OMCR

Oxford Medical Case Reports, 2018;12, 414–418

doi: 10.1093/omcr/omy096
Case Report

CASE REPORT

Bloom syndrome with myelodysplastic syndrome that was converted into acute myeloid leukaemia, with new ophthalmologic manifestations: the first report from Syria

Sara Aljarad[1], Ahmad Alhamid[2,*], Ahmad Rami Rahmeh[2], Abdelaziz Alibraheem[2], Abdulsamad Wafa[3], Walid Alachkar[3], Ziad Aljarad[4,*] and Ghasan Aziz[1]

[1]Department of Hematology, Faculty of Medicine, University of Damascus, Damascus, Syria, [2]Faculty of Medicine, University of Aleppo, Aleppo, Syria, [3]Chromosomes Laboratory, Human Genetics Division, Molecular Biology and Biotechnology Department, Syrian Atomic Energy Commission, Damascus, Syria, and [4]Department of Gastroenterology, Faculty of Medicine, University of Aleppo, Aleppo, Syria

*Correspondence address. Department of Gastroenterology, Faculty of Medicine, University of Aleppo, Aleppo, Syria. Tel: +963 988 666 282; E-mail: dr.ziad-aljarad@hotmail.com

Abstract

Bloom syndrome is a rare autosomal recessive disease, in which BLM gene is mutated, leading to genome instability and proneness to malignancy. It is characterized by short stature, sun-sensitive rash and immunodeficiency. We present a case of bloom syndrome with myelodysplasia complicated by acute myeloid leukaemia. This case has new ophthalmologic manifestations. We confirmed the diagnosis by detection of high rate of sister chromatid exchange. The patient received chemotherapy but did not tolerate it well and developed fungal pneumonia.

INTRODUCTION

Bloom syndrome (BS) is an autosomal recessive disease caused by a mutation in the BLM gene (chromosome 15q26). Since BLM gene encodes the protein RecQ DNA helicase which is responsible for DNA repair, BS is considered a genome instability syndrome, associated with high predisposition to malignancy [1]. BS was first discovered in 1954 by the dermatologist David Bloom [2]. This syndrome is characterized by the following features: short stature, sun sensitivity, immunodeficiency and cancer proneness. It has many other manifestations [3]. The Bloom's Syndrome Registry is a cooperative effort in clinical and basic scientific investigation between a certain small group of human geneticists and BS patients [4]. In this article, we report a new case of this syndrome. The patient is a 22-year-old Syrian man. It is the first case report of this disease in Syria. Our patient developed myelodysplasia, which was converted into acute myeloid leukaemia (AML), something not common among BS patients [3]. This case has new ophthalmologic manifestations that are not previously mentioned in the medical literature. Karyotype revealed numerous abnormalities. We

Received: March 20, 2018. **Revised:** July 18, 2018. **Accepted:** September 3, 2018

confirmed the diagnosis by detecting a high rate of sister chromatid exchange (SCE).

CASE REPORT

A 22-year old, Syrian, Caucasian, university student male presented to Al-Mouwasat Hospital in Damascus with a recurrent fever started 15 days before admission. Vomiting accompanied the fever during the first 2 days. The patient also presented with aphthous ulcers, fatigue, polyuria and polydipsia. He had no anorexia or significant weight loss. His parents reported a low birth weight, but they could not remember the exact weight. He had a sparse subcutaneous tissue through his infancy and childhood. Also, his parents noticed anorexia during infancy. He had a short stature and high-pitch voice that had been studied in his infancy without discovering the reason behind them. He had undescended testis, and orchiopexy was successfully performed at the age of 10. The patient had always been suffering from recurrent chest and middle ear infections. Furthermore, he complained of gastroesophageal reflux disease (GERD) started 8 years ago and continued until now. His parents are consanguineous. His father is a type 2 diabetic, and his mother is hypertensive. Interestingly, his sister has a proportionate short stature and the same disordered facial appearance of the discussed patient.

The patient takes augmentin (amoxicillin clavulanate) 1 g (1 × 2), cefixime 400 mg (1 × 1), paracetamol (1000 mg) when he has fever. He also takes omeprazole (20 mg) to relieve GERD Symptoms. The patient lives in a rural area and he does not smoke or drink alcohol.

