Blau Syndrome Complicated by Atypical Type IIa Takayasu Arteritis

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Abstract

Blau syndrome (BS) is a rare, autosomal dominant monogenic autoinflammatory disease, usually presenting as a triad of symptoms (granulomatous dermatitis, uveitis, and nonerosive arthritis) and caused by gain-of-function mutations in the nucleotide oligomerization domain 2 (*NOD2*) gene. However, very few reports in children of copresence of BS with large vessel vasculitis exist. We hereby describe a case of BS associated with clinical features of Takayasu arteritis. An 8.5-year-old boy presented with hypertension, cardiac insufficiency, arthritis, and ocular disease. Among other investigations, he underwent cervical and chest computed tomography and computed tomography angiography scans that revealed the presence of type IIa Takayasu arteritis lesions. Genetic analysis revealed a heterozygous mutation of *NOD2* gene leading to the amino acid exchange Arg-587-Cys in the NACHT domain of the NOD2 protein (R587C) as pathogenic cause of BS. He received treatment with prednisolone, methotrexate, and infliximab (antitumor necrosis factor-α) in addition to antihypertensive medication with a favorable clinical response. Cases of BS should be investigated for the coexistence of Takayasu arteritis. However, further research is required to delineate a possible common pathogenic mechanism between the two clinical entities.

Keywords
- autoinflammatory disease
- Blau syndrome
- Takayasu
- NOD2
- anti-TNF-α

Introduction

Blau's syndrome (BS) is a rare, monogenic autoinflammatory disease with an autosomal dominant inheritance pattern,[1,2] although sporadic cases caused by de novo mutations have also been described. The syndrome's prevalence is estimated at $<1: 10^6$, but due to its rarity as well as the relatively short interval time since it was first described (1985),[2] both its incidence, exact epidemiology and natural course remain mostly unknown. It is caused by gain-of-function mutations of the nucleotide oligomerization domain 2 (*NOD2*) gene, located on chromosome 6, leading to the activation of inflammatory pathways.[3–5] NOD2 protein also known as *caspase recruitment domain-containing protein 15* or *inflammatory bowel disease protein 1* is an intracellular pattern recognition receptor implicated in the innate immune responses through the activation of nuclear factor kappa B pathway and autophagy.[6]

BS typically presents in early childhood with a "triad" of symptoms: granulomatous dermatitis, uveitis, and nonerosive arthritis.[2,7] However, as further cases of BS are described, novel reports of involvement of various systems

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have emerged.[1–3,5,7–11] Limited reports of vascular insult exist,[8] with a total of seven available references, mainly in the form of Takayasu's arteritis.[9,10] Herein, we describe a case of BS with Takayasu's arteritis lesions in an Afghan patient.

Case Report

An 8.5-year-old Afghan boy, offspring of nonconsanguineous parents with unremarkable family medical history, was referred to our department for further investigation and management of hypertension, cardiac insufficiency, arthritis, and ocular disease. The boy had been diagnosed with "heart failure" at the age of 3.5 years for which he received digoxin and furosemide. The patient reported recurrent episodes of fever since the age of 1 year. He was diagnosed with juvenile idiopathic arthritis at the age of 2.5 years based on the findings of oligoarthritis and severe uveitis and was treated with nonsteroidal anti-inflammatory drugs, corticosteroids and hydroxychloroquine. He underwent lens replacement due to cataract of his right eye at the age of 5 years. Furthermore, he was diagnosed with severe hypertension (systolic blood pressure up to 180 mm Hg) 4 months prior to admission. However, being an immigrant, he had not been under consistent follow-up.

On admission, his physical examination revealed the presence of 3/6 systolic heart murmur, mild hepatomegaly, malnutrition with low body mass index(12.8 kg/m^2, $<$2 standard deviation), tenosynovitis of both wrists, as well as a fine, macular, tan-colored, pigmented rash on the extremities (►**Fig. 1**). Ophthalmology testing highlighted the presence of an old, bilateral anterior and posterior uveitis with concurrent mild flare in the left eye as well as elevation of intraocular pressure bilaterally. On cardiology assessment, the patient was found to have hypertrophy of the left ventricle and severe mitral valve regurgitation. The ejection fraction of the left ventricle was measured at 45 to 60% on repeated scans.

