

ETHICAL APPROVAL

Ethics approval for this case report was waved. Parental consent was gained prior to creating this manuscript.

CONSENT

All images and information presented about the minor patient were used with informed consent from the patient's parents. All images were anonymized.

GUARANTOR

Mariko Shimizu is a guarantor for this publication.

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