Physical examination showed a low weight (33 kg) and a proportionate short stature (146 cm), and the BMI was (15.48 kg/m^2). Vital signs were all normal except for tachypnoea with a respiratory rate RR of (26 breath/min). His temperature at admission was (37.5°) measured axillary. Head and neck examination revealed, he had an elongated head (dolichocephaly), a prominent nose, and there was pallor of conjunctiva with no scleral icterus. He had lateral strabismus and amblyopia in his right eye, and ectropion of inferior eyelids in both eyes. The pupils were morphologically normal and responded to light normally, The lens was normally located, the transparent media of the eye were clear and did not contain opacities, and the fundus was normal. We noticed sun-sensitive malar butterfly rash on nose and cheeks with telangiectasias (Fig. 1). His parents reported that the sun-sensitive malar butterfly rash started in infancy. He had cheilitis with peeling vesicles and had an originally absent upper incisor. On his trunk, we detected several hypopigmented areas, café-au-lait lesions and telangiectasia on his upper chest. There were no enlarged or palpated lymph nodes in his whole body. There was no purpura or petechiae, but he had recurrent epistaxis. Other systems were normal on examination, except for decreased breath sounds without crackles or wheezing.

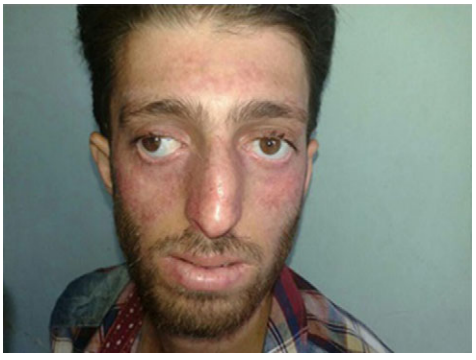

Figure 1: Dolicocephaly, ectropion of inferior eyelids, right lateral strabismus, right amblyopia, malar rash and blistered fissured lower lip.

Chest X-ray showed no abnormality and urine microscopic and strip analysis was normal. ECG was normal. A complete blood count (CBC), serum chemistry and blood coagulation tests were performed and revealed the following abnormal values: glucose (237 mg/dL), haemoglobin (6.4 g/dL), haematocrit (18.9%), mean corpuscular volume MCV (85 fL), platelets (19 × 10^3/mL), LDH (692 IU/L), ALP (273 IU/L), C-reactive protein CRP (145 mg/dL), ESR (105 mm/h). WBCs count was normal at admission. Tuberculin and QuantiFERON tests were negative. antineutrophil cytoplasmic antibodies (ANCA) and antinuclear antibodies (ANA) were negative, and rheumatoid factor (RF) was normal. Spirometry was done and FEV1/FVC = 75%. Fever, epistaxis, bicytopenia, elevated CRP and ESR, hyperglycaemia, low weight, short stature and abnormal facial appearance stimulated us to do further investigations. We have diagnosed type I diabetes mellitus by islet cell antibodies test. GH, testosterone, FSH and LH levels were all normal. Azoospermia was also detected in the patient. Peripheral blood smear was done to study the bicytopenia detected by CBC. Hypochromic microcytic anaemia, anisocytosis, spherocytosis, elliptocytes and tear drop blood cells were detected by microscopic examination of blood smear. There was also giant platelets and hyposegmented granulocytes.

We performed flow cytometry of bone marrow (BM) aspiration. We detected an inversion of CD4/CD8 ratio and 6% myeloblasts. BM examination showed hypercellular BM. We detected multilineage dysplasia like dysplastic erythroid lineage and dismegakaryopoiesis. Iron stain revealed several ringed sideroblasts. The findings of histopathological examination and flow cytometry are consistent with myelodysplastic syndrome with excess blasts 1 (MDS EB1). Serum protein electrophoresis showed reduction in immunoglobulins. Immunoglobulins quantification revealed low IgG (4.68 g/L) and normal IgM and IgA.

These features are consistent with BS. MRI of abdomen and pelvis was done without abnormalities. After platelets transfusion, we did colonoscopy, to exclude colon cancer which is common among BS patients; it revealed no abnormalities.

