PORTUGUESE JOURNAL OF PEDIATRICS

PERMANYER

Check for updates

CASE REPORT

Recurrent infections and short stature – Listening may be the key. A Bloom syndrome case report

Margarida Almendra[1], Ana I. Cordeiro[1,2,3], Rosa Pina[4], Catarina Martins[2,3], Conceição Neves[1,3], and João Farela Neves[1,3]*

[1]Primary Immunodeficiencies Unit, Hospital Dona Estefânia, Centro Hospitalar Universitário Lisboa Central, EPE; [2]NOVA Medical School|Faculdade de Ciências Médicas, Universidade NOVA de Lisboa; [3]Comprehensive Health Research Centre (CHRC), NOVA Medical School|Faculdade de Ciências Médicas, Universidade NOVA de Lisboa; [4]Endocrinology Unit, Hospital Dona Estefânia, Centro Hospitalar Universitário Lisboa Central, EPE. Lisbon, Portugal

Abstract

Introduction: Bloom syndrome is a rare autosomal recessive disorder characterized by chromosomal instability caused by mutations in the BLM gene that increase the risk of developing neoplasia, particularly at an early age. Bloom syndrome is typically characterized by short stature, photosensitivity, telangiectatic erythema, learning difficulties, immunodeficiency, and malignancy. **Case report:** We report a case of an adolescent girl with short stature and recurrent infections, who does not present typical erythematous sun-sensitive skin lesions to the face and whose high-pitched voice led to the diagnosis of BS caused by a novel L753X mutation. **Discussion:** To date, she has not presented with any malignancy or characteristic malar rash.

Keywords: Bloom syndrome. Chromosomal instability. Sister chromatid exchange. Novel mutation. Case report

Infeções recorrentes e baixa estatura – Ouvir pode ser a chave. Um caso de síndrome de Bloom

Resumo

Introdução: A síndrome de Bloom é uma doença autossómica recessiva, caracterizada por instabilidade cromossómica resultante de mutações no gene BLM, que aumentam o risco de desenvolver neoplasia, sobretudo, em idade precoce. **Relato de caso:** A síndrome de Bloom é caracterizada habitualmente por baixa estatura, fotossensibilidade, eritema telangiectásico, dificuldades de aprendizagem, imunodeficiência e neoplasia. Descrevemos um caso de uma adolescente com baixa estatura e infeções recorrentes, mas sem lesões clássicas eritematosas faciais associadas a fotossensibilidade e cuja voz aguda levou ao diagnóstico de síndrome de Bloom, resultante de uma mutação não descrita previamente, L753X. **Discussão:** Atualmente, a doente não apresenta evidência de neoplasia nem de eritema malar clássico.

Palavras-chave: Síndrome de Bloom. Instabilidade cromossómica. Troca cromatídea irmã. Mutação *de novo*. Caso clínico.

***Correspondence:**
Margarida Almendra
E-mail: margaridaalmendra@hotmail.com

Received: 12-09-2022
Accepted: 26-01-2023
https://pjp.spp.pt

Available online: 18-04-2024
Port J Pediatr. 2024;55(3):193-198
DOI: 10.24875/PJP.M24000448

Keypoints

What is known

- Bloom syndrome is a rare autosomal recessive disorder, characterized by chromosomal instability caused by mutations in the BLM gene.
- Diagnosing Bloom syndrome is challenging because it is a rare condition, but also because of the variations in the severity of its hallmark features.

What is added

- Classic, sun-sensitive facial skin rash features of Bloom syndrome may be absent.
- Awareness of this phenotypic variability without the "hallmark" feature of Bloom syndrome could prevent a diagnostic delay.
- A novel private homozygous variant in BLM (p.L753X) was identified in our patient, which led to the diagnosis of Bloom syndrome.

