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Clinical characterization and genetic analysis of transient abnormal myelopoiesis without the down syndrome phenotype

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ABSTRACT

Background: Transient abnormal myelopoiesis (TAM) is a congenital leukemia specific to neonates with Down syndrome (DS) or trisomy 21. However, rare cases of TAM can also occur with acquired trisomy 21 mutations or mosaic trisomy 21, leading to potential misdiagnosis due to the absence of the DS phenotypes.
Method: We present a case of TAM in a neonate without typical DS phenotypic features. We documented medical records from hospitalizations and a one-year follow-up period. Additionally, through a literature review, we summarized the clinical phenotype and genotypic characteristics observed in similar neonates.
Results: Despite the lack of typical DS phenotype the neonate was diagnosed with TAM upon detection of trisomy 21 and the GATA1 gene mutation, the condition resolved spontaneously without requiring chemotherapy. We monitored the neonate for a full year, during which no hematologic or developmental abnormalities were observed. Thirteen previous cases of neonates with TAM but without the DS phenotype have been reported. During the onset of TAM, the presence of trisomy 21 can be detected in peripheral blood cells or bone marrow cells, but some patients may not show evidence of trisomy 21 in fibroblasts. In these patients, trisomy 21 in peripheral blood cells or bone marrow cells may gradually decrease and even disappear as TAM improves. All patients experienced self-limiting remission with a favorable prognosis, although one case progressed to myeloid leukemia associated with DS by age two.
Conclusions: A negative obstetrical diagnosis and the absence of clinical DS phenotype should not preclude the consideration of TAM in neonates, especially when trisomy 21 mutations are detected.

1. Introduction

Down syndrome (DS), or trisomy 21, is the most common chromosomal disorder associated with intellectual disability. Individuals with DS often exhibit distinctive facial features, intellectual disabilities, growth impairments, and various malformations. Hematological disorders are frequent among children with DS, presenting as transient myelodysplasia, childhood iron deficiency, and an increased risk of leukemia [1]. Transient abnormal myelopoiesis (TAM) occurs in 5–10 % of neonates with DS. It is characterized by abnormal megakaryocyte proliferation and immature blood cells in the peripheral circulation, driven by the hematopoietic transcription factor *GATA1*, and is exclusive to trisomy 21 [2,3]. The clinical presentation of TAM varies widely, ranging from asymptomatic to severe. However, the prognosis for TAM is generally favorable, with most patients resolving spontaneously. In rare instances, TAM may also occur with acquired trisomy 21 mutations or mosaic trisomy 21 [2,3], leading to potential misdiagnosis due to the absence of characteristic DS features. Given the limited number of reported cases, there is insufficient information regarding the clinical and genetic characteristics of these neonates, necessitating further reporting and integration of data. Here, we present a case of TAM in a neonate without typical DS features. We detail the treatment history, laboratory findings, and genotypic characteristics conduct a comprehensive review and analysis of previously reported cases of TAM in neonates lacking the DS phenotype. This aims to enhance our understanding of the disease and provide insights for early diagnosis and effective management in the future.

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2. Patients and methods

2.1. Patients

We report a case of TAM involving a neonate admitted to the neonatology department of the Affiliated Hospital of North Sichuan Medical College shortly postnatally. Subsequent diagnosis revealed trisomy 21 without the typical DS phenotype.

2.2. Methods

2.2.1. Data collection

We retrieved the medical records of the neonates during hospitalization and follow-up over one year from the case database of the Affiliated Hospital of North Sichuan Medical College. This included details of hospital admissions, general laboratory tests, and genetic tests.

2.2.2. Literature review

Up to May 1, 2024, we conducted a comprehensive search and collected data on all reported cases of TAM without DS phenotype from PubMed, Embase, and Web of Science databases.

3. Results

3.1. Clinical information

3.1.1. Patient characteristics

The neonate male patient (gestational age, 38 + 2 weeks; weight, 3570 g) was delivered vaginally, with Apgar scores of 10–10-10. There were no abnormalities noted in the placenta, umbilical cord, or amniotic fluid. Throughout the pregnancy, the mother underwent regular obstetric examinations at the Obstetrics Department of the Affiliated Hospital of North Sichuan Medical College. Fetal nuchal translucency (NT) ultrasound at 13 weeks, systemic ultrasound, and cardiac ultrasound at 23 weeks revealed no abnormalities. Non-invasive prenatal DNA testing (NIPT) at 17 weeks indicated a low risk for trisomy 13, 18, and 21. The mother had a history of subclinical hypothyroidism and persistent eczema during pregnancy. The mother was 36 years old, and the father was 37 years old, both in good health. The paternal grandmother and great aunt had polydactyly, but there was no family history of other diseases.

