Transient myeloproliferative disorder with vesiculopustular eruption: Early smear is useful for quick diagnosis.

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Funding sources: None.

The authors certify that they have no conflict of interest related to the contents of this paper.

Prior presentation: None.

Reprint is not available from the authors.

Word count: 1384, Number of references: 15, Table: 0, Figures: 4

Abstract

Transient myeloproliferative disorder (TMD) is a common myeloid disorder that affects 10–20% of newborn infants with Down syndrome (DS: OMIM; #190685) and is accompanied by vesiculopustular eruption in rare cases. We report an infant with DS showing TMD and skin lesions. A male infant was transferred to a neonatal intensive care unit because of low body weight, fetal edema, disseminated intravascular coagulation and 10% of blast cells in peripheral blood. On postnatal day (PD) 1, erythema with small papules, vesicles or pustules appeared on the face, trunk, and proximal extremities. Smear preparation from the pustules on PD 2 showed 10% blast cells in mixed cells. Biopsy specimen on PD 5 revealed subcorneal pustules containing neutrophils and eosinophils. The results of chromosomal analysis of peripheral blood lymphocytes were: 47, XY, +21. Nonsense mutation (197G>T, Glu295Stop) in exon 2 of *GATA-1* was detected in genomic DNA extracted from bone marrow mononuclear cells but not in genomic DNA extracted from the patient's nail. On PD 10, the eruptions diminished spontaneously and the population of blast cells in peripheral blood decreased to 1%. In our case, the number of blastic cells in pustules decreased markedly after only three days. Therefore, the cytological examination should be performed as early as possible.

Transient myeloproliferative disorder (TMD) is a common myeloid disorder that affects 10 to 20% of newborn infants with Down syndrome (DS: OMIM;#190685) [1,2]. Although TMD resolves spontaneously in most cases without therapy, acute megakaryoblastic leukemia (AMKL) subsequently develops in nearly 30% of patients. In rare cases, TMD is accompanied by vesiculopustular eruption [3–13]. Here, we report an infant with DS showing TMD and skin lesions, in whom genetic analyses detected somatic mutation of *GATA-1* 197G>T(Glu295Stop).

Case Report

A male infant weighing 2111 g was born after 32 weeks gestation. Because of severe fetal edema, distress, and disseminated intravascular coagulation, he was transferred to a neonatal intensive care unit and received mechanical respiratory assist for two weeks. Peripheral blood demonstrated about 10% blast cells immediately after birth. On postnatal day (PD) 1, erythema with small papules, vesicles or pustules appeared on the face, trunk, and proximal extremities. Our dermatology department was consulted on PD 2. Our first impression was erythema toxicum neonatorum (Fig 1). Smear preparation from the pustules showed 10% blast cells in mixed cells (Fig 2). The results of chromosomal analysis of peripheral blood lymphocytes were: 47, XY, +21. Immunophenotypic analysis demonstrated that peripheral blast

cells were positive for CD33 and CD41, but not for CD3, CD20, or myeloperoxidase. These findings suggested TMD. On PD 5, papules with pustules were enlarged (Fig 3). Biopsy specimen from the skin lesion showed subcorneal pustules containing neutrophils and eosinophils (Fig 4). Immunohistochemical staining showed that the infiltrating cells were positive for myeloperoxidase but negative for CD3 and CD20. Furthermore, there were no CD41-positive cells, suggesting that TMD cells had already disappeared. On PD 10, the eruptions diminished spontaneously and the population of blast cells in peripheral blood decreased to 1%. Nonsense mutation (197G>T, Glu295Stop) in exon 2 of *GATA-1* was detected in genomic DNA extracted from bone marrow mononuclear cells but not in genomic DNA extracted from the patient's nail. These observations suggested that the mutation in *GATA-1* was a somatic change.

