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Blau syndrome: A case report with unusual symptoms and literature review

Seyda Dogantan [a,*], Sema Nur Taskin [b], Erkan Akkus [c]

[a]Başakşehir Çam and Sakura City Hospital, Clinic of Pediatric Rheumatology, Istanbul, Türkiye
[b]Eskişehir City Hospital, Clinic of Pediatric Rheumatology, Eskişehir, Türkiye
[c]Başakşehir Çam ve Sakura City Hospital, Clinic of Pediatric Gastroenterology, Istanbul, Türkiye
*Corresponding author: drseydacayan@gmail.com (Seyda Dogantan)

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ABSTRACT

Blau syndrome (BS) is an autosomal dominant disease that is brought on by changes in the gene that codes for the NOD-like receptor (NLR) protein (*NOD2*). It is characterized by the trinity of granulomatous polyarthritis, rash, and uveitis One-third to one-half of BS patients were found to have atypical symptoms. This case report presents the clinical experience of a BS patient with unusual findings at a tertiary care center in Istanbul.

A 7-year-old male patient admitted to the outpatient clinic with a complaint of abdominal pain. There were rash attacks with fever for 2 years. He has had abdominal pain that has been going on for years and was previously operated on due to intussusception. There were no hereditary familial diseases found in the patient's family history. In the superficial tissue ultrasonography, intussusception was observed in an intestinal segment. Pathological examination of segmental resection of ileum, cecum, and appendix showed that there were findings of acute appendicitis, peritonitis with surface fissuration, and ulcer. The skin biopsy showed noncaseating, granulomatous infiltration with epithelioid cells and lymphocytes. In the genetic test, the *NOD2* c.1835C>T heterozygous mutation was detected. Based on this, BS was diagnosed. The patient was started on adalimumab and additional colchicine treatment.

This syndrome can mimic other systemic inflammatory diseases in the early stages. This case report shows that we need to consider the diagnosis of BS in more detail in cases who raise clinical suspicion.

Keywords: Blau syndrome, Invagination, NOD2 mutation

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INTRODUCTION

Blau syndrome (BS, OMIM #186580) is a rare, autosomal dominant inflammatory disorder caused by mutations in the nucleotide-binding oligomerization domain-containing 2 (*NOD2*) gene (OMIM 605956), which encodes a NOD-like receptor (NLR) protein. The classical clinical triad of BS includes granulomatous polyarthritis, dermatitis, and uveitis. A skin rash typically appears within the first year of life, although exceptions have been reported. Polyarthritis commonly develops between the ages of two and four, often presenting as "boggy" synovitis and tenosynovitis—distinctive features of Blau arthritis. According to data from the Blau International Registry, 96% of patients with polyarticular arthritis at onset exhibited a boggy or exuberant joint appearance [1].

The proximal interphalangeal joints of the hands, along with the knees, ankles, and wrists, are the commonly affected peripheral joints. In contrast, the axial skeleton and temporomandibular joint are typically spared, and other peripheral joints are less frequently involved. Tenosynovitis is another hallmark of the disease, characterized by visibly swollen tendon sheaths. The commonly affected tendons include the tibialis posterior, pes anserinus, peroneal tendons, and wrist extensors. Despite the chronic and exuberant nature of the arthritis, range of motion is generally well preserved, especially in larger joints, and joint damage is rare. Finally, uveitis develops in approximately 60–80% of patients by the age of 48 months [1].

Here we present a 7-year-old male patient with unusual findings including abdominal pain and intussusception.

CASE REPORT

A 7-year-old male patient was admitted to the outpatient clinic with a chronic abdominal pain that had persisted for several years. He had previously undergone cataract surgery at the age of three and later he was operated on for intussusception. Over the past two years, he has experienced recurrent episodes of fever accompanied by rash. There were no complaints such as arthritis, oral or genital aphthae, Raynaud's phenomenon, dry mouth, or dry eyes. The parents were non-consanguineous, and no hereditary familial diseases were reported in the family history.

Superficial soft tissue ultrasonography was performed in the region of the abdominal complaint and showed that a 3.5 cm palpable mass (measuring approximately 33x34 mm in transverse axis) was detected in the right lower quadrant. Ultrasonographic characteristics of the mass suggested an intussusception in the bowel segment with surrounding mesenteric inflammation and multiple adjacent millimeter lymph nodes. A clear distinction between ileo-ileal and ileocecal regions was noted.

Segmental resection and appendectomy were performed and histopathological examination showed that cecum, and appendix showed findings consistent with acute appendicitis, surface fissuring, ulceration, and peritonitis. Subepithelial non-caseating granulomas were identified within lymphoid follicles, along with perineural and perivascular granulomatous inflammation. Some areas demonstrated inflammatory infiltration involving vessel walls and nerve plexuses. The small intestine also exhibited mucosal inflammation with focal fissures, cryptitis, and reactive lymphoid hyperplasia of Peyer's patches. There was non-granulomatous perivascular inflammation around medium-sized vessels.