The neonate was admitted to the neonatology department 10 min postnatally due to “bleeding spots found all over the body”. Upon physical examination, the baby appeared full-term with scattered red petechiae visible throughout the skin (Fig. 1). These spots did not blanch upon pressure and were slightly raised above the skin surface. The neonate exhibited respiratory distress with noticeable difficulty in breathing. Palpation revealed hepatosplenomegaly, with the liver palpated 3 cm below the rib margin and the spleen 1.5 cm below the rib margin.Additionally, Six fingers were present on the right hand, with syndactyly affecting the thumb (Fig. 2), while transverse palmar crease is visible on the right hand, no other anomalies were observed.

On the day of admission, peripheral blood tests revealed a significantly elevated white blood cell count of 156.17 $\times$ 10^9/L. The neonate received non-invasive ventilator-assisted respiration, antibiotics for infection, and underwent bone marrow aspiration, which indicated a 63.5 % immature cell count. By the third day of treatment, new red petechiae appeared on the skin, but a subsequent hematology review showed a decrease in white blood cell count to 133.89 $\times$ 10^9/L and platelets to 54 $\times$ 10^9/L. As active bleeding was absent, no specific treatment was administered. By the fifth day, the neonate's shortness of breath had worsened significantly, necessitating a switch to invasive mechanical ventilation. Investigation revealed significant pericardial effusion, promptly urgent pericardiocentesis, and continuous drainage of approximately 10 mL of light red pericardial fluid daily, which gradually decreased over time. The respiratory effort of the neonate gradually improved, with follow-up blood tests on the eleventh day showing a total white blood cell count of 94.86 $\times$ 10^9/L and platelets at 44 $\times$ 10^9/L. On the eleventh day, cardiac ultrasound confirmed resolution of the pericardial fluid, allowing the removal of the invasive ventilator and drains. Further blood tests on the 20th day indicated a white blood cell count of 53.25 $\times$ 10^9/L and platelets at 90 $\times$ 10^9/L. By the twentieth day of treatment, the breathing of the neonate stabilized, skin erythema resolved, and repeat blood tests showed a white blood cell count of 14.08 $\times$ 10^9/L, with immature cells reduced to 12 %. Antibiotics were discontinued, and the neonate was discharged from respiratory support the next day. After 24 days of hospitalization, the patient was discharged, and regular follow-ups continued until the child reached one year of age.We found that this child's facial features and other appearances were indistinguishable from those of ordinary

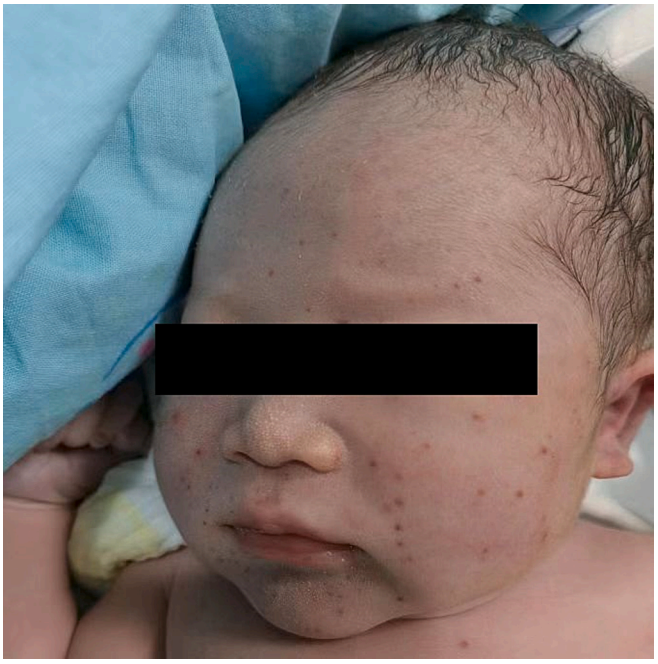

Fig. 1. Red petechiae scattered on the facial skin.

Fig. 2. Polydactyly of the right hand with thumb syndactyly.

individuals. Considering the possibility of spontaneous disappearance of trisomy 21, we recommended a re-examination of the chromosomes in the peripheral blood, but we did not obtain the parents' consent. However, we monitored his peripheral blood counts every three months and found no abnormalities in blood cell counts. Additionally,at 3 months, 6 months, and 1 year, we conducted intelligence assessments for this child and found no differences compared to children of the same age.

3.1.2. Laboratory tests

The morphology of bone marrow cells revealed active myeloproliferation, with 63.5 % immature cells observed. The granulocyte-red ratio is 6.9:1.The granulocyte lineage was reduced, comprising 27.5 % of cells,Within the granulocyte lineage, early granulocytes and earlier stages accounted for 0.5 %, middle granulocytes for 3.5 %, and late granulocytes for 1.5 %. Rod-shaped nuclei were present in 3.5 % of cells, while lobular nuclei were observed in 18 %, In addition, eosinophilic myelocytes for 0.5 %. The erythropoietic lineage was reduced, comprising 4 % of cells, including mature red blood cells of varying sizes (0.5 % early and 3.5 % late red blood cells). Lymphocytes accounted for 4 % of the cell population, all of which were mature. Monocytes constituted 1 % of the cells observed. A single megakaryocyte was identified across the whole film, with platelets appearing scattered and rare.The results are considered indicative of acute leukemia in the bone marrow, leaning towards myeloid origin. Wright's stain and chemical staining of immature cells are shown in Fig. 3.