Discussion

Including the present case, a total of 16 patients with trisomy 21 accompanied by skin lesions have been reported to date [3–13]. Half of these patients had DS and the remaining cases were phenotypically normal neonates with trisomy 21 mosaicism. As TMD occurs predominantly in DS but to a much lesser extent in mosaics [2], the skin lesions may have a predilection for trisomy 21 mosaicism rather than DS. In half of the patients, eruptions appeared at birth or on PD 1

(median in all cases: PD 2). The face, especially the cheek, was the most common site of skin lesions, which were also seen on the trunk and extremities. The eruptions were frequently located at sites that could be easily subjected to mechanical pressure by a nasal cannula or irritation by tape application. The skin lesions diminished spontaneously in all reported cases—within one month in two-thirds of cases and 3 months in the remaining cases (median: 1 month). Acute leukemia developed in 3 patients (19%), of whom 2 had DS and the remaining one patient showed mosaicism. Leukemia developed after 2 years in 2 of 3 patients, and followed remission of the first pustular eruption by systemic corticosteroid administration in one case.

Recent studies have suggested that both TMD and AMKL in children with DS/mosaic trisomy 21 require a *GATA1* mutation [1, 2]. GATA-1 is the hematopoietic transcription factor, which plays essential roles in the normal development of erythroid cells and megakaryocytes. The *GATA1* mutation was found in almost all cases of DS/trisomy 21 children with TMD and AMKL but not detected in non-DS/non-trisomy 21 children with other types of leukemia or AMKL. Furthermore, the *GATA1* mutation was not detected after resolution of TMD or AMKL [14]. Pine *et al.* suggested that detection of the *GATA1* mutation at birth, in addition to screening for TMD, could be important to predict the development of DS-related AMKL [14].

There are a number of infectious and noninfectious diseases that cause vesiculopustular eruptions in neonates [15]. The most common

causes of infectious pustular skin lesions are bacterial infections (*Staphylococcus aureus* or septicemia caused by *Listeria monocytogenes*), viral infections (herpes simplex, varicella zoster, and cytomegalovirus infections), fungal infections (candidiasis, malassezia), or parasitic disorders (scabies). Noninfectious pustuloses include erythema toxicum neonatorum, infantile acropustulosis, incontinentia pigmenti, transient neonatal pustular melanosis, and neonatal acne. In reports of TMD with skin lesions, several authors indicated that erythema toxicum or herpes infection were mainly suspected on first consultation. A cytological smear preparation is required not only for rapid diagnosis of herpetic and other infections but also for diagnosis of noninfectious pustular eruptions. An abundance of eosinophils in erythema toxicum and incontinentia pigmenti or neutrophils in infantile acropustulosis may be diagnostic clues. In addition, blast cells in superficial pustules suggest TMD. As smear preparation is safe for neonates and can provide results more quickly than biopsy, this examination should be considered for diagnosis of neonatal pustular eruptions. In addition, the cytological results should be evaluated carefully because some studies have indicated a failure to obtain a diagnosis despite rapid Tzank smear test to detect herpes infection. Furthermore, in our case, the number of blastic cells in pustules decreased markedly after only three days. Therefore, the cytological examination should be performed as early as possible.

References

1 Carpenter E, Valverde-Garduno V, Sternberg A, Mitchell C, Roberts I, Vyas P, et al. GATA1 mutation and trisomy 21 are required only in haematopoietic cells for development of transient myeloproliferative disorder. Br J Haematol. 2005;128:548-51.

2 Massey GV, Zipursky A, Chang MN, Doyle JJ, Nasim S, Taub JW, et al. A prospective study of the natural history of transient leukemia (TL) in neonates with Down syndrome (DS): Children's Oncology Group (COG) study POG-9481. Blood. 2006;107:4606-13.

3 Brodeur GM, Dahl GV, Williams DL, Tipton RE, Kalwinsky DK. Transient leukemoid reaction and trisomy 21 mosaicism in a phenotypically normal newborn. Blood. 1980;55:691-3.

4 Konishi N, Kashiwa H, Kobayashi M, Kawaguchi Y, Tanaka Y, Ueda K. Transient abnormal myelopoiesis with trisomy 21 karyotype on leukemoid blast cells and cutaneous involvement. Japanese Journal of Pediatric Hematology. 1989 3:367-371 (Japanese)

5 Ridgway D, Benda GI, Magenis E, Allen L, Segal GM, Braziel RM, et al. Transient myeloproliferative disorder of the Down type in the normal newborn. Am J Dis Child. 1990;144:1117-9.

