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Case Report

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A Boy With Blau Syndrome Misdiagnosed as Refractory Kawasaki Disease

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ABSTRACT

Blau syndrome is a systemic autoinflammatory disease presenting with non-caseating granulomatous dermatitis, chronic uveitis, and arthritis. It is caused by a gain-of-function variant of the nucleotide-binding oligomerization domain protein 2 gene, which leads to the overactivation of inflammatory cytokines and eventually causes autoinflammation. Since the symptoms of Blau syndrome are nonspecific and usually do not appear simultaneously, it is challenging to differentiate Blau syndrome from other inflammatory disorders. This is a case report of a 13-month-old boy who had suffered from recurrent skin rash and fever. The patient was previously misdiagnosed as refractory Kawasaki disease twice and was treated with intravenous immunoglobulin and systemic glucocorticoid, which only resulted in transient improvement of the symptoms. He was eventually diagnosed with Blau syndrome.

Keywords: Skin rash; Uveitis; Arthritis; Sarcoidosis; Kawasaki disease

INTRODUCTION

Blau syndrome, classified as an autoinflammatory disease, is characterized by chronic non-caseating granulomatous dermatitis, multiple arthritis, and uveitis. The syndrome was first described by Edward Blau in 1985 and is caused by a pathogenic variant of nucleotide-binding oligomerization domain protein 2 (*NOD2*) gene, either by autosomal dominant inheritance or *de novo* variant. We report a case of a 13-month-old boy with fever and skin rash who was initially misdiagnosed with Kawasaki disease. He was treated with intravenous immunoglobulin (IVIG) and systemic glucocorticoid twice, but was later confirmed as having Blau syndrome.

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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CASE

A 13-month-old boy visited Samsung Medical Center with chief complaints of recurrent fever and whole-body skin rash. When he was 2 months old, he started to have a whole-body erythematous skin rash that did not respond to oral antibiotics. At 11 months old, he developed a fever in addition to a waxing and waning whole-body skin rash. He was diagnosed with incomplete Kawasaki disease and was treated with 2 consecutive doses of IVIG (2 g/kg per dose). However, IVIG did not have any effect and he was further treated with a high-dose steroid (methylprednisolone, 30 mg/kg), resulting in a transient improvement of his symptoms. The symptoms relapsed after 1 month, and he was again treated with 2 doses of IVIG (2 g/kg per dose), followed by a high-dose steroid (methylprednisolone, 30 mg/kg). The steroid therapy improved his symptoms, but the fever and skin rash recurred 1 month later. He then presented to our hospital for further evaluation. **Fig. 1A** describes the changes in his symptoms during the hospitalizations and the management.

At the first presentation to our hospital, his tympanic temperature was 38.7°C. He had a bilateral conjunctival injection, multiple cervical lymph node enlargements, and whole body erythematous-to-brownish maculopapular skin rash (**Fig. 1B**). He had no family history of infectious, autoimmune or systemic inflammatory disease. In the laboratory test, complete blood count revealed white blood cells count of 13,090 /μL (48% segmented neutrophil, 45% lymphocyte), hemoglobin concentration of 8.9 g/dL, and platelet count of 501,000 /μL. C-reactive protein level were elevated at 5.97 mg/dL (normal range, 0–0.5 mg/dL). Aspartate aminotransferase and alanine aminotransferase levels were 45 U/L and 15 U/L, respectively. N-terminal pro b-type natriuretic peptide level was 502 pg/mL (normal range, 0–88 pg/mL) and ferritin level was 66.4 ng/mL. No specific pathogen was detected.

During the first week of admission, he was treated with intravenous antibiotics (ampicillin/sulbactam), but the fever persisted. We discontinued antibiotics and started naproxen (5 mg/kg/dose twice a day). Naproxen therapy resulted in clinical improvement, and he was discharged. While he was admitted, we performed a skin biopsy and the result showed findings of multifocal non-caseating granulomas (**Supplementary Fig. 1**). There were no other signs of sarcoidosis, such as hilar lymphadenopathy or erythema nodosum. For further confirmative evaluation, a diagnostic exome sequencing was performed.

While waiting for the result of the gene study, the fever and skin rash relapsed after 1 month and he was re-admitted. He also developed tachypnea with aggravating abdominal distension (**Fig. 1C**). Pleural effusion, ascites, and hepatosplenomegaly were present. Weighing on the possibility of systemic inflammation rather than any infection, we started methylprednisolone (20 mg/kg/day) and his symptoms improved rapidly. We tapered methylprednisolone to 1 mg/kg/day of prednisolone. After 1 month, we added methotrexate (10 mg/m^2 body surface area, weekly) to further reduce the prednisolone to the dose of 0.5 mg/kg/day. The exome sequencing test later revealed a heterozygous variant of the *NOD2* gene (c.1000C>T, p.Arg334Trp), which was consistent with Blau syndrome.