Introduction

Bloom syndrome (BS; MIM #210900) is a rare autosomal recessive disorder. Ever since the first time it was reported, more than half a century ago[1], fewer than 300 cases are known to the Bloom syndrome registry (BSR)[2]. It has been reported to be more prevalent in populations where the rate of parental consanguinity is higher. In particular, it is more common in the Eastern European Ashkenazi Jewish population, which constitutes about one quarter of the affected families in the BS registry, with a 1% carrier rate[2-5].

BS is characterized by chromosomal instability caused by mutations in the BLM gene, one of the so-called "guardians of the genome"[6], which encodes a RecQ helicase, the BLM helicase (RECQL3)[7]. The BLM helicase is essential to maintaining the structure and integrity of DNA[8], contributing to the preservation of genomic stability[6]. Defects in the BLM gene and the absence of a functional BLM protein lead to chromosome instability, excessive homologous recombination, and a markedly increased rate of sister chromatid exchange (SCE) that is pathognomonic of BS[4]. BS cells are characterized by a SCE rate that is ten times higher than average[9]. The main clinical features of BS include pre- and post-natal growth deficiency, a sun-sensitive erythematous face rash, high-pitched voice, dysmorphic features, varying degrees of immunodeficiency manifested by recurrent respiratory and gastrointestinal tract infections, a predisposition to developing a wide variety of malignancies at an early age, and early-onset type 2 diabetes[2,5,10].

Diagnosing BS is challenging because it is rare, but also because its hallmark features may vary in severity.

We report the case of an adolescent girl of short stature with recurrent infections, who does not present the classic erythematous sun-sensitive skin lesions to the face and whose high-pitched voice led to the diagnosis of BS caused by a novel L753X mutation.

Case report

A 15-year-old girl, the second child of a non-consanguineous non-Jewish family, was born prematurely at 27 weeks of gestation due to severe intrauterine growth restriction and oligohydramnios.

She had a mild cognitive delay, low weight, and symmetric short stature, with normal IGF1 and IGF1-BP3. She reported having recurrent respiratory infections, leading to conductive hearing impairment. She had a long, narrow face (Fig. 1) and a high-pitched voice was noted. She had no skin lesions or sun-sensitive rash. Her neurological and cardiac examinations were unremarkable.

She presented 3-lineage hypogammaglobulinemia and impaired vaccine responses, as well as CD4 and CD8 naïve lymphopenia, but preserved class-switched B cells. Autoimmunity screening was negative (Table 1).

The combination of her extremely short stature, recurrent infections, and high-pitched voice led to the clinical hypothesis of BS and genetic testing revealed a novel private homozygous variant in BLM (p.L753X), inherited from her healthy parents. The nonsense mutation causes a stop gain in the BLM DNA helicase domain and is predicted to be pathogenic by *in silico* prediction methods (CADD score 38). SCE frequency was elevated, thereby confirming the diagnosis (Fig. 2).

She recently developed diabetes mellitus with negative autoantibodies (anti- insulin, anti-tyrosine phosphatase, and anti-glutamic decarboxylase).

Currently, at the age of 19, she is under multi-disciplinary monitoring with no signs of malignancy.

Discussion

In rare diseases, a possible phenotype-genotype correlation is hard to establish due to the limited number of cases and its potential range of manifestations.

Figure 1. Facial features of the patient.

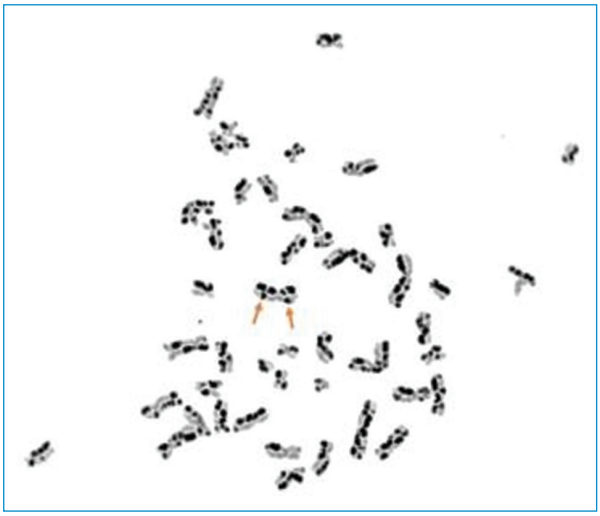

Figure 2. Karyotype of the patient highlighting the increased proportion of sister chromatid exchanges (arrows pointing to examples).