6 Bhatt S, Schreck R, Graham JM, Korenberg JR, Hurvitz CG, Fischel-Ghodsian N. Transient leukemia with trisomy 21: description of a case and review of the literature. Am J Med Genet. 1995;58:310-4.

7 Lerner LH, Wiss K, Gellis S, Barnhill R. An unusual pustular

eruption in an infant with Down syndrome and a congenital leukemoid reaction. J Am Acad Dermatol. 1996;35:330-3.

8 Nijhawan A, Baselga E, Gonzalez-Ensenat MA, Vicente A, Southern JF, Camitta BM, et al. Vesiculopustular eruptions in Down syndrome neonates with myeloproliferative disorders. Arch Dermatol. 2001;137:760-3.

9 Burch JM, Weston WL, Rogers M, Morelli JG. Cutaneous pustular leukemoid reactions in trisomy 21. Pediatr Dermatol. 2003;20:232-7.

10 Solky BA, Yang FC, Xu X, Levins P. Transient myeloproliferative disorder causing a vesiculopustular eruption in a phenotypically normal neonate. Pediatr Dermatol. 2004;21:551-4.

11 Viros A, Garcia-Patos V, Aparicio G, Tallada N, Bastida P, Castells A. Sterile neonatal pustulosis associated with transient myeloproliferative disorder in twins. Arch Dermatol. 2005;141:1053-4.

12 Wirges ML, Stetson CL, Oliver JW. Pustular leukemoid reaction in a neonate with Down syndrome. J Am Acad Dermatol. 2006;54 (Suppl):S62-4.

13 Moriuchi R, Shibaki A, Yasukawa K, Onozuka T, Sato T, Kaneda M, et al. Neonatal vesiculopustular eruption of the face: a sign of trisomy 21-associated transient myeloproliferative disorder. Br J Dermatol. 2007;156:1373-4.

14 Pine SR, Guo Q, Yin C, Jayabose S, Druschel CM, Sandoval C. Incidence and clinical implications of GATA1 mutations in newborns with Down syndrome. Blood. 2007;110:2128-31.

15 Van Praag MC, Van Rooij RW, Folkers E, Spritzer R, Menke HE, Oranje AP. Diagnosis and treatment of pustular disorders in the neonate. Pediatr Dermatol. 1997;14:131-43.

Legends

Fig 1: Erythemas with small papules, vesicles, or pustules were scattered over the face and trunk (PD 2).

Fig 2: Smear preparation from the pustule shown in Figure 1. About 10% blast cells were observed. (×400, Giemsa staining)

Fig 3: The papules were enlarged and developed into pustules (PD 5).

Fig 4: The biopsy specimen from pustular papules in Figure 3 showed subcorneal pustules containing neutrophils and eosinophils. (×200, HE staining)