At the time of diagnosis, he did not show any signs or symptoms of arthritis. However, he developed arthritis of both knee joints at 3 years of age, while he was on methotrexate and prednisolone. We discontinued methotrexate and started adalimumab (24 mg/m^2 body surface area, every 2 weeks), an anti-tumor necrosis factor (TNF)-α agent. With the use of adalimumab, there has been no exacerbation of his arthritis signs or symptoms. His

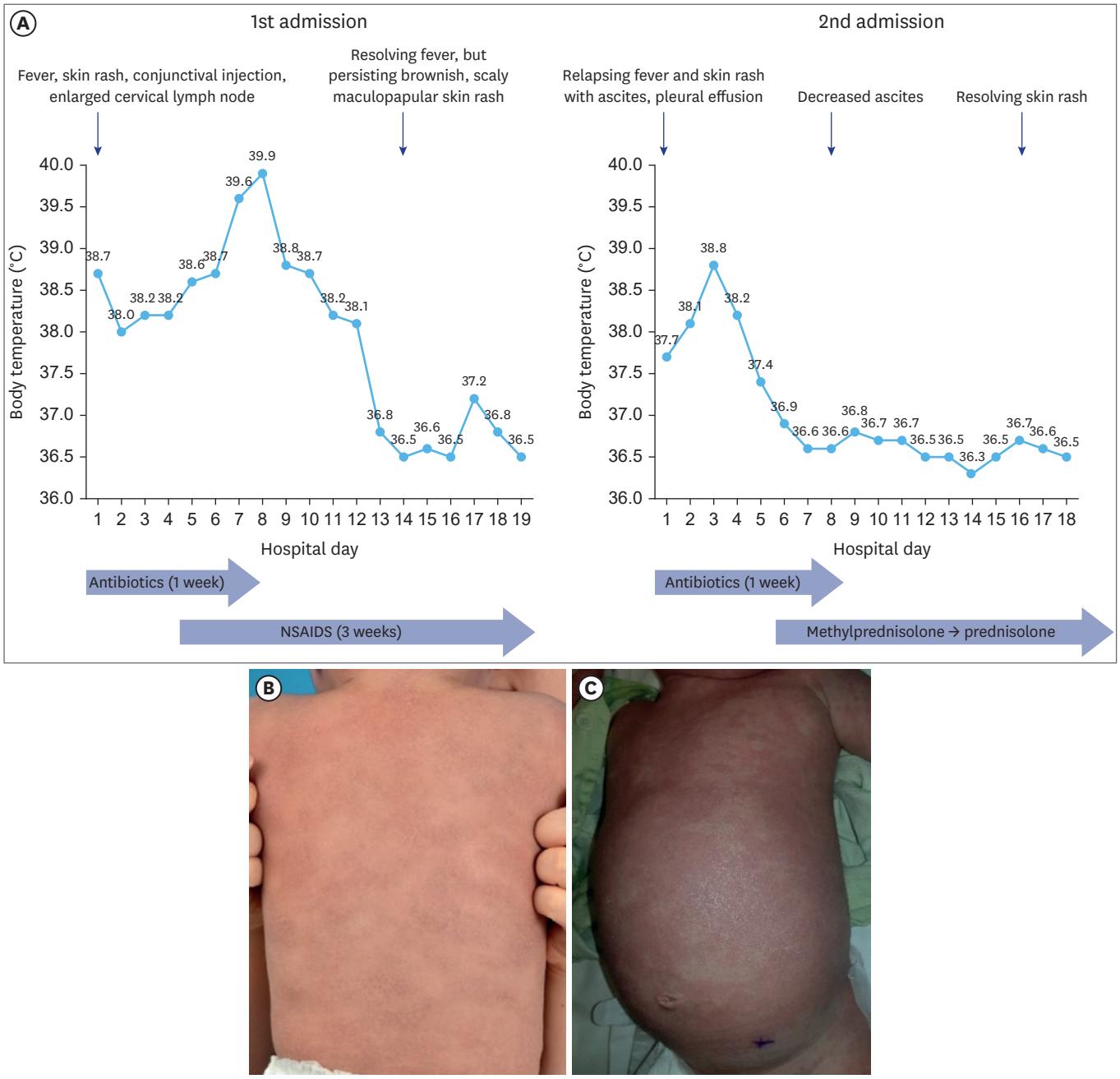

Fig. 1. (A) Clinical course and treatment during the admissions. (B) Erythematous papules involving the entire body, especially the trunk. (C) Significant abdominal distension due to ascites was also present.

eyes have been regularly examined by an ophthalmologist and have shown normal visual development. However, at the age of 4 years, anterior uveitis with mild optic disc swelling was observed in both eyes. Topical corticosteroid eyedrops were prescribed, and the condition is carefully followed-up. This study was approved by the Institutional Review Board (IRB) of Samsung Medical Center (IRB No. 2022-07-147).