Although BS was first described in 1954, there are currently no clinical diagnostic criteria for BS. The only up-to-date BS patient cohort indicates a likely genetic heterogeneity[3].

In this case report, we describe a 15-year-old adolescent girl with BS. She presented with typical features of this condition, but without the classic feature of erythematous sun-sensitive skin lesions to the face. The clinical features that fit with BS are her pre-natal and post-natal growth deficiency, facial dysmorphism (long, narrow face), high-pitched voice, and recurrent infections. According to the BSR, type 2 diabetes mellitus was identified in 16% of patients, with onset prior to the age of 20 in more than 25% of these[2,7], which resembles our case report.

However, it is surprising that our patient has not reported any symptoms of sun sensitivity or malignancy by the age of 19.

The first symptom described by dermatologist Dr. David Bloom was a face eruption resembling lupus erythematous in addition to bullous eruptions on the lips related to sunlight hypersensitivity[1]. Pigmentation disorders are also frequent, with both hypo- and hyper-pigmented lesions coexisting, mainly on the torso and extremities, leading to the appearance of *café-au-lait* spots[2,7].

However, this "hallmark" feature of BS may not always be present. Indeed, there have been six case reports describing a total of thirteen BS patients, twelve of them in pediatric age, who did not suffer from any facial skin lesions at all[11-16]. Boduroglu et al.[11] reported two siblings, both with BS, where the boy did not show sun-sensitive facial skin lesions but the sister experienced severe sun-related facial skin lesions. There has been some debate about the possible role of environmental factors and gender[11,12]. Conversely, skin lesions are usually milder among female and dark-skin phototypes of BS patients[15,17,18].

A predisposition to developing a wide range of malignancies at an abnormally early age is well described in BS, making it the most serious medical complication seen and the leading cause of death in BS patients[2,4,5,10]. Cancers of virtually any type at any location have been reported[9].

Of particular note, four case reports regarding five pediatric BS patients have no findings suggestive of any malignancy[13,15,19,20], although none had yet reached adulthood. Due to its wide variations and non-specific clinical features, BS diagnosis requires a cytogenetic and/or molecular confirmation.

BS results from mutations in both copies of the BLM gene, which is located on chromosome 15 (band 15q26.1)[21]. German et al.[3] identified multiple recurrent mutations in the BLM gene. To date, 151 different BLM mutations have been described all over the world in different ethnicities, most of them missense/nonsense