Cytoimmunology: Setting the gate analysis on the cluster of differentiation 45/side scatter (CD45/SSC) point map, an abnormal cell population was identified within the distribution area of immature cells, comprising approximately 67 % of nucleated cells. These cells showed positive expression of human leukocyte antigen - DR isotype (HLA-DR), CD4, CD7, CD13, CD33, CD34, CD38, CD58, CD117, and CD123. Lymphocyte proliferation was notably suppressed, suggesting a high probability of myeloid origin for the abnormal cells, as shown in the flow analysis in Fig. 4.

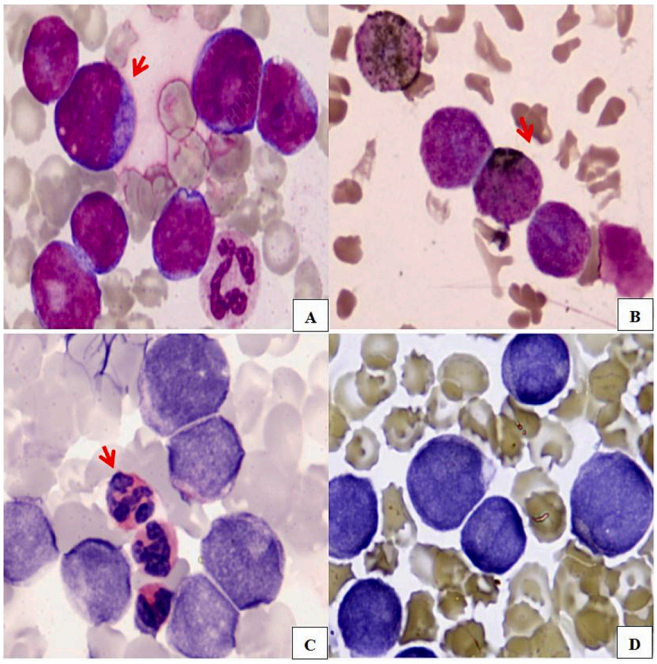

Fig. 3. A: Wright's stain:The bone marrow hyperplasia shows clear activity. The immature cell morphology depicted by the arrow is characterized by cells of varying sizes, with rounded or round-like nuclei, finely granular nuclear chromatin, one to several nucleoli, and a small to moderate amount of cytoplasm that stains blue. Granules are visible in a few cells. **B:**Myeloperoxidase stain(MPO):Purple-black granules are observed in the cytoplasm of the positively stained cells marked by the arrow, accounted for 3 %. **C:** Periodic Acid-Schiff's stain (PAS): The cytoplasm of the positively stained cells indicated by the arrows appears red, with fine or coarse granules visible, comprising 1 % of the cells. **D:** Alkaline alpha-naphthol butyrate lipase stain (α-NBE): The cytoplasm with a positive reaction shows blue granules, with no positively stained cells observed across the entire slide.

Cytogenetics: Bone marrow and peripheral blood specimens from the neonate were cultured separately. Analysis of 20 metaphase cells in both specimens revealed the presence of an additional chromosome 21, resulting in a karyotype of 47, XY, +21 [20], karyotype analysis of bone marrow is shown in Fig. 5.

Molecular biology: Nine gene mutations, including a *GATA1* gene mutation, were detected. The specific *GATA1* gene mutation was identified as NM_002049.4: exon2: c.187dup: p.Y63Lfs*5, located at chromosome position chrX: 48649702➔T, with a variant frequency of 97.8 %. This mutation is associated with abnormal myeloid proliferation in affected children. Other mutations detected include those in *PARP1, WRN, NACA, SETD18, PER1, MLLT1, TYK2,* and *LAMA5* genes, detailed in Table 1.