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DISCUSSION

Blau syndrome is an autoinflammatory disease associated with a pathogenic variant of *NOD2* gene. In this study, we report a patient with Blau syndrome who was treated for refractory Kawasaki disease which is a more commonly known disease to general pediatricians. This patient's convoluted course provides valuable information on an autoinflammatory disease that mimics some features of Kawasaki disease.

The *NOD2* gene is located on chromosome 16q12.1 and the encoded *NOD2* receptor protein is expressed in monocytes, macrophages, and dendritic cells. The *NOD2* receptor protein is involved in innate immune responses against pathogens through the nuclear factor kappa B (NF-κB) signaling pathway to produce inflammatory cytokines. Blau syndrome is caused by a gain-of-function variant in *NOD2*, which results in the overproduction of cytokines by activating NF-κB, leading to systemic autoinflammation. There are both familial and sporadic forms of Blau syndrome. The familial form shows autosomal dominant inheritance. In our case, since the patient's parents showed no *NOD2* gene variant, we consider this case a sporadic form of Blau syndrome.

Blau syndrome is characterized by the clinical triad of chronic granulomatous dermatitis, arthritis, and uveitis. Cutaneous symptoms usually appear as the initial sign and frequently manifest as erythematous papules as in our patient. Joint involvement manifests as multiple arthritis and mostly develops after the cutaneous symptoms occur. Involved joints can eventually develop irreversible deformities, such as camptodactyly. Uveitis often occurs after the presentation of skin rash, according to other case reports. **Table 1** summarizes the onset of symptoms, age at diagnosis, genetic variants, and management in other reported cases of Blau syndrome in Asia.[1-10] The 50 genetically proven cases in Japan, which are reviewed

Table 1. Summary of the reported Blau syndrome cases in Asia

Reference	No. of cases	Sex/Age at diagnosis (yr)	Age at onset of symptoms			*NOD2* variants	Treatment
			R	A	U		
Current case	1	M/1	2 mon	–	–	c.1000C>T (p.R334W), het	PD, MTX, ADA
Kurokawa et al. (2003)[1]	3	M/10	+	6 yr	6 yr	c.1000C>T (p.R334W), het	PD
		F/12	?	+	+	c.1000C>T (p.R334W), het	PD
		M/51	?	Infancy	?*	?	?
Son et al. (2010)[2]	2	F/2	5 mon	+	?	c.1000C>T (p.R334W)	?
		F/32y	+	+	?†	c.1000C>T (p.R334W)	?
Kim et al. (2016)[3]	2	F/8	6 mon	–	8 yr	c.1439A>G (p.H480R), het	No treatment
		M/10	6 mon	–	+	c.1439A>G (p.H480R), het	No treatment
Leong et al. (2019)[4]	1	F/1	10 mon	12 mon	–	c.1000C>T (p.R334W), het	PD, MTX
Paç Kisaarslan et al. (2019)[5]	6	M/4	4 mon	–	–	c.802C>T (p.P268S), c.2863G>A (p.V955I)	Steroid, canakinumab
		F/10	–	2 yr	–	c.1538C>T (p.M513T), het	MTX, IFX
		F/6	5 yr	5 yr	–	c.2104C>T (p.R702W), het	MTX
		M/8	–	9 mon	–	c.1027C>T (p.H343Y)	Steroid, siklosporin
		M/11	–	Infancy	–	c.2863G>A (p.V955I), c.1471A>C (p.M491L)	MTX, IFX
		F/9	–	Infancy	–	c.1471A>C (p.M491L)	MTX, IFX
Iriqat et al. (2021)[6]	1	F/18	–	1 yr	7 yr	c.1001G>A (p.R334Q), het	PD, ADA
Jindal et al. (2021)[7]	1	F/3	–	3 yr	13 yr	c.1001G>A (p.R334Q)	PD, MTX, ADA, MMF
Okazaki et al. (2021)[8]	1	F/8	Infancy	–	5 yr	c.1535A>T (p.D512V), het	PD, MTX
Su et al. (2021)[9]	1	M/4	6 mon	1 yr	–	c.1001G>A (p.R334Q), het	MTX
Wang et al. (2022)[10]	1	F/10	4 mon	3 yr	4 yr	c.1759C>T (p.R587C), het	PD, MTX, etanercept, thalidomide

Abbreviations: R, rash; A, arthritis; U, uveitis; *NOD2*, nucleotide-binding oligomerization domain protein 2; het, heterozygous; PD, prednisolone; MTX, methotrexate; ADA, adalimumab; IFX, infliximab; MMF, mycophenolate mofetil; +, present, but no information on age at onset; –, not present; ?, not mentioned.
*Blind at age 14; †Blind at age 5.

