Diagnosis of Bloom Syndrome in a Patient with Short Stature, Recurrence of Malignant Lymphoma, and Consanguineous Origin

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Abstract

Bloom syndrome is an autosomal recessive disorder characterized by prenatal and postnatal growth deficiency, photosensitive skin changes, immune deficiency, insulin resistance, and a greatly increased risk of early-onset cancer and development of multiple malignancies. Loss-of-function variants of the \textit{BLM} gene, which codes for a RecQ helicase, cause Bloom syndrome. We report a consanguineous family, with 2 siblings showing clinical signs of suspected chromosome breakage disorder. One of them developed recurrent malignant lymphoma during lifetime. We performed next-generation sequencing analysis, focusing on cancer predisposition syndromes. We identified a homozygous pathogenic nonsense variant c.1642C>T (p.Gln548\(^*\)) in the \textit{BLM} gene in the proband, associated with Bloom syndrome. Sanger sequencing validated the presence of a homozygous pathogenic variant in the proband and also in the brother with short stature. In this article, we will focus on the clinical presentation of the syndrome in this particular family as well as the characteristics of malignancies found in the proband.
Seemanová et al., 2002]. Recurrent founder mutations are present in individuals with Bloom syndrome, notably the $BLM^{Ash}$ mutation [German et al., 2007; Kaseb and Hozayen, 2019] and c.1642C>T in the Slavic population [Sokolenko et al., 2012; Prokofyeva et al., 2013]. Bloom syndrome has an estimated risk of malignancy around 40–50% [Foretová and Petraková, 2019]. There is a wide variety of cancer types and anatomic sites in patients with Bloom syndrome. Cancer typically occurs at a younger age and might be recurrent. Hematologic malignancies (acute myeloid leukemia, acute lymphoblastic leukemia, and lymphoma) are the most common malignancies in individuals with Bloom syndrome. Among solid tumors, digestive tract cancers are the most common, particularly adenocarcinoma of the upper and lower intestinal tract. Squamous cell carcinomas of the head and neck as well as breast cancer have also been frequently reported. In addition to common malignancies, persons with Bloom syndrome have an excess of rare cancers, particularly Wilms tumor [Cairney et al., 1987; Berger et al., 1996]. Although there is currently no treatment for the underlying genetic abnormality, persons with Bloom syndrome benefit from sun protection, aggressive treatment of infections, surveillance for endocrinopathies, and early identification of cancer [Cunniff et al., 2017; Flanagan and Cunniff, 2019].

**Case Report**

**Personal History**

We report a female patient with short stature and facial dysmorphism (Fig. 1). She had a medical history of failure to thrive, dermatological symptoms (café-au-lait spots, keratosis pilaris, and onychodystrophy), hypothyreosis, premature ovarian failure, persistent bronchial asthma, bronchiectasis, and recurring episodes of pneumonia during her childhood and adolescence.

**Manifestation of First Malignancy**

At the age of 15, the patient was diagnosed with non-Hodgkin lymphoma. Few data are available due to the patient’s treatment in
the year 1998. The disease was classified as centroblastic B-cell non-Hodgkin lymphoma of the neck and nasopharynx. The treat-
ment was administered per NHL-BFM 95 protocol and consisted of vincristine, etoposide, cytarabine, ifosfamide, cyclophosphamide, prednisolone, and doxorubicin with concomi-
tant intrathecal applications of chemotherapy. The final assess-
ment confirmed complete remission.