General laboratory tests: Peripheral blood cell analysis revealed elevated counts: white blood cells at 156.17 $\times$ 10^9/L, neutrophils at 44.44 $\times$ 10^9/L, lymphocytes at 34.20 $\times$ 10^9/L, and monocytes at 77.15 $\times$ 10^9/L. The red blood cell was 4.03 $\times$ 10^{12}/L, and the platelet count was 120 $\times$ 10^9/L,with hemoglobin at 145 g/L. Biochemical analysis showed levels of aspartate aminotransferase at 106 U/L, alanine aminotransferase at 8 U/L, Total bile acids: 0.93 mg/dL, Total bilirubin: 0.427 mg/dL, Indirect bilirubin: 0.236 mg/dL, and albumin at 38.7 g/L, Creatinine was measured at 0.835 mg/dL, Infection markers included C-reactive protein (CRP) at 2.30 mg/dL and procalcitonin(PCT) at 0.852 ng/mL. Except for the significant increase in white blood cells, none of these biochemical indicators or infection markers showed any significant abnormalities.In addition,Coagulation function and cerebrospinal fluid tests were negative, as were tests for toxoplasmosis, other (includes rubella, varicella-zoster virus, and parvovirus B19), syphilis,cytomegalovirus, and herpes simplex virus infections, EB virus DNA, cytomegalovirus DNA, Mycoplasma Urealyticum DNA, hepatitis B and C, human immunodeficiency virus and syphilis. Cultures of various tissue fluids also yielded negative results.

3.2. Literature review

A literature search identified 10 studies [4–13], documenting a total of 13 patients with TAM without the typical DS phenotype, which includes a pair of twins. Table 2 summarizes the clinical features and genetic characteristics reported for these neonates.

3.2.1. Summary of clinical phenotypes

Among the 13 patients reviewed, there were five males and eight females. The onset of the disease occurred around one week postnasal, with three neonates born prematurely(No.6,12,13),the youngest at 32 weeks of gestational age. None of the neonates exhibited a typical DS phenotype. Clinical manifestations associated with TAM included red petechiae in five patients(No.4,7,8,9,11), respiratory distress in three patients(No.7,9,13), hepatosplenomegaly in five patients (No.1,4,9,10,13), pericardial effusion in one patients(No.7), and severe shock with acute renal failure in one case(No.13). Initial hematologic findings showed increased white blood cell counts in 10 out of 12 patients, with all having more than 10 % immature cells. Five patients exhibited decreased platelet counts(No.5,9,11–13). Immunophenotypic analysis revealed positive expression of CD7, CD33, and CD117 in most patients, which correlated with primitive megakaryocyte proliferation. In terms of clinical outcomes, all the patients showed improvement with treatment, returning white blood cell and immature cell counts to normal levels. Only one case exhibited recurrent abnormal hematologic features at two years of age(No.8), necessitating chemotherapy, which successfully cleared tumor cells.Only one patients died early(No.6),who achieved normal white blood cell counts by two weeks postnatally but