The patient received 90 mg of 5-azacitidin daily for a week and the patient showed good improvement. He developed a fever again after 20 days. Examination of BM revealed 40% blasts, which suggested transformation to AML, so 5-azacitidin was replaced with cytarabine (120 mg) for 5 days, then doxorubicin (50 mg) for 2 days.

SCE was performed, and analysis of 100 cells showed an average of 73 SCE/cell, while the control showed 5 SCE per normal cell (Fig. 2).

BM *in vitro* cellular culture revealed the following karyotype: 43, -X, Y, −1 x(2), −3, −8, −9 x(2), del(5q), del(6q), del(7q), del (12q), −19 x(2), +21, +22, +4mar[70%] and 46, XY normal [30%].

After one week of chemotherapy, the patient developed high fever and severe BM suppression without evident infectious cause. We put the patient on broad-spectrum antibiotics without any benefit. After 4 days, the patient had dyspnoea, hypoxaemia and low urinary output. We put the patient on ceftazidime and vancomycin, but he did not show any improvement. After 3 days, we added amphotericin B, which improved the patient symptoms significantly. As BS patients are prohibited form X-ray imaging and considering the lack of suitable diagnostic tools; we made a clinical diagnosis of fungal pneumonia.

the patient became stable, was on antibiotics, as on insulin for his diabetes and all necessary medical care was given to the patient in the hospital. After 2 months, he developed pancytopenia with blasts. We put him on subcutaneous cytarabine 100 mg twice a day for 5 days as a palliative treatment without any improvement. He developed a cellulitis in his arm with high fever. We tried to treat it with antibiotics and blood transfusion but he died after one month. He has lived only 8 months since we diagnosed the syndrome, and died at the age of 23 years.

DISCUSSION

BS is an autosomal recessive disease, caused by mutation in the gene designated as BLM, traced to the chromosome band 15q26. BLM gene encodes a RecQ DNA helicase that is important for DNA repair, mutations of this gene lead to genome instability [1]. Clinical characteristics of BS patients manifest only in homozygous persons, while heterozygous carriers are asymptomatic. BS occurs rarely in all ethnic groups, with <300 cases registered in the BS Registry until 2016, but is more prevalent in Ashkenazi Jews [3], with a heterozygote prevalence of 1:110, and a disease prevalence of 1/48000 [5, 6].

Low birth weight, sparse subcutaneous tissue, wasted appearance and short stature of the reported patient define the most impressive clinical feature of BS which is pre- and post-natal growth deficiency [3]. GH deficiency was excluded. The BS facial appearance is characterized by small cranium, underdeveloped malar and lower mandibular areas and relatively prominent nose and ears [3]. Many ophthalmologic abnormalities were reported in the literature. The reported abnormalities of the eyelids include: Café au lait lesion, sun-sensitive telangiectatic erythema and madarosis. The reported abnormalities of the conjunctiva include bulbar conjunctival telangiectasia and conjunctivitis. Narrow angles and Sectoral iris pigment alteration are reported abnormalities of the anterior chamber and iris, respectively. Lens opacities were reported. The reported abnormalities of the retina include early-onset drusen, unilateral retinoblastoma, non-proliferative diabetic retinopathy and leukaemic retinopathy. Bilateral hypoplasia of the optic nerve was also reported [7–10]. To our knowledge, this is the first report of lateral strabismus (unilateral) and ectropion (bilateral) in a BS patient. The absence of upper lateral incisor and high-pitched voice are also characteristics of BS patients [3, 11]. A child with BS characteristically shows a lack of interest in nursing, and then in eating. In a minority of infants with BS, nursing and eating are normal [3]. Parents of the discussed patient, however, reported a normal nursing but anorexia in early childhood. The patient had also a cryptorchidism (undescended testis), which can be found in BS male patients [12, 13]. BS patients show skin lesions including sun-sensitive erythematous rash (butterfly rash) on nose and cheeks with or without telangiectasia, blistered and fissured lower lip, café-au-lait macules, and hypopigmented areas of skin. BS patients are usually immunodeficient [3], where plasma concentration of one or more of immunoglobulins is low. IgG in our case was low but IgA and IgM were normal. BS has serious complications, including lower urinary tract obstruction in men and chronic obstructive pulmonary disease (COPD) [3]. The first one was excluded by clear history and normal physical examination, and the latter was excluded by chest x-ray and spirometry (FEV1/FVC = 75%). GERD is also seen in BS patients [3]. BS patients experience recurrent chest and middle ear infections due to immunodeficiency and repeated micro-aspirations in GERD patients [3]. Another complication is diabetes mellitus that was diagnosed in 17.7% of BS registry patients at a mean age of 26 years [3]. Infertility is a BS complication seen in appropriately examined men, but women are usually fertile [3]. Our patient has azoospermia.