The patient underwent extended laboratory investigations, and the results were mostly unremarkable with the exception of mild elevation of inflammation markers (erythrocyte sedimentation rate, C-reactive protein, procalcitonin, and serum amyloid A), borderline elevation of serum angiotensin-converting enzyme (SACE) (78 IU/L, reference values $<$52), and calciuria. Imaging investigations included X-rays, abdominal ultrasound scan, brain, heart, and abdominal magnetic resonance imaging, as well as cervical and chest computed tomography (CT) and CT angiography (CTA) scans. The CT scans were performed in a Multislice CT scanner of 16 slices with transverse slices of 1.25 and 5 mm thickness before and after the administration of intravenous (IV) contrast medium, and they revealed the presence of a concentric thickening of the ascending aorta as well as the aortic arch and its branches (brachiocephalic artery and its branches, left common carotid artery, and central part of the left subclavian artery). In addition, ectasia was noted on both common carotid arteries, all in consistence with type IIa Takayasu's arteritis (►**Fig. 2**). Interestingly, the patient also manifested a saccular aneurysm of the left iliac artery and a mild stenosis of the left renal artery.

Genetic analysis with next-generation sequencing led to the diagnosis of BS, as a heterozygous NOD2 mutation was found on exon 4 of the *NOD2* gene (rs104895479, c.1759C $>$ T). The analysis of the whole DNA extracted from a peripheral blood sample was performed using the SeqCap EZ HyperCAp Library (Roche) method, and the nucleotide sequencing was performed with IlluminaNovaSeq 6000. Bioinformatics systems were applied on a special panel for autoinflammatory diseases for the further analysis of the results.

The patient initially received immunosuppressive treatment with prednisolone, a synthetic glucocorticoid (0.5 mg/kg/d with gradual tapering over the following

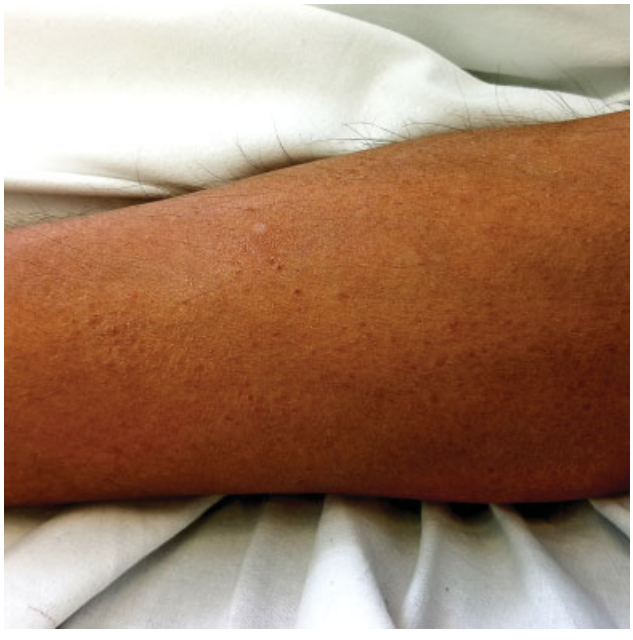

Fig. 1 Fine, macular, tan-colored, pigmented rash on patient's legs on presentation.