Table 1. Laboratory testing

	Patient value	Reference value
Hemoglobin	13.6 x 10 g/L	12.0-16.0
Leukocytes	7.07 x 10 g/L	4.5-13.0
Lymphocytes	2.22 x 10 g/L	1.0-5.3
CD3+T cells	1584.83/µL	1000-2200
CD4+T cells	795.94/µL	330-920
CD8+T cells	756.94/µL	330-920
CD3+CD4+CD45RA T cells	27% ↓	40-95%
CD3+CD8+CD45RA T cells	30% ↓	40-95%
CD19+B cells	343.69/µL	110-570
CD19+CD27+IgD B cells	9.9%	5-120%
CD3- CD16+CD56+NK cells	358.43/µL	70-480
Platelets	405×10 g/L	150-450
IgG	4.17 g/L ↓	6.50-18.50
IgA	0.29 g/L ↓	0.70-4.00
IgM	0.19 g/L ↓	0.40-2.30
Growth hormone	0.166 ng/mL	0.010-3.607
Insulin-like growth factor 1 (IGF1)	522.00 ng/mL	143-693
Insulin-like growth factor binding protein-3 (IGFBP-3)	5.80 ng/mL	2.4-8.4
Anti-diphtheria toxin antibodies (IgG)	0.06 UI/mL ↓	> 0.10: vaccine protection
Anti-tetanus toxin antibodies (IgG)	0.01 UI/mL ↓	> 0.10: vaccine protection
Thyroid peroxidase antibodies (TPO)	< 1.00 UI/mL	< 5.61
Antithyroglobulin antibodies (ATG)	< 1.00 UI/mL	< 4.11
Anti-insulin antibodies (AIA)	Negative	-
Anti-tyrosine phosphatase antibodies (IA2)	Negative < 1	Positive > 2
Anti-glutamic acid decarboxylase (GAD) antibodies	Negative	-
IgA antigliadin antibodies (AGAs)	Negative < 5.2 UQ	< 30
IgG antigliadin antibodies (AGAs)	Negative < 3 UQ	< 30
IgA anti-tissue transglutaminase antibodies (tTG)	Negative < 1.90 UQ	< 30
IgG anti-tissue transglutaminase antibodies (tTG)	Negative < 3.80 UQ	< 30
Anti-smooth muscle antibody (ASMA)	Negative	-
Anti-mitochondrial M2 antibody (AMA-M2)	Negative	-
Liver kidney microsome type 1 (anti-LKM-1) antibodies	Negative	-
Liver cytosol specific antibody type 1 (anti-LC1)	Negative	-

NK: natural killer.

mutations[5]. A common founder mutation (a 6-bp deletion and 7-bp insertion at nucleotide position 2281 in the *BLM* cDNA, commonly known as *blm*Ash) is present in about 1/100 in the Eastern European Jewish population and it is the most common of the BLM mutations. A prevalence of 1:48,000 is estimated for BS in Ashkenazi Jews[3].

BLM is a protein that temporarily links to other compounds to form a complex with the Topoisomerase IIIα (Topo IIIα), RecQ-mediated genome instability protein 1 (RMI1) and 2 (RMI2) and single-stranded DNA (ssDNA)-binding protein.

RPA[22]. This complex (BTR complex or BLM dissolvasome) also has a role in DNA replication repair[23].

In addition to BLM mutations, loss of function mutations in the BTR complex (Topo IIIα, RM1 and RM2) have been implicated in BS-like disorders[3,24,25].

The phenotypic features of patients with biallelic Topo IIIα mutations were identical to those of patients with homozygous BLM mutations in terms of pre-natal growth retardation, microcephaly, and *café-au-lait* spots[24]. However, dilated cardiomyopathy was also reported[24], which is not a typical feature of BS. Interestingly, elevated SCE were also identified but facial malar rash, cancer, and diabetes were not present[24].

Hudson et al.[25] described a milder phenotypic feature in two siblings with a homozygous deletion in the RMI2 gene, who presented a mild growth retardation and *café-au-lait* spots. Similarly to BS, increased SCE were identified. However, both siblings showed no evidence of photosensitivity, recurrent infections, cancer, or diabetes.

Recently, Gönenc[16] demonstrated that pathogenic variants in the different members of the BTRR complex may have a fluctuating impact on phenotype significance, especially when comparing BLM and RM1 associated phenotypes. Patients with pathogenic BLM variants had a major BS phenotype when compared to patients carrying RM1 pathogenic variants. Indeed, none of the patients with RM[1] pathogenic variants presented signs of skin lesions, *café-au-lait* spots, or recurrent infections.

A novel private homozygous variant in BLM (p.L753X) was identified in our patient which led us to the diagnosis of BS. We are not aware of the existence of specific BLM mutations associated with a mild, or even absent, skin facial rash phenotype. Hence, we can only speculate about a possible phenotype-genotype correlation that would have explained the phenotypic variability that is present among BS patients.

There are no evidence-based guidelines for the treatment of BS patients[4,5]. Management consists of monitoring and treating complications. Although most BS patients survive to adulthood, the average age of death is 26[2], usually from cancer. This highlights the importance of early diagnosis and appropriate cancer screening.