Given the presence of granulomatous appendicitis, further evaluation for systemic granulomatous diseases (e.g., Crohn's disease, infections, immunodeficiencies, and vasculitis) was recommended. Inflammatory involvement of the appendix and small intestinal vessels suggested possible vasculitic changes, either secondary to inflammation or as part of a primary vasculitis process. While some granulomas exhibited necrotic changes, necrosis was not identified in most.

Colonoscopy revealed skip lesions with ulceration and hyperemia in the terminal ileum. The cecal mucosal vascular pattern was normal, with no erosions, ulcers, or polypoid lesions. The ascending colon showed normal mucosal vasculature and no ulcerative lesions. However, the descending colon and rectum were hyperemic with ulceration and membranous lesions. The rectosigmoid junction appeared particularly hyperemic.

Comprehensive laboratory and imaging evaluations were performed. ANA profile, ANCA, ACE levels, spot urine protein/creatinine, calcium/creatinine ratios, and immunoglobulin levels were tested. Uveitis screening, renal Doppler ultrasound, abdominal ultrasonography, high-resolution computed tomography (HRCT), and Interferon-γ Release Assay (IGRA) were also performed. Thoracic CT, renal Doppler, and abdominal US findings were within normal limits. Our laboratory findings showed a negative ANA and antiphospholipid antibody profiles, normal complement levels (C3 and C4), elevated liver enzymes (AST 52 U/L, ALT 63 U/L), positive stool occult blood, negative IGRA test. There were no evidence of uveitis on ophthalmologic examination.

Skin biopsy revealed non-caseating granulomatous inflammation with epithelioid cells and lymphocytes. Genetic testing identified a heterozygous *NOD2* c.1835C>T mutation. Based on clinical, pathological, and genetic findings, a diagnosis of Blau syndrome was established. The patient was started on adalimumab 40 mg subcutaneously once weekly under off-label approval. Colchicine was also added to the treatment regimen.

A signed consent form was obtained from the patient on 29/04/2025.

DISCUSSION

BS, a granulomatous autoinflammatory disease, was first described by Blau in 1985 [2]. Although symptoms of BS typically appear before the age of five, a proper diagnosis may not be made until later in life, especially if the presentation does not include the typical triad of clinical manifestations or if the symptoms appear one after the other rather than all at once [3]. Even though it is primarily recorded among Caucasians, there have been reports of BS in East Asia, including 34 instances in Japan [4], 19 cases in China [5], and 4 cases in South Korea [6]. In BS and sarcoidosis, there are many similar features, such as noncaseating granuloma, skin rash, and eye involvement. Early-onset sarcoidosis (EOS, MIM No. 609464) was previously thought to be a form of childhood sarcoidosis that began at a young age and had a progressive course. Since it was eventually shown that both BS and EOS have mutations in the *NOD2* gene, they are now regarded as one and the same disease [7-9].

A member of the NOD-like receptor family, the *NOD2* protein is mostly produced by antigen-presenting cells like macrophages and monocytes. In order to bind muramyl dipeptide (MDP), a breakdown product of the bacterial peptidoglycan, *NOD2* has a tripartite structure that includes two N-terminal caspase recruitment domains, one centrally located NTPase triphosphatase domain (NACHT domain), and a C-terminal domain with several leucine rich repeat motifs. Inflammation and apoptosis result from the MDP's activation of *NOD2*, which in turn promotes nuclear factor kappa light chain enhancer of activated B cells (NF-κB) [7]. Variants in the *NOD2* gene (OMIM *605956), which codes for the protein known as nucleotide-binding oligomerization domain 2, were known to cause BS in 2001. The 334 residue is regarded as the mutational hot point since the bulk of BS cases are caused by two known *NOD2* pathogenic variants, p.(Arg334Trp) and p.(Arg334Gln), which are found in exon

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4 [10]. The parents of the patient were healthy, despite the fact that BS is inherited from autosomal dominant. We believe the disease was caused by a de novo mutation in our case, and BS stemming from de novo mutations may manifest sporadically.

BS can have a variety of differential diagnosis. BS is frequently confused with other inflammatory disorders that are more prevalent or well-known since the symptoms are typically nonspecific and do not manifest at the same time. Prior to being identified with BS, the main diagnoses in the study by Matsuda et al. [11], were juvenile idiopathic arthritis, Behçet's diseases, Takayasu's arteritis, and Kawasaki disease. In our patient, unusually, abdominal pain was at the forefront. The patient underwent intussusception surgery for the second time

There are many therapeutic modalities that are available with a varying degree of efficacies. A modest dose of corticosteroids can be administered as a maintenance treatment after high-dose corticosteroids have been used to manage the acute inflammatory phase of BS.