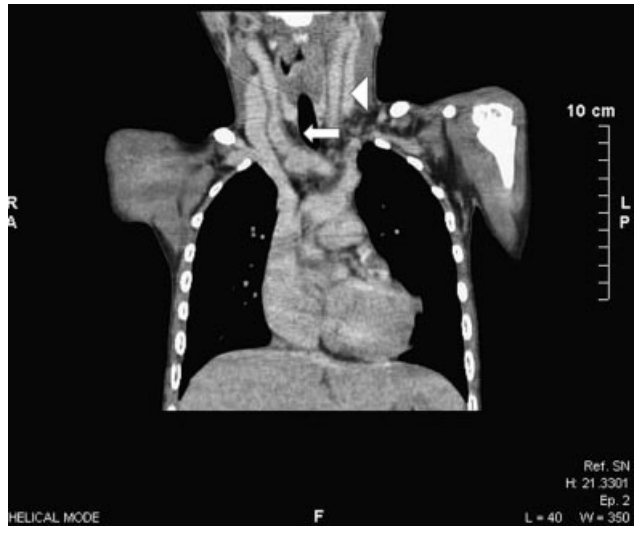

Fig. 2 Initial chest and cervical computed tomography scan (prior to treatment with biological agent): Arrow shows concentric wall thickening of the brachiocephalic artery. Arrowhead shows ectasia of the left common carotid artery.

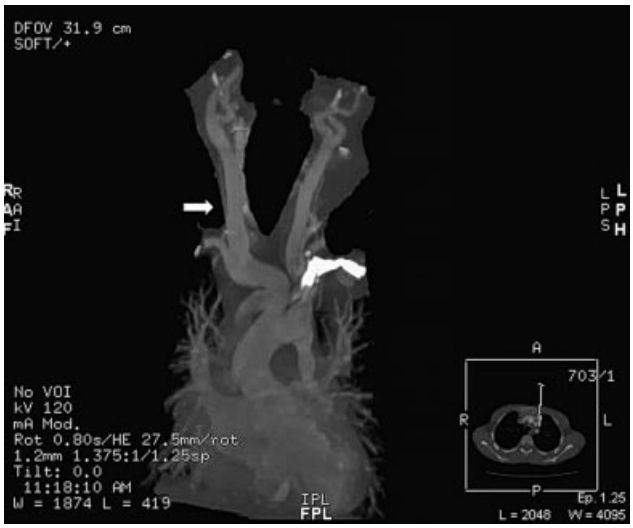

Fig. 3 Chest and cervical computed tomography angiography scan 4 months following infliximab treatment commencement. Large vessel wall appears smooth and not thickened. Arrow shows ectasia of the common carotid arteries.

months), and methotrexate, a folate antagonist (15 mg/m^2/wk) on top of his antihypertensive medication. Subsequently, in view of the presence of the vascular lesions, he was also commenced on infliximab (a chimeric anti–tumor necrosis factor [TNF]-α antibody given IV) at a dose of 6 mg/kg every 4 to 6 weeks. His clinical course was favorable over a period of 15 months of follow-up regarding elimination of disease flares and blood pressure control. Moreover, on repeat CTA, significant improvement of the previous findings was noted (►**Fig. 3**). However, the anti-TNF-α treatment had to be continued in view of recurrences of severe uveitis, but the IV treatment was replaced by the more flexible regimen of adalimumab (anti-TNF-α monoclonal antibody) given subcutaneous at a dose of 40 mg every other week. Subsequently, the clinical course of his ocular disease has shown marked improvement.

Discussion

We presented a case of BS with Takayasu's arteritis which is a rather rare finding among patients with this disease. The patient has responded well to the treatment with an anti-TNF-α agent.

BS presents in early childhood, whereas sporadic cases in older patients have also been described.[2,11,12] However, due to the rarity of the disease and its overlapping features with other rheumatic diseases, it is often initially misdiagnosed, as it was in our case. BS was previously characterized as infantile or early-onset sarcoidosis, since it shares features with typical (adult type) sarcoidosis, such as intermittent fever, nonerosive arthritis, panuveitis, granulomata formation, calciuria and mildly raised inflammatory markers (including SACE).