Figure 2: Increased sister chromatid exchange. Test (left) and control (right).

BS patients tend to develop malignancies as a result of excessive genomic instability. Cancer is the most common medical complication and the most common cause of death in BS patients [3]. Our patient was diagnosed with myelodysplasia,

Table 1: Prevalence and age distribution of the 207 malignant neoplasms diagnosed in 131 persons in the Bloom's Syndrome Registry, 1954–2016

Anatomic sites/types		Mean age at diagnosis (range)	Number
Epithelial (carcinoma)	Lower enteric tract	35.0 (16–49)	31
	Integument	31.7 (18–46)	27
	Upper entero/respiratory tract	37.8 (25–48)	22
	Genitalia and urinary tract	16.6 (<1–43)	17
	Breast	35.8 (21–48)	16
	Lower respiratory tract	33.0 (26–40)	9
	Liver	15.0	1
Lymphoid	Lymphoma	21.7 (4–49)	35
	Acute lymphoblastic leukaemia	19.6 (5–40)	12
Hematopoietic	Acute myelogenous leukaemia	18.1 (2–47)	26
Other	Connective tissue (sarcoma)	16.3 (4–30)	4
	Germ-cell	24.0 (22–26)	2
	Central nervous system (brain)	3.0	1
	Retinoblastoma	1.0	1
	Primary site unidentified, metastatic	33.7 (28–33)	3
All		26.6 (<1–49)	207

and this explains the fever of unknown origin in this patient. Myelodysplastic syndromes (MDS) are malignant hematopoietic stem-cell diseases that are characterized by disturbances of differentiation and maturation. The presence of bi- or pancytopenia is a 'red-flag' for MDS [13]. The diagnosis was confirmed by flow cytometry and histopathologic study of BM aspiration. MDS was detected in 23 of 272 patients in the registry (8.45%) [3]. Myelodysplasia in the reported patient was converted into AML. This conversion happened in at least 7 of the 23 patients diagnosed with MDS in the registry [3]. Table 1 shows the prevalence and age distribution of the 207 malignant neoplasms diagnosed in 131 Persons in the Bloom's Syndrome Registry, 1954–2016 [3].

Studying of peripheral blood culture revealed a high rate of chromatid breaks, but that does not distinguish BS from other growth deficiency and chromosomal instability, including the following: Fanconi anaemia, Ataxia-telangectesia, Ataxia-telangectesia-like disorder, Werner syndrome and Nijmengen breakage syndrome. The excessive number of SCE, which is specific for BS [3], confirmed the diagnosis.

The patient was put on 90 mg of 5-azacitidine daily for a weak to treat myelodysplasia, but was stopped because of developing AML. The 120 mg cytarabine for 5 days and 50 mg doxorubicin for 2 days were applied as a chemotherapy for AML which is called (5 + 2) protocol. A (5 + 2) protocol was preferred over (7 + 3) protocol considering the impaired tolerance in BS patients. However, using the attenuated protocol did not protect the patient from developing fungal infection.

The patient died at the age of 23 years. The 26 years is the mean age at death among the 62 male BS patients from whom data are available for the registry [14].

We could not investigate his sister, who has a short stature and the same facial appearance, because of the local traditions that make it difficult to diagnose a genetic disease in a girl. Parents have worries that no one will get married of their daughter and their female relatives if she is diagnosed with this syndrome.