As steroid-sparing agents, immunosuppressants such as methotrexate and azathioprine are frequently added. Biologic agents may be utilized if these treatments are unable to control the illness. Since the overproduction of TNF by macrophages is believed to be a major factor in the autoinflammation associated with BS, tumor necrosis factor-alpha (TNF-α) inhibitors are the commonly utilized therapeutic agents. While limited examples exist, inhibitors of interleukin (IL)-1β and IL-6 have demonstrated efficacy in specific clinical scenarios [12]. We started the patient on adalimumab, a fully human recombinant monoclonal antibody with high affinity. This drug is used as a TNF-α inhibitor in various autoimmune conditions.

CONCLUSION

In this case report, we present a confirmed case of BS. It shows that BS mimics other systemic inflammatory diseases in the early stages, leading to diagnostic difficulties. The diagnosis depends on clinical suspicion.

Informed Consent: It was conducted in compliance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. A signed consent form was obtained from the patient on 29/04/2025.

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REFERENCES

1. Rosé CD, Wouters CH, Meiorin S, et al. Pediatric granulomatous arthritis: an international registry. *Arthritis Rheum.* 2006 Oct;54(10):3337-44. doi: 10.1002/art.22122. PMID: 17009307.
2. Blau EB. Familial granulomatous arthritis, iritis, and rash. *J Pediatr.* 1985 Nov;107(5):689-93. doi: 10.1016/s0022-3476(85)80394-2. PMID: 4056967.
3. Rosé CD, Pans S, Casteels I, et al. Blau syndrome: cross-sectional data from a multicentre study of clinical, radiological and functional outcomes. *Rheumatology (Oxford).* 2015 Jun;54(6):1008-16. doi: 10.1093/rheumatology/keu437. Epub 2014 Nov 20. PMID: 25416713.
4. Otsubo Y, Okafuji I, Shimizu T, Nonaka F, Ikeda K, Eguchi K. A long-term follow-up of Japanese mother and her daughter with Blau syndrome: Effective treatment of anti-TNF inhibitors and useful diagnostic tool of joint ultrasound examination. *Mod Rheumatol.* 2017 Jan;27(1):169-173. doi: 10.3109/14397595.2014.964388. Epub 2014 Nov 10. PMID: 25381727.
5. Wang W, Wei M, Song H, Qiu Z. [Mutations of *NOD2* gene and clinical features in Chinese Blau syndrome patients]. *Zhonghua Er Ke Za Zhi.* 2014 Dec;52(12):896-901. PMID: 25619344.
6. Kim W, Park E, Ahn YH, et al. A familial case of Blau syndrome caused by a novel *NOD2* genetic mutation. *Korean J Pediatr.* 2016 Nov;59(Suppl 1):S5-S9. doi: 10.3345/kjp.2016.59.11.S5. Epub 2016 Nov 30. PMID: 28018435; PMCID: PMC5177712.
7. Kanazawa N, Okafuji I, Kambe N, et al. Early-onset sarcoidosis and CARD15 mutations with constitutive nuclear factor-kappaB activation: common genetic etiology with Blau syndrome. *Blood.* 2005 Feb 1;105(3):1195-7. doi: 10.1182/blood-2004-07-2972. Epub 2004 Sep 30. PMID: 15459013.
8. Paç Kısaarslan A, Sözeri B, Şahin N, et al. Blau syndrome and early-onset sarcoidosis: a six case series and review of the literature. *Arch Rheumatol.* 2019 Nov 6;35(1):117-127. doi: 10.5606/ArchRheumatol.2020.7060. PMID: 32637927; PMCID: PMC7322314.
9. Sönmez HE, Karadağ ŞG, Aktay Ayaz N. Musculoskeletal complaints: when should we consult a pediatric rheumatologist? Musculoskeletal Complaints in Children. *JPA.* 2022;3(1):6–10. doi: /10.51271/jpea-2022-152.
10. Brichova M, Klimova A, Heissigerova J, et al. Blau Syndrome: Challenging Molecular Genetic Diagnostics of Autoinflammatory Disease. *Genes (Basel).* 2024 Jun 18;15(6):799. doi: 10.3390/genes15060799. PMID: 38927735; PMCID: PMC11203189.
11. Matsuda T, Kambe N, Ueki Y, et al. Clinical characteristics and treatment of 50 cases of Blau syndrome in Japan confirmed by genetic analysis of the *NOD2* mutation. *Ann Rheum Dis.* 2020 Nov;79(11):1492-1499. doi: 10.1136/annrheumdis-2020-217320. Epub 2020 Jul 9. PMID: 32647028.
12. Lu L, Shen M, Jiang D, et al. Blau syndrome with good Reponses to Tocilizumab: A case report and focused literature review. *Semin Arthritis Rheum.* 2018 Apr;47(5):727-731. doi: 10.1016/j.semarthrit.2017.09.010. Epub 2017 Sep 25. PMID: 29110911.

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