Fig. 1

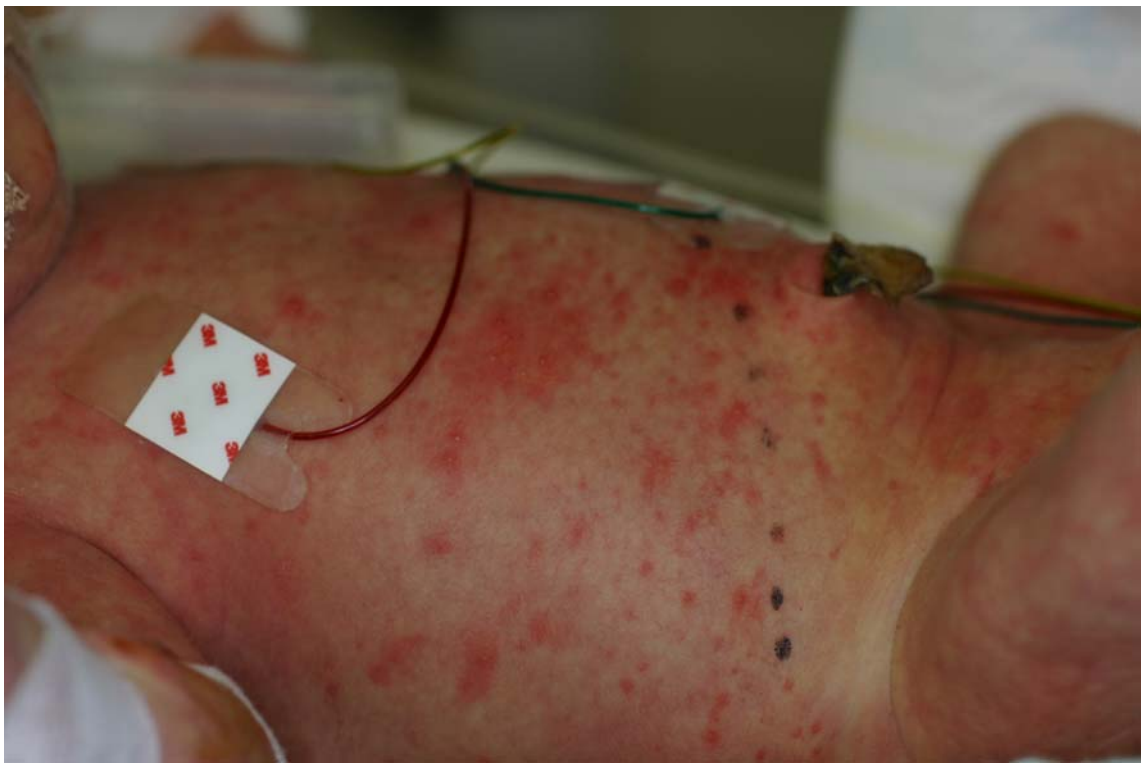

Fig. 2