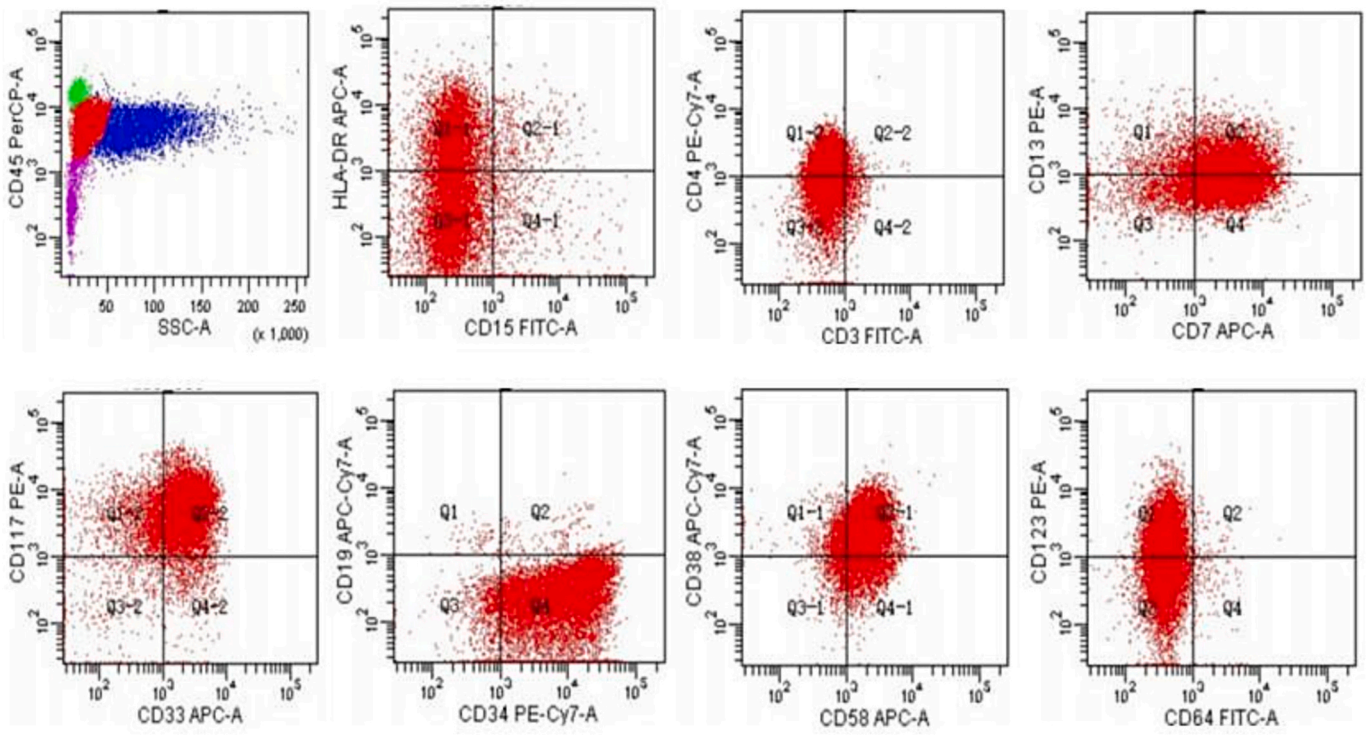

Fig. 4. Expression of various antigens in the immature cell population.

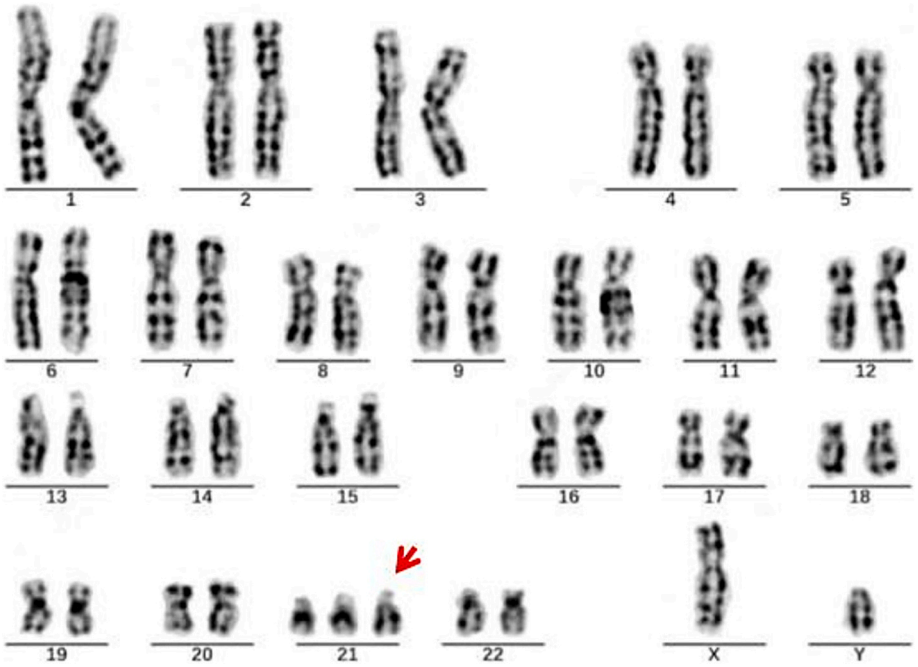

Fig. 5. Chromosome karyotyping of metaphase cells from bone marrow specimens reveals the presence of an additional chromosome 21.

succumbed to infection,

3.2.2. Summary of genetic characteristics

Among the 13 reported patients, all underwent chromosome culture of peripheral blood or bone marrow cells, showing the presence of trisomy 21 mutations. Among them, 7 cases underwent fibroblast chromosome culture (No. 1, 5, 8, 10–13), and only one case showed a karyotype with trisomy 21 (No. 12), while the remaining cases had a normal karyotype. In 3 patients(No. 2, 3, 13), initial chromosome cultures without stimulation showed trisomy 21, which disappeared after phytohemagglutinin (PHA) stimulation. Seven cases described changes in chromosome karyotypes during subsequent follow-ups(No. 4,8–13 , of which 5 underwent chromosome culture of bone marrow cells (No. 4, 8, 9, 10, 12), with 4 showing disappearance of trisomy 21 (No. 4, 8, 9, 10) and 1 showing a decrease in trisomy 21 (No. 12). In the remaining two cases, one case underwent chromosome culture of peripheral blood (No. 11), showing a decrease in trisomy 21; another case underwent fibroblast chromosome culture (No. 13), showing complete

Table 1
Genetic mutations associated with hematologic tumors in this case.

Genes	Mutation information	Mutant locus[a]	Variant frequency	Sequencing depth	evaluation[b]
GATA1	NM_002049.4:exon2:c.187 dup:p.Y63Lfs*5	chrX:48649702- > T	97.80 %	137	Level 2
PARP1	NM_001618.4:exon10:c.1531G > T:p.V511F	chr1:226567635C > A	53.50 %	198	Level 3
WRN	NM_000553.6:exon13:c.1598 A > G:p.N533S	chr8:30946427 A > G	41.00 %	83	Level 3
NACA	NM_001365896.1:exon1:c.-5 A > G	chr12:57119049 T > C	47.40 %	483	Level 3
SETD1B	NM_001353345.2:exon9:c.3239C > T:p.A1080V	chr12:122255537C > T	46.10 %	91	Level 3
PER1	NM_002616.3:exon18:c.2402 T > C:p.L801P	chr17:8048128 A > G	50.60 %	510	Level 3
MLLT1	NM_005934.4:exon9:c.1363C > T:p.R455C	chr19:6213994G > A	33.30 %	30	Level 3
TYK2	NM_003331.5:exon7:c.661C > T:p.R221W	chr19:10476543G > A	53.60 %	84	Level 3
LAMA5	NM_005560.6:exon28:c.3457G > T:p.G1153C	chr20:60907523C > A	26.70 %	30	Level 3