Manifestation of Second Malignancy

In December 2017, the proband was admitted to the surgical
department because of abdominal pain, intussusception, and
suspicions of tumor in the cecum per imaging procedures. She
complained about 2–3 months of nonspecific gastrointestinal
problems, cramps, obstipation, and 2 kg weight loss. Her actual
weight was only 29 kg, height was 140 cm, and BMI was 14.8 kg/
m² per duBois formula. The patient also referred to previous sus-
picions of celiac disease. Laparotomic hemicolectomy with termi-
nal ileostomy was performed, and a 45-mm tumor in the cecum
was removed together with 12 regional mesenteric lymph nodes.
Histopathological evaluation of the involved tissues (tumor, bowel, mesenteric lymph nodes) was performed by the experi-
enced pathologist with the conclusion of high-grade B-lympho-
ma, not otherwise specified, possibly Burkitt-like lymphoma with
11q aberration. The clinical stage was II AE per Ann Arbor clas-
sification, aaIPI 1 (LDH level 4.59 slightly above normal range).
Microscopically, the tumor consisted of medium-sized immuno-
blasts and centroblasts with high mitotic activity, Ki67 80–100%.
Immunophenotyping of malignant cells showed positivity on
CD20, CD10, bcl-6, MUM-1 and MYC, and negativity on CD3,
bcl-2, CD5, cyclin D1 and CD30. Due to her poor nutritional
status, radical surgical resection of the involved tissues, low-risk
aaIPI, and a lack of therapeutic guidelines in such cases, we ad-

Fig. 2. Picture of the sibling with short stature and facial dysmorphism. Note the prolonged face, abnormal chin, and high forehead.
ministered “standard” combined chemotherapy regimen consisting of 6 R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) cycles with respect to cumulative doses of anthracyclines used before and initial omission of vincristine. One more single agent rituximab was administered in May 2018. The whole treatment was not accompanied by significant adverse events, and the final restaging PET/CT scan was evaluated as complete remission of the lymphoma. In June 2018, terminal ileostomy was canceled. So far, the patient remains in complete remission more than one year after treatment completion. The main ongoing problem is severe malnutrition, weight 27.5 kg and BMI 14.0 kg/m².

Family History
The brother of the proband also displayed short stature and facial dysmorphism (Fig. 2). He was diagnosed with growth restriction, pubertas praecox, retention of testes, and telangiectasias on sun-exposed areas. There was no history of cancer or other difficulties. The parents of the siblings were consanguineous, with a potential carrier of the founder mutation, originating from the east Ukraine/Russian region (Fig. 3). There was a sporadic occurrence of solid cancer in the pedigree, not segregating with obligate carriers.

Methods and Results
Mutational Screening and Confirmation
A homozygous pathogenic variant c.1642C>T (p.Gln548*) in the *BLM* gene (NM_000057.3) was detected in the proband (Fig. 4). This variant results in a premature termination codon predicted to cause a truncated or absent BLM protein due to nonsense-mediated decay. The variant is classified as pathogenic – class 5, according to ACMG/AMP standards and guidelines [Richards et al., 2015; Kleinberger et al., 2016]. The presence of the pathogenic variant was confirmed by Sanger sequencing (Fig. 5).

Predictive testing was performed in the male sibling. Testing by Sanger sequencing confirmed the presence of a homozygous c.1642C>T pathogenic variant in the *BLM* gene.

Cytogenetic Studies
Samples from the proband and her brother were studied by conventional karyotyping, followed by chromosome breakage analysis. Cytogenetic study determined a normal female karyotype (46,XX) in the proband and a normal male karyotype (46,XY) in her brother. Acquired chromosomal aberrations were present in 27% of all metaphase nuclei in the proband, and in 7% in her brother, respectively (Fig. 6, 7).
Discussion

In this report, we describe a 35-year-old woman with Bloom syndrome. She presented with short stature, facial dysmorphism, premature ovarian failure, endocrine abnormalities, lung involvement, and recurrent malignant lymphoma at 15 and 34 years. At the time of the second oncological diagnosis, we considered other chromosome instability syndromes, notably Nijmegen breakage syndrome, Werner syndrome, and ataxia telangiectasia. Other RecQ-related disorders: Rothmund Thomson, RAPADILINO, and Baller Gerold syndrome, associated with RECQL4 pathogenic variants, and disorders caused by pathogenic variants in RMI1, RMI2, and TOP3A heli-case genes (OMIM 610404, 612426, and 618097) were also considered (for phenotypic comparison, and see Table 1).