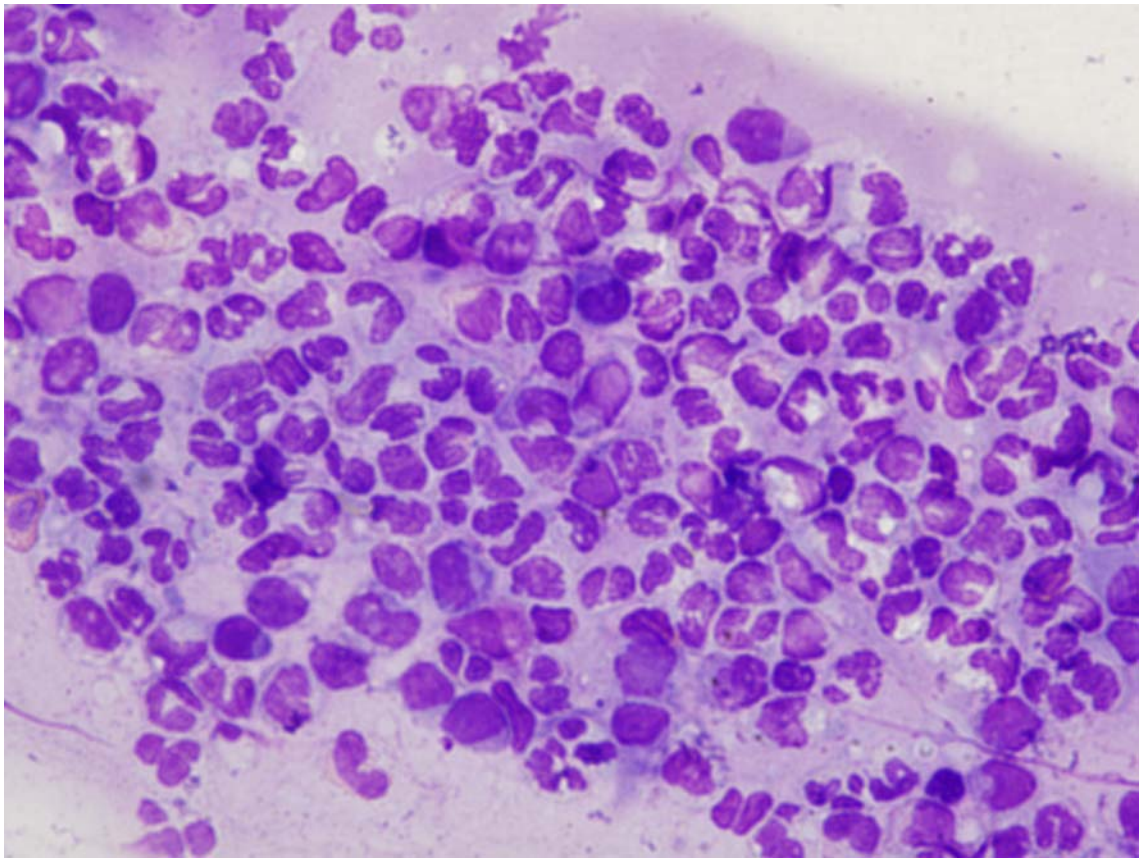

Fig. 3

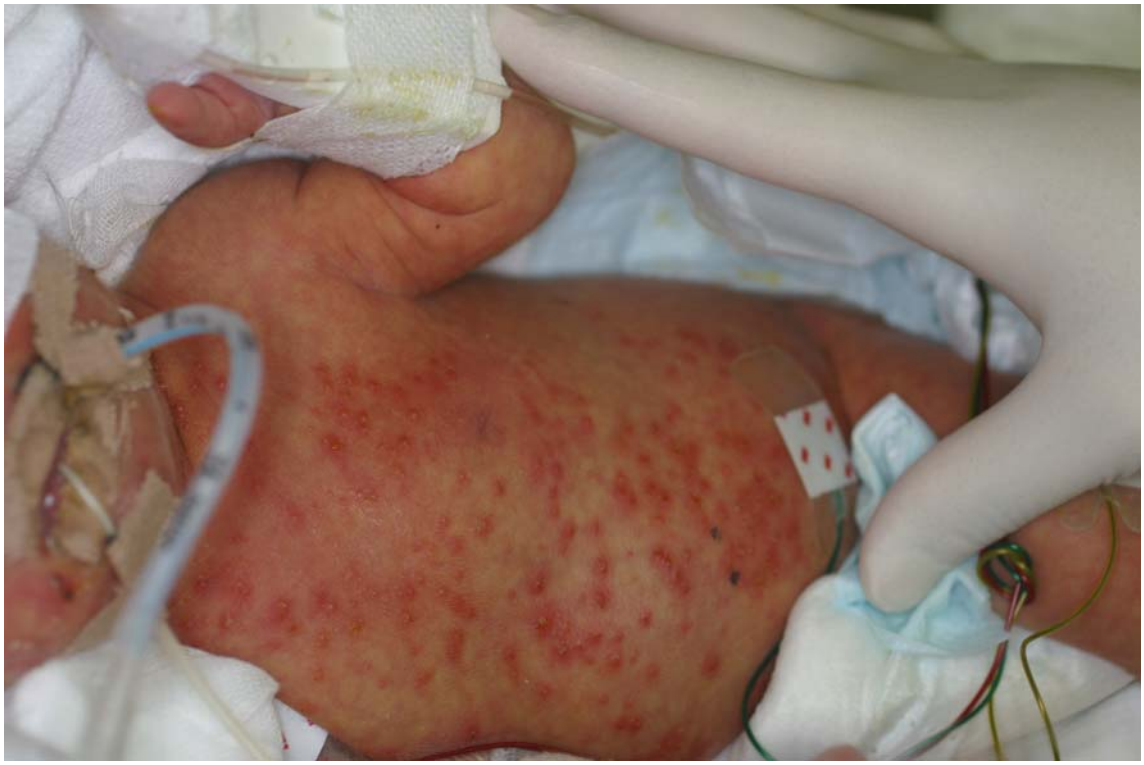

Fig. 4