[a] The referenced genome is GRCh37.
[b] The evaluation is divided into three categories:Level 1, Clear pathogenic factor;Level 2, Likely pathogenic;Level 3, Variants of uncertain clinical significance.

disappearance of trisomy 21.

4. Discussion

In this study, we present a neonate diagnosed with TAM, characterized by the postnatal onset of generalized erythema, respiratory distress, hepatosplenomegaly, and pericardial effusion. The neonate exhibited a significantly elevated peripheral white blood cell count with 63.5 % immature cells, along with a karyotype showing trisomy 21 and a molecular biology mutation in the *GATA1* gene. Remarkably, the neonate experienced natural remission without requiring chemotherapeutic intervention and was followed up for a full year with a favorable prognosis. The clinical features and genetic findings of this case are consistent with the diagnostic criteria for TAM in the 2018 guidelines of the British Society for Hematology [3]. Despite the presence of trisomy 21 and a *GATA1* mutation, this neonate was classified as low-risk by NIPT and did not exhibit any clinical features of DS postnatally. Throughout follow-up, the child demonstrated developmental progress more akin to that of typical peers of the same age, including intellectual development.TAM typically manifests in neonates with DS but can also occur in patients with acquired somatic trisomy 21 mutations and chimeric phenotypes [2,3,14–16], occasionally lacking the typical DS phenotype. Therefore, the accuracy of the initial DS diagnosis in this neonate warrants reconsideration, particularly given the low-risk NIPT result, which influences early clinical judgment.

The principle of NIPT primarily assesses placental karyotype and detects abnormal DNA proportions. However, in patients with restrictive placental mosaicism, where both normal and abnormal cell lines coexist, the accuracy of fetal chromosomal karyotyping can be compromised. The presence or absence of restrictive placental mosaicism strongly correlates with NIPT results [17,18]. Variations in mosaicism location and degree can affect the quantity of abnormal DNA in maternal blood, potentially leading to false-negative results by diluting the proportion of abnormal DNA within the NIPT assay range. The mother of the neonate in this case underwent NIPT at 17 weeks of gestation. If the TAM in this neonate originated from trisomy 21 mosaicism or acquired somatic trisomy 21 mutations, NIPT would likely fail to accurately detect these conditions. Previous reports on neonates without typical DS phenotype indicate that karyotyping of peripheral blood and bone marrow cells in active and recovery phases of TAM often reveals diminishing or disappearing trisomy 21, while fibroblasts often fail to detect the presence of trisomy 21, suggesting that abnormal karyotypes are transient [5,6,10–13]. For neonates presenting clinical symptoms resembling TAM postnatally, the reliability of prenatal genetic testing is compromised due to the close relationship between TAM and trisomy 21. Therefore, early and repeated karyotyping, especially of fibroblasts, may be essential for accurate diagnosis in neonates exhibiting clinical manifestations similar to TAM postnatally.

Early diagnosis of TAM without typical DS phenotypes remains challenging. A review of previously reported cases revealed highly variable karyotypes among these neonates, due to the limited number of cases, no clear correlation was established between clinical phenotypes and karyotypes. In cases where peripheral blood counts and immunophenotypes were recorded, varying degrees of elevated white blood cell counts and immature cells were observed, supporting primitive megakaryocyte proliferation. Nevertheless, cellular morphology and immunophenotypes have shown considerable variability and are not consistently reliable for diagnosis [19,20]. The presence of *GATA1* gene mutations is necessary for diagnosing TAM [2,3,21]. In all neonates with the TAM without typical DS phenotype who underwent molecular analysis, *GATA1* gene mutations were detected, consistently located in exon 2. The *GATA1* gene, a key hematopoietic transcription factor, plays an important role in megakaryocyte-erythroid differentiation. *GATA1* gene mutations, mainly in exons 2 and 3, lead to premature termination codons and n-break truncation of the GATA1 protein [2,3,16,20–22]. However, it is important to note that *GATA1* gene mutations alone are not enough to cause TAM; they are associated with thrombocytopenia instead [20].

A study using human-induced multifunctional stem cells and genome or chromosome editing technology has highlighted the significant role of trisomy 21 in hematopoiesis. Trisomy 21 accelerates aberrant immature cell proliferation by enhancing the production of hematopoietic primordial cells and promoting the *GATA1* mutation [23]. Therefore, the presence of trisomy 21 cells is necessary for the development of TAM. The close association between the *GATA1* gene and trisomy 21 is further supported by the findings of Yanase et al. [13], who indicated that *GATA1* gene mutations disappear as TAM improves alongside trisomy 21.