Takayasu's arteritis is an extremely rare complication of BS anecdotally described in the literature, whereas there are referrals of large vessel vasculopathy in patients with sarcoidosis, even before BS was described.[13] The existence of Takayasu's arteritis in our case stresses that it should always be included in the diagnostic approach and management of patients whose features do not unanimously fit under the same diagnostic umbrella. The exact pathophysiological mechanism of the above-mentioned remains unclear, while various therapeutic options have been proposed.[2,9,10]

Our patient was found positive for a heterozygous mutation of *NOD2* gene (rs104895479, c.1759C > T). This mutation leads to the amino acid exchange Arg-587-Cys in the NACHT domain of the NOD2 protein and has been previously described in the literature (R587C).[4,11,12,14,15] The role of *NOD2* gene in the expression of Takayasu's arteritis is yet to be clarified. Taking into consideration the presence of non-caseating granulomas in the inflamed arteries in patients with Takayasu's arteritis, similar to the ones found in the affected organs in patients with BS, it would be reasonable to speculate that the two conditions share a common pathophysiological pathway.[16] In terms of pathophysiology, while the causative mechanism of Takayasu's arteritis remains mostly unknown, there have been reports of Th1 CD4+ lymphocytes regulating the formation of granulomas via interferon (IFN)-γ, alongside the implication of Th17 lymphocytes. Additionally, patients with Takayasu's arteritis exhibit increased serum levels of interleukin (IL)-6 among other cytokines (i.e., TNF-α, IFN-γ, IL-2, IL-3, IL-4, IL-8, Regulated on Activation, Normal T Expressed and Secreted).[17] Regarding BS, studies using immunohistochemistry have highlighted the presence of inflammatory cytokine expression in situ in the granulomas with prominent expression of IFN-γ,[18] IL-6, transforming growth factor-β, IL-17, and IL-23 receptor.[2,19] Therefore, it appears that there are adequate common mediators to support the hypothesis of crossing pathways, regarding Blau and Takayasu pathophysiology. Moreover, both conditions exhibit satisfactory response to TNF blockade,[15,20] while TNF has been suggested as an important mediator of the tissue damage caused in Takayasu's arteritis.[21] TNF-α inhibitors also reduce the expression and production of vascular endothelial growth factor (VEGF), nitric oxide (NO), and inducible NO synthase.[22] VEGF is known to be a mediator of inflammation leading to endothelial dysfunction and cardiovascular pathology.[22] Therefore, the administration of TNF-α inhibitors is a promising treatment of immune-mediated diseases by reducing the systemic inflammation and improving both the clinical course of the disease itself and the endothelial function, thus, potentially decreasing the risk of acute cardiovascular and/or cerebrovascular events.[22]

Furthermore, the prevalence of inflammatory bowel disease appears to be higher in patients with Takayasu's disease compared with the general population,[17] and given the role of NOD2 protein in the pathophysiology of Crohn's disease,[2,12,14] the hypothesis of NOD2 protein being the mediator of all three conditions can be further supported.

Although the exact pathophysiology mechanism of this combined severe clinical phenotype is yet to be decided, based on the available data, vascular involvement in the form of vasculitis is an indication for a more aggressive treatment

approach (e.g., use of biological agents). So far, the results are quite promising, but it still remains a quite severe complication that requires close monitoring with collaboration of different medical specialties.

Our patient seems to be responding well to the applied treatment course so far, mainly in terms of vascular inflammation, blood pressure regulation, cardiac function, and disease flares. The most persistent condition appears to be his ocular manifestation, whereas his weight gain remains poor despite all efforts to support his caloric intake.

Poor weight gain most likely constitutes part of the disease's clinical phenotype. However, it is believed that it should be taken into account for the proper clinical follow-up of the child.

Conclusion

Patients with BS should be further investigated for the presence of Takayasu's arteritis, especially in cases with atypical clinical presentation, since its early diagnosis is of great importance for the treatment and the future prognosis of the disease.

Anti-TNF-α monoclonal antibody administration is a quite promising treatment for patients with this severe combined clinical phenotype. Systematic follow-up of our patient in the long term is necessary for the evaluation of the outcome of the applied treatment and the future morbidity. Moreover, it may further facilitate our understanding of the disease's pathophysiology and response to treatment.

Further research is needed to clarify the possible common pathogenetic mechanisms for the coexistence of Takayasu's arteritis and BS, and this could prove useful in the application of targeted therapies.

Conflict of Interest
None declared.

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