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in a study by Matsuda et al.,[11] are not included in the table because detailed information on each patient was not available. In most cases of their report, dermatitis appeared as the first manifestation, followed by arthritis and ocular involvement. Beyond the clinical triad, other features including fever, lymphadenopathy and hepatomegaly can also be present. At the time of initial presentation to our hospital, our patient only had chronic dermatitis among the clinical triad, along with fever and cervical lymphadenopathy.

Differential diagnoses can vary in Blau syndrome. Since the symptoms are usually nonspecific and do not appear simultaneously, Blau syndrome can easily be misdiagnosed with other inflammatory diseases that are more common or familiar. In the study by Matsuda et al.,[11] the primary diagnoses before being diagnosed with Blau syndrome included juvenile idiopathic arthritis (JIA), Behçet's disease, Takayasu's arteritis, and Kawasaki disease. Our patient was misdiagnosed with Kawasaki disease, which delayed the appropriate diagnosis and treatment. **Table 2** briefly describes the differences in clinical manifestations between Blau syndrome and Kawasaki disease. Genetic testing advances and becomes more accessible. Therefore, when a patient is clinically suspicious of having autoinflammatory disease, performing genetic testing at an early stage should be considered to confirm the diagnosis and initiate appropriate management.

There are various treatment options for Blau syndrome, although their clinical effectiveness is unclear. High-dose corticosteroids can be used to control an acute inflammatory phase of Blau syndrome, followed by a low dose of corticosteroids as a maintenance therapy. Immunosuppressants, such as methotrexate and azathioprine, are often added as steroid-sparing agents. If these agents fail to control the disease, biologics can be used. Among the biologics, TNF-α inhibitors are primarily used since the overproduction of TNF by macrophages is known to play a key role in the autoinflammation in Blau syndrome. Interleukin (IL)-1β inhibitors and IL-6 inhibitors are also reported to be effective in some cases, but the number of the cases are limited.[16,17]

In our case, we started with high-dose corticosteroid, which dramatically improved the acute inflammatory phase. To minimize the adverse effects of the steroids, we added methotrexate and further reduced the prednisolone. This combination was effective in controlling the fever and the skin rash, but could not prevent the arthritis. By reviewing other reported cases with joint involvement, we decided to use a TNF-α inhibitor. We specifically chose adalimumab,

Table 2. Comparison between Kawasaki disease and Blau syndrome

Characteristics	Kawasaki disease (incidence in South Korea, %*)	Blau syndrome
Signs and symptoms		
Fever	+	+
Conjunctivitis	+ (87.8)	–
Cervical lymphadenitis	+ (57.2)	+
Mucosal involvement	+ (82.8)†	–
Skin rash	+ (76.4)‡	+
Redness and swelling of hands and/or feet	+ (65.7)	–
Cardiovascular complications	Coronary artery dilatation (17.1)	Large-vessel vasculitis (Takayasu's-like arteritis)[12]
	Coronary artery aneurysm (1.7)	Sinus of Valsalva aneurysm[13]
Histopathological findings of skin rash	Dilatation of small vessels in papillary dermis Infiltration of $CD4^+$ T cells and $CD13^+$ macrophages in dermis and epidermis[14]	Non-caseating granulomas

*Based on the nationwide epidemiologic data of Kawasaki disease in South Korea, 2015–2017.[15]
†Red and/or cracked lips, strawberry tongue
‡Diffuse erythematous polymorphous rash

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of which the recommended dosage for younger children (>2 years) with JIA or uveitis were available, and it seems to have effect on the arthritis.

In this case report, we present a patient who was initially misdiagnosed as refractory Kawasaki disease, but was eventually confirmed as Blau syndrome. This case highlights that Blau syndrome mimics other systemic inflammatory diseases in the early phase, resulting in diagnostic difficulties. By reporting this case, we emphasize the importance of considering other possible diagnoses of patients who are diagnosed with refractory Kawasaki disease.

SUPPLEMENTARY MATERIAL

Supplementary Fig. 1

The skin biopsy result showed multifocal non-caseating granulomas with some giant cells (hematoxylin-eosin stain, ×200).

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요약

블라우 증후군(Blau syndrome)은 nucleotide-binding oligomerization domain protein 2 (*NOD2*) 유전자의 변이에 의해 발생하는 질환으로 육아종성 피부염 및 만성 포도막염, 관절염을 특징으로 한다. 증상이 비특이적이고 동시다발적으로 발생하지 않아 진단이 어려운 경우가 많다. 반복되는 피부 발진 및 발열에 대해 두 차례 가와사키병으로 오진되어 면역글로불린과 전신 스테로이드로 치료받은 바 있는 13개월 남자 환자에서 블라우 증후군을 진단한 증례를 보고하고자 한다.