In summary, when evaluating neonates suspected of TAM, prompt genetic, cytomorphological, cellular immunological, and molecular biology assessments are essential for a comprehensive diagnosis. Most neonates with TAM experience improvement with supportive management alone [2,3,14,20], affording clinicians adequate time to gather diagnostic evidence. Therefore, caution is advised regarding the initiation of clinical interventions, particularly chemotherapeutic agents, until a definitive diagnosis is established.

Although most patients with TAM resolve spontaneously without treatment, TAM can lead to early death in 15–23 % of patients, and 20–23 % of survivors may develop myeloid leukemia associated with DS (ML-DS), within the first four years of life [2,20]. However, there is insufficient data from samples to confirm whether similar excess mortality and conversion rates to ML-DS occur in neonates with acquired somatic cell trisomy 21 mutations and trisomy 21 mosaicism. From previously reported cases of neonates without typical DS phenotype, it was observed almost all patients showed self-limited improvement in the natural course of TAM, Regarding transformation to ML-DS, one case that initially showed undetectable trisomy 21 experienced a relapse with significant trisomy 21 cell production but responded well to chemotherapy and became morphologically and genetically negative post-treatment [10].

The primary cause of death in TAM is cholestatic liver disease due to infiltration of primitive megakaryocytes, leading to hepatic fibrosis,

Table 2
Summary of clinical characteristics and gene mutations of TAM without Down syndrome phenotype.

Year, Author	Patient No.	Gender	Gestational age (weeks)	Age at diagnosis	Clinical characteristics	Characteristics of the initial blood picture	Immunophenotype at diagnosis	Cytogenetics at diagnosis	*GATA1* mutation	Outcome and follow up
2014, Corazza et al. [4]	1	F	37	6 days	One-handed passing palm, jaundice, hepatosplenomegaly	WBC:34.14*109/L; PLT: 224*109/L; PB blasts: 33 %	$CD45^{+}$,$CD7^{+}$, $CD56^{+}$, $CD11b^{+}$, $CD33^{+}$, $CD41a^{+}$, $CD61^{+}$, $CD71^{+}$, $CD38^{+}$, $CD34^{+}$, $CD117^{+}$,	46, XY [36] 47, XY, +21[2] 48, XY, +21, +22[2] (from peripheral blood) 46 , XY(from fibroblasts)	Exon 2	Survived , 5 years old
2018, Hassan et al. [5]	2,3	F/F , monozygotic	N/A	N/A	N/A	PB blasts: 20 %	$CD34^{+}$, $CD117^{+}$, $CD33^{+}$, $CD36^{+}$, $CD7^{+}$,	47, XX, +21 (unstimulated) 46, XX, (PHA stimulated)(from peripheral blood)	Exon 2	Survived , 2 months
1998, Kempski et al. [6]	4	F	full-term	12 h	Facial ecchymosis, hepatosplenomegaly	WBC: 33*109/L; PB blasts: 48 %	CD3+, CD7+, CD11c+, CD15+, CD19+, HLA-DR+,	46, XX [2] 48, XX, +18,+21[18] (from bone marrow)	N/A	Survived, 15 weeks (Negative white blood cell count at 3 weeks; negative karyotype from bone marrowat at 15 weeks of age)
2022, Kobayashi et al. [7]	5	M	37	After birth	Low weight: 1514 g	WBC: 16.7*109/L; PLT: 50*109/L; PB blasts: 12 %	CD7+, CD13+, CD33+, CD34+, CD41+, HLA-DR+,	48, XXY, +21 46, XY (from peripheral blood and buccal membrane swab)	Exon 2	Survived , No follow-up
2018, Murray et al. [8]	6	F	34	After birth	N/A	WBC: 100*109/L; PB blasts: 56 %	CD7+, CD34+, CD33+, CD56+, CD117+, CD41+, CD42b	47, XX, +21[44] 46, XX [6] (from peripheral blood)	N/A	Died; death due to severe infection after 2 weeks (The white blood cells have turned negative)
2020, Prudowsky et al. [9]	7	F	37	8 days	Fever, jaundice, breathlessness, ecchymosis, pericardial effusion	WBC: 62.2*109/L; PB blasts: 33 %	$CD33^{+}$, $CD11b^{+}$, $CD34^{+}$, $CD117^{+}$, $CD99^{+}$, $CD58^{+}$, $CD38^{+}$, $CD71^{+}$	47, XX, +21(from peripheral blood and bone marrow)	Exon 2	Survived , 3 years old
1998, Richards et al. [10]	8	F	37	1 week	Ecchymosis, arteriosclerosis	WBC: 29.3*109/L; PLT: 158*109/L; PB blast: 15 %	$CD33^{+}$, $CD61^{+}$,	47, XX, +21(from bone marrow) 46, XX(from fibroblasts)	N/A	Survived , 2 years old (negative karyotype from bone marrowat at 3 months of age; ML-DS at 2 years of age)
	9	M	N/A	6 days	Breathlessness, hepatosplenomegaly, ecchymosis, conjunctivitis	WBC: 52*109/L; PLT: 39*109/L; PB blast: 60 %	N/A	47, XX, +21 , (from bone marrow)	N/A	Survived , 2 months (Trisomy 21 disappears from bone marrowat)
2015, Salvatori et al. [11]	10	F	37	2 days	Hepatomegaly, hypotonia	WBC: $134*10^{9}$/L	CD33+, CD34+, CD117+,	47, XX, +21 (from bone marrow) 46 , XX(from and fibroblasts)	Exon 2	Survived , 7 months (Normal karyotype and loss of tumor cells from bone marrow)
2011, Williams et al. [12]	11	F	full-term	After birth	Ecchymosis	WBC: 43.5*109/L; PLT: 83*109/L; PB blast: 30 %	CD4+, CD7+, CD33+, CD41+, CD61+	47, XX, +21 ((from peripheral blood and skin biopsy) 46, XX (from buccal membrane swab)	N/A	Survived , 5 months (Trisomy 21 decrease from peripheral blood)