As a conclusion, BS and the other genome instability syndromes should be considered in the differential diagnosis of growth retardation despite their rarity. This will help with early detection, and then preventing the patient from X-ray imaging and extended sun exposure, doing periodic screening for malignancy detection, adequate managing of their recurrent infections adequately, and putting patients in special learning programs that take into account their diminished mental abilities. Doctors should always be aware of rare manifestations and complications of the disease, report and publish them, like loss of an upper incisor, the new ophthalmologic signs mentioned above and developing of MDS complicated by AML as in our case. BS may mimic other genome instability syndromes. The differential diagnosis can only be made by detecting high rate of SCE. This is the first report of BS from Syria. Many obstacles make the diagnosis of such syndromes difficult in our country. First, genetic and molecular tests are often not available, leading to failure in detection of many genetic diseases. We hope that health organizations help with providing Syrian health centres with these tests and train staff on using them. Second, social causes that make people afraid of diagnosis of genetic disorders in their families, especially in females. Finally, practicing physicians and medical education in Syria are not aware of this extremely rare syndrome. So, this syndrome should be considered more seriously while practicing medicine in Syria. More research should be made to develop special chemotherapy protocols for BS patients since their tolerance is weak.

CONFLICT OF INTEREST STATEMENT

None declared.

FUNDING

There is no funding.

ACKNOWLEDGEMENT

To Salam Rajjoub, MD, Clinical Instructor of Medicine, School of Osteopathic Medicine, West Virginia; for critical revision and proofreading of the article. To Aos Alhamid, a medical student, University of Aleppo, Faculty of Medicine; for Technical support.

PATIENT CONSENT

A written informed consent was obtained from the patient

REFERENCES

1. 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;**83**:655–66.
2. Bloom D. Congenital telangiectatic erythema resembling lupus erythematosus in dwarfs; probably a syndrome entity. *Am J Dis Child* 1954;**88**:754–8.
3. Sanz MM, German J, Cunniff C. Bloom's syndrome, 2006 In. Adam MP, Ardinger HH, Pagon RA, *et al*, eds. *GeneReviews® [Internet]*. Seattle (WA): University of Washington, Seattle; 1993–2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1398/.
4. Weill Cornell Medical Center | Bloom's Syndrome Registry, Weill Cornell Medical College. pre.weill.cornell.edu/bsr/.
5. Shahrabani-Gargir L, Shomrat R, Yaron Y, Orr-Urtreger A, Groden J, Legum C. High frequency of a common Bloom syndrome Ashkenazi mutation among Jews of Polish origin. *Genet Test* 1998;**2**:293–6.
6. Roa BB, Savino CV, Richards CS. Ashkenazi Jewish population frequency of the Bloom syndrome gene 2281 delta 6ins7 mutation. *Genet Test* 1999;**3**:219.
7. Bhisitkul RB, Rizen M. Bloom syndrome: multiple retinopathies in a chromosome breakage disorder. *Br J Ophthalmol* 2004;**88**:354–357.
8. Aslan MD, Őztűrk G, Kaya Z, Bideci A, Ozdogãan S, Ozdek S, *et al*. Early-onset Drusen in a girl with Bloom syndrome: probable clinical importance of an ocular manifestation. *Pediatr Hematol Oncol* 2004;**26**:256–7.
9. Cefle K, Ozturk S, Gozum N, Duman N, Mantar F, Guler K, *et al*. Lens opacities in Bloom syndrome: case report and review of the literature. *Ophthalmic Genet* 2007;**28**:175–8.
10. Jian-Bing W, Cheng-Rang L, Yi-Ping M, Sheng N, Hui L, Lin L. A case of Bloom syndrome with uncommon clinical manifestations confirmed on genetic testing. *Cutis* 2016;**97**:E10–13.
11. Bloch-Zupan A, Sedano HO, Scully C. Missing teeth (hypodontia and oligodontia). In: *Dento/Oro/Craniofacial Anomalies and Genetics* 2012,9–74. doi:10.1016/b978-0-12-416038-5.00002-0.

12. Gretzula JC, Hevia O, Weber PJ. Bloom's syndrome. *J Am Acad Dermatol*. 1987;**17**:479–88.
13. Germing U, Kobbe G, Haas R, Gattermann N. Myelodysplastic syndromes: diagnosis, prognosis, and treatment. *Dtsch Arztebl Int* 2013;**110**:783–90.
14. 'Data from the Bloom's Syndrome Registry, 2009.' *Weill Cornell Medical Center | Bloom's Syndrome Registry*, Weill Cornell Medical College. pre.weill.cornell.edu/bsr/data_from_registry/.