Although it was first described more than 60 years ago, there is still little that is known about the clinical and molecular aspects of BS. Indeed, the wide spectrum of clinical manifestations, together with this rarely-remembered entity, contribute towards the underdiagnosis of this disorder worldwide.

Given the high risk of malignancy, close multi-disciplinary monitoring focused on early detection and appropriate cancer treatment are the cornerstones of BS management.

This case report proves that BS does not always present with a sun-sensitive facial skin rash. Awareness of this phenotypic variability without the “hallmark” feature of BS could prevent a delay in diagnosis.

Authors’ contribution

Margarida Almendra: Conceived and designed the study; acquired data from patients, research studies, or literature; analyzed and interpreted data; drafted the article; critically reviewed the article for important intellectual content; gave final approval of the version to be published; agreed to be accountable for the accuracy or integrity of the work. Rosa Pina and Conceição Neves: Critically reviewed the article for important intellectual content; gave final approval of the version to be published; agreed to be accountable for the accuracy or integrity of the work. João Farela Neves: Conceived and designed the study; acquired data from patients, research studies, or literature; analyzed and interpreted data; critically reviewed the article for important intellectual content; gave final approval of the version to be published; agreed to be accountable for the accuracy or integrity of the work. Ana Isabel Cordeiro and Catarina Martins: Acquired data from patients, research studies, or literature; analyzed and interpreted data; critically reviewed the article for important intellectual content; gave final approval of the version to be published; agreed to be accountable for the accuracy or integrity of the work.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Bloom D. Congenital telangiectatic erythema resembling lupus erythematosus in dwarfs. Probably a Syndrome Entity. *AMA Am J Dis Child* 1954;88(6):754-758 2. Flanagan M, Cunniff CM. Bloom Syndrome. In: GeneReviews [Internet], Adam MP, Ardinger HH, Pagon RA, et al. (Eds), University of Washington, Seattle 2019. 3. German J, Sanz MM, Ciocci S, et al. Syndrome-causing mutations of the BLM gene in persons in the Bloom's Syndrome Registry. *Hum Mutat* 2007; 28(8):743- 753.
2. Cunniff C, Bassetti JA and Ellis NA. Bloom's syndrome: clinical spectrum, molecular pathogenesis, and cancer predisposition. *Mol Syndromol* 2017; 8(1): 4-23.
3. Ababou M. Bloom syndrome and the underlying causes of genetic instability. *Molecular Genetics and Metabolism* 133 (2021) 35-48.
4. Larsen NB, Hickson ID. RecQ helicases: conserved guardians of genomic integrity. *Adv Exp Med Biol* 2013.767: 161-184.
5. Lu H, Davis AJ. Human RecQ Helicases in DNA Double-Strand Break Repair. *Front Cell Dev Biol*. 2021;9:279.
6. Ellis NA, Groden J, Ye TZ, Straughen J, Lennon DJ, Ciocci S et al. The Bloom's syndrome gene product is homologous to RecQ helicases. *Cell* 1995 Nov 17;83(4):655-66.
7. Chaganti RS, Schonberg S, German J. A many fold increase in sister chromatid exchanges in Bloom's syndrome lymphocytes. *Proc. Natl. Acad. Sci*. U. S. A. 71 (11) (1974) 4508-4512.
8. German J. Bloom's syndrome. XX. The first 100 cancers. *Cancer Genet Cytogenet* 1997;93:100.