According to medical records, in the year 2000, the proband tested negative for the c.657del5 NBN pathogenic variant, and positive for chromosomal instability. Definitive diagnosis of Bloom syndrome was confirmed only after the identification of a homozygous c.1642C>T pathogenic variant in the BLM gene. These results were consistent with consanguineous origin, identifying a probable founder from Slavic East-Europe in the pedigree.

The treatment with immunochemotherapy was started without prior knowledge of NGS results. Therefore, it was tailored more to the clinical and nutritional state of the patient than genetics. Standard combined chemotherapy regimen with curative intent was used, consisting of 6 R-CHOP cycles with initial omission of vincristine.
Fig. 6. Metaphase nuclei of the proband showing acquired chromosomal aberrations.
The patient experienced no major complications, such as cytopenias or life-threatening infections. In hindsight, a nonintensive regimen was definitely optimal. With prior knowledge of Bloom syndrome diagnosis, an even more moderate treatment, such as Nijmegen protocol with 20% dose reduction [Dembowska-Baginska et al., 2009], could have been used. In the recent reviews, dose reduction up to 50% is recommended [Cunniff et al., 2018]. Some authors report more dramatic toxicity of treatment [Fedhila-Ben Ayed et al., 2016], while others report successful

**Fig. 7.** Metaphase nuclei of the sibling showing acquired chromosomal aberrations. Frequency of breakages is much lower than in the proband.
treatment with similar regimens [Jastaniah, 2017]. Despite generally high treatment response rates in some of the aggressive B-cell lymphomas, relapses can occur, mostly in the first 2–3 years after treatment completion. In the case report as described above, there is not only a high risk of another relapse, but also of secondary malignancies.

Classifications of lymphoid malignancies developed dramatically during the last decades, reflecting morphology, immunophenotype, clinical presentation, cytogenetics, and molecular genetics. During the manifestation of the first malignancy in the 1990s, REAL (Revised European-American Lymphoma) classification was used. The tumor was classified as centroblastic B-NHL. During the manifestation of the second malignancy in 2017, revised WHO classification was used [Swerdlow et al., 2016]. The patient’s lymphoma was classified as high-grade B-lymphoma, not otherwise specified, possibly Burkitt-like lymphoma with 11q aberration. We cannot rule out the possibility of a late relapse because the tumors share some features (presence of centroblasts, sudden onset and aggressivity). However, due to different anatomical locations of onset, we suggest that an entirely new lymphoproliferative disease might have occurred. This could be confirmed only using genome profile expression techniques. Unfortunately, no histological sample was available from the time of first diagnosis.