(*continued on next page*)

Table 2 (*continued*)

Year, Author	Patient No.	Gender	Gestational age (weeks)	Age at diagnosis	Clinical characteristics	Characteristics of the initial blood picture	Immunophenotype at diagnosis	Cytogenetics at diagnosis	*GATA1* mutation	Outcome and follow up
	12	M	32	After birth	N/A	WBC: 77*109/L; PLT: 77*109/L	CD4+, CD7+, CD33+	47, XX, +21 (from buccal membrane swab、skin biopsy and peripheral blood) 46 , XX(from fibroblasts)	Exon 2	Survived , 6 months (Trisomy 21 decrease from bone marrowat)
2010, Yanase et al. [13]	13	M	35	After birth	Breathlessness, hepatosplenomegaly, DIC, acute renal failure	WBC: 132*109/L; PLT: 26*109/L; PB blasts: 70 %	$CD7^{+}$, $CD34^{+}$, $CD41^{+}$, $CD61^{+}$, $CD117^{+}$,	47, XX, +21 (unstimulated) 46, XX (PHA stimulated) (from bone marrow)	Exon 2 (disappears during follow-up)	Survived , 12 months (Trisomy 21 disappears from buccal membrane swab)

Abbreviation:WBC, white blood cell; PLT, platelet; DIC,disseminated intravascular coagulation;PHA, Phytohaemagglutinin;N/A:data not available.

disseminated intravascular coagulation, and multi-organ failure [2,3,14,16]. The absence of severe hepatic impairment in previously reported neonates without typical DS phenotype suggests favorable clinical improvement in this group. However, whether neonates with acquired somatic cell trisomy 21 mutations and trisomy 21 mosaicism exhibit fewer hepatic impairments or clinical features remains to be elucidated through further extensive reporting. Regular follow-up for TAM is recommended even in neonates without typical DS phenotype. Most patients with ML-DS present in the second year of life and are rare after four years. The optimal monitoring frequency has not been established, but the British Society of Hematology recommends a complete blood count every three months for early detection of ML-DS. A drop in platelet count is a significant predictor of early ML-DS in neonates with a history of TAM [3], while pleural effusion has been identified through multifactorial analysis as another risk factor for TAM progression to ML-DS [19]. In the present case, the neonate experienced transient severe pericardial effusion during hospitalization, placing them at high risk for ML-DS conversion. Despite normal blood monitoring findings between discharge and one year of age, close follow-up is imperative.

In conclusion, we present a rare case of TAM without the typical DS phenotype, which has been infrequently reported previously. This myelodysplasia may originate from trisomy 21 mosaicism or acquired somatic trisomy 21 mutations. Our review of similar patients from past reports reveals that such patients cannot always be identified early through prenatal diagnosis or clinical phenotype assessment. In some instances, trisomy 21 anomalies and *GATA1* gene mutations can diminish or disappear gradually as the myelodysplasia follows a self-limiting course. Furthermore, these patients generally have a favorable prognosis, which underscores the importance of early recognition to avoid unnecessary treatments.

Ethical statement

The study was approved by the Medical Ethics Committee of North Sichuan Medical College(Ethics Approval Number:2024058).

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CRediT authorship contribution statement

Junpeng Cai: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Xiaomin Zhou:** Formal analysis, Data curation. **Yu Zhou:** Visualization, Supervision, Resources, Investigation. **Guanghuan Pi:** Visualization, Supervision, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no financial conflicts of interest with regard to the content of this report。 .

Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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