9. Boduroglu K, Tuncbilek E. 1999. Two siblings with Bloom's syndrome exhibit different clinical features: possible effect of sex. *Turk J Pediatr* 41(1):107-111
10. Vojtkova J, Ciljakova M, Jesenak M, Misovicova N, Banovcin P. 2016. Bloom syndrome without typical sun-sensitive skin lesions in three Slovak siblings. *Int J Dermatol* 55(6):687-690.
11. Vekaria R, Bhatt R, Saravanan P, de Boer RC. 2016. Bloom's syndrome in an Indian man in the UK. *BMJ* Case Rep 2016.
12. A. Bouman, S. van Koningsbruggen, M.Bariş. Karakullukcu, W.H. Schreuder, P. Lakeman. Bloom syndrome does not always present with sun-sensitive facial erythema, *European Journal of Medical Genetics* (2017), doi: 10.1016/j.ejmg.2017.10.010
13. Chavez-Alvarez S, Villarreal-Martinez A, Velasco-Campos MR, Moreno-Veja I, Martinez-de-Villareal LE, Herz-Ruelas M, et al. Bloom syndrome sans characteristic facial features in a Mestizo patient – a diagnostic challenge. *Indian J Dermatol Venereol Leprol* 2019;85:130. 16 – Gönenc II, Elcioglu NH, Martinez Grijalva C, et al. Phenotypic spectrum of BLM- and RMI1-related Bloom syndrome. *Clinical Genetics*. 2022; 101(5-6):559-564. doi:10.1111/cge.14125
14. German J, Bloom D, Passarge E. 1984. Bloom's syndrome XI. Progress report for 1983. *Clin Genet* 25(2):166-174.
15. German J, Takebe H. 1989. Bloom's syndrome. XIV. The disorder in Japan. *Clin Genet* 35(2):93-110.
16. Shah H, Sheth FJ, Pandit VS, Langanecha B. Bloom syndrome: report of two cases in siblings. *International Journal of Dermatology* 2013, 52, 990-992. 20 – Tayebi N, Khodaei H. Bloom's syndrome in a 12-year-old Iranian girl. *Indian Journal of Human Genetics* September-December 2008 Volume 14 Issue 3, 103-105.
17. German J, Roe AM, Leppert MF, Ellis NA. Bloom syndrome: an analysis of consanguineous families assigns the locus mutated to chromosome band 15q26.1. *Proc Natl Acad Sci USA*. 1994;91:6669-6673.
18. Meetei AR, Sechi S, Wallisch M, Yang D, Young MK, Joenje H et al. A multiprotein nuclear complex connects Fanconi anemia and Bloom syndrome, *Mol. Cell. Biol*. 23 (10) (2003) 3417-3426.
19. K.A. Manthei, J.L. Keck, The BLM dissolvasome in DNA replication and repair, *Cell. Mol. Life Sci*. 70 (21) (2013) 4067-4084.
20. Martin CA, Sarlós K, Logan CV, Thakur RS, Parry DA, Bizard AH et al. Mutations in TOP3A Cause a Bloom Syndrome-like Disorder. *Am J Hum Genet*. 2018;103(2):221-231. doi:10.1016/j.ajhg.2018.07.001
21. Hudson DF, Amor DJ, Boys A, Butler K, Williams L, Zhang T et al. Loss of RMI2 Increases Genome Instability and Causes a Bloom-Like Syndrome. *PLoS Genet*. 2016;12(12):1-24. doi:10.1371/journal.pgen.1006483
22. Meetei AR, Sechi S, Wallisch M, Yang D, Young MK, Joenje H, et al. A multiprotein nuclear complex connects Fanconi anemia and Bloom syndrome. Mol. Cell. Biol. 23 (10) (2003) 3417–3426.
23. Manthei KA, Keck JL. The BLM dissolvasome in DNA replication and repair. Cell. Mol. Life Sci. 70 (21) (2013) 4067–4084.
24. Martin CA, Sarlós K, Logan CV, Thakur RS, Parry DA, Bizard AH, et al. Mutations in TOP3A Cause a Bloom Syndrome-like Disorder. Am J Hum Genet. 2018;103(2):221-231. doi:10.1016/j.ajhg.2018.07.001
25. Hudson DF, Amor DJ, Boys A, Butler K, Williams L, Zhang T, et al. Loss of RMI2 Increases Genome Instability and Causes a Bloom-Like Syndrome. PLoS Genet. 2016;12(12):1-24. doi:10.1371/journal.pgen.1006483