| Clinical features | Nijmegen breakage syndrome | Werner syndrome | Bloom syndrome | Ataxia telangiectasia | Beller-Gerold | Rotmund-Thompson | RAPADILINO | Helicase disorders: RMI1, RMI2, TOP1A |
|------------------|---------------------------|----------------|----------------|-----------------------|--------------|----------------|-----------|----------------------------------|
| IUG              | +                         | +              | +              | +/−                   | +            | +              | +         | +                                |
| Short stature    | +                         | +              | +              | +/−                   | +            | +              | +         | +                                |
| Microcephaly     | +                         | +              | +              | +/−                   | +            | +              | +         | +                                |
| Facial dysmor-   | Receding mandible, bird-like face | Long and narrow face, retrognathia, micrognathia | +/− | Oxycephaly, turicephaly | Craniostenosis | + | +/− | + |
| lophism          |                           |                |                |                       |              |                |           |                                  |
| Skeletal abnor-  | −                         | −              | −              | −                     | Radial aplasia, ulnar hypoplasia | Frontal bossing, saddle nose, radial ray defects | Radial and patellar aplasia | − |
| malities         |                           |                |                |                       |              |                |           |                                  |
| Skin manifesta-  | Café-au-lait patches, telangiectasia | Café-au-lait patches, malar rash | Café-au-lait patches, malar rash | Café-au-lait patches | − | − | Café-au-lait patches | Mild |
| tions            |                          |                |                |                       |              |                |           |                                  |
| Intellectual dis- | Normal/mild               | −              | −              | −                     | +/−                   | +              | −         | −                                |
| ability           |                            |                |                |                       |              |                |           |                                  |
| Cardiac malfi-   | −                         | −              | −              | −                     | +/−                   | +              | −         | +                                |
| rmations         |                           |                |                |                       |              |                |           |                                  |
| Endocrine dysf-  | +                         | Premature diabetes mellitus | Premature diabetes, hypothyreosis | − | − | − | − | − |
| unction          |                            |                |                |                       |              |                |           |                                  |
| Pulmonary mani-   | Bronchiectasia            | −              | Pulmonary fibrosis, bronchiectasia | − | − | − | − | − |
| festations       |                            |                |                |                       |              |                |           |                                  |
| GIT manifesta-   | −                         | −              | −              | −                     | −                     | −              | −         | −                                |
| tions            |                            |                |                |                       |              |                |           |                                  |
| Neurological ma-  | −                         | −              | −              | −                     | Ataxia, progressive degeneration | −              | −         | −                                |
| nifestations     |                            |                |                |                       |              |                |           |                                  |
| Infertility      | +                         | +              | +              | +                     | −                     | −              | −         | Unknown                          |
| Immune defici-   | +                         | +              | +              | +                     | +/−                   | +              | +         | −                                |
| ency             |                            |                |                |                       |              |                |           |                                  |
| Increased risk of | Lymphomas, leukemias, CNS tumors | Lymphomas, leukemias, breast cancer | Unknown | Unknown | Osteosarcoma, skin cancer | Unknown | Unknown | Unknown |
| malignancy       |                            |                |                |                       |              |                |           |                                  |
| Chromosome insta- | +                         | +              | +              | +                     | −                     | −              | −         | +                                |
| bility           |                            |                |                |                       |              |                |           |                                  |

CNS, central nervous system; GE, gastroesophageal; GIT, gastrointestinal tract; IUG, intrauterine growth restriction.
Our case also demonstrates individual variability in patients with Bloom syndrome, even within a single family. While the proband developed recurrent malignant lymphoma and suffered from multiple endocrine dysfunctions as well as severe underweight, the brother had no major health conditions, apart from increased sensitivity to sun (Table 2). Interestingly, there were significant differences in the rate of spontaneous chromosomal aberrations between the siblings. This could be partially attributed to the genotoxic treatment undergone by the proband. However, more factors (functionality of other gene-repair mechanisms, immune surveillance for cancer) could have caused this difference.

Conclusions

We present a sibling pair with Bloom syndrome with consanguineous origin and recurrence of lymphoid malignancies in the proband. These are among the first reported cases of Bloom syndrome in the Czech Republic. Early diagnosis of similar disorders may lead to early cancer detection and prevention, correct dosage of cytostatic regimens, improved clinical outcomes, and improved life expectancy of affected individuals.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Table 2. Comparison of clinical findings in the female proband and her brother

| Clinical findings                  | Proband                        | Brother                     |
|-----------------------------------|---------------------------------|-----------------------------|
| Short stature                     | Yes                             | Yes                         |
| Microcephaly                      | Yes                             | Yes                         |
| Facial dysmorphism                | Prolonged face, micrognathia, retrognathia, gothic plate, prominent features | Prolonged face, retrognathia |
| Skin manifestations               | Keratosis plaris, café-au-lait spots | Teleangiectasia             |
| Intellectual disability           | No                              | No                          |
| Endocrine dysfunction             | Yes                             | No                          |
| Pulmonary manifestations          | Pulmonary fibrosis, asthma, bronchiectasia | No                  |
| Infertility                       | Primary amenorrhea              | Yes                         |
| Immune deficiency                 | Yes                             | Unknown                     |
| Malignancies                      | Duplicity of malignant lymphoma | No                          |
| Chromosome instability            | 29% aberrant nuclei             | 7% aberrant nuclei          |

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