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 delayed 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
She was noted to have pale skin, abdominal distension, with spontaneous heart rate. Electrocardiography revealed asystole. On physical examination (Fig. 1a-1). Laboratory results revealed the left rib arch as well as generalized petechiae were noted. The patient’s death resulted from a rapid progression of 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 intravenous 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, 1204000/μL with 95.0% blasts; haemoglobin, 2.2 g/dL; platelet count, 23000/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 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.

**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 leukemic 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 [2], 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
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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.

REFERENCES
1. Somers GR, Smith CR, Perrin DG, Wilson GJ, Taylor GP. Sudden unexpected death in infancy and childhood due to undiagnosed neoplasia: an autopsy study. *Am J Forensic Med Pathol* 2006;27:64–9. https://doi.org/10.1097/01.paf.0000203267.91806.ed.

2. Bryant VA, Booth J, Palm L, Ashworth M, Jacques TS, Sebire NJ. Childhood neoplasms presenting at autopsy: a 20-year experience. *Pediatr Blood Cancer* 2017;64:e26474. https://doi.org/10.1002/pbc.26474.

3. Tomizawa D. Recent progress in the treatment of infant acute lymphoblastic leukemia. *Pediatr Int* 2015;57:811–9.

4. Palman J, Karam M, Chee Y, Kandala V. Neonatal acute lymphocytic leukaemia: an unusual presentation of a rare disease. *BMJ Case Rep* 2015;2015:1–3. https://doi.org/10.1136/bcr-2015-210606.

5. Bresters D, Reus AC, Veerman AJ, Wering ER, Berg AD, Kaspers GJ. Congenital leukaemia: the Dutch experience and review of the literature. *Br J Haematol* 2002;117:513–24.

6. Ding YY, Ramakrishna S, Long AH, Phillips CA, Montiel-Esparza R, Diorio CJ et al. Delayed cancer diagnoses and high mortality in children during the COVID-19 pandemic. *Pediatr Blood Cancer* 2020;67:e28427. https://doi.org/10.1002/pbc.28427.

7. Parasole R, Stellato P, Conter V, De Matteo A, D’Amato L, Colombini A et al. Collateral effects of COVID-19 pandemic in pediatric haematology: fatalities caused by diagnostic delay. *Pediatr Blood Cancer* 2020;67:e28482. https://doi.org/10.1002/pbc.28482.

8. Brasme JF, Morfouace M, Grill J, Martinot A, Amalberti R, Bons-Letouzey C et al. Delays in diagnosis of paediatric cancers: a systematic review and comparison with expert testimony in lawsuits. *Lancet Oncol* 2012;13:e445–59.

9. Tomizawa D, Miyamura T, Imamura T, Watanabe T, Moriya Saito A, Oguwa A et al. A risk-stratified therapy for infants with acute lymphoblastic leukaemia: a report from the JPLSG MLL-10 trial. *Blood* 2020;136:1813–23. https://doi.org/10.1182/blood.2019004741.