Bloom’s Syndrome Complicated by Myelodysplastic Syndrome and Multiple Neoplasia

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The patient, a Japanese male born to a highly consanguineous family, was diagnosed as Bloom’s syndrome at the age of 33 when he presented with diabetes mellitus and refractory anemia with excess blasts. Chromosome abnormalities of bone marrow cells included 5q-, -7/7q-, and unusual translocations. During the ensuing years, he developed squamous cell carcinoma of the external auditory meatus, adenocarcinoma of the colon, and squamous cell carcinoma of the tonsil. The patient died of pneumonia at the age of 38. Autopsy revealed intestinal polyposis and hemochromatosis secondary to massive blood transfusions.

Introduction

Bloom’s syndrome (BS) is a rare autosomal recessive disorder characterized by retarded growth, sun-sensitive facial erythema, defective immunity, and cancer proneness (1, 2). Chromosome instability and increased sister chromatid exchange are the hallmark of this syndrome (3, 4). We describe a diabetic BS patient who developed myelodysplastic syndrome and three cancers. This case was reported in a preliminary form before the development of malignancies (5).

Case Report

A 33-year-old Japanese man was admitted to our hospital in December 1985 for evaluation of anemia. He was an offspring of first-cousin marriages through three successive generations (Fig. 1). Three of his five siblings died of unknown cause shortly after birth and one of his two maternal uncles died of stomach cancer. His birth weight was 1,500 g despite a full-term delivery and his growth was always stunted. Sun-sensitive facial erythema first appeared at four months of age. He had repeated respiratory tract and ear infections. Diabetes mellitus was diagnosed at the age of 19 years.

Physical examination on admission revealed a thin small male, 135.5 cm tall, who spoke with a high-pitched voice. He had dolichocephaly with a narrow characteristic facies as illustrated previously (5). The face showed diffuse telangiectasia with areas of pigmentation and depigmentation. Cafe-au-lait spots were distributed over the trunk and extremities. Axillary and pubic hairs were normal but the testes were small. Super-

Fig. 1. Six-generation pedigree of the BS family showing first-cousin marriages (arrowheads) of the parents, grandparents, and great grandparents. The subject of this report is indicated by an asterisk. Squares denote men, circles women, and diagonal bars deceased persons.

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Received for publication October 9, 1992; Accepted for publication March 18, 1993
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Internal Medicine Vol. 32, No. 5 (May 1993) 399

Key words: preleukemia, multiple cancers, diabetes mellitus, hemochromatosis
CD8 ratio of 0.3. Cytogenetic analysis of phytohemagglutinin-stimulated lymphocytes revealed chromosome breaks and 70–80 sister chromatid exchanges per metaphase as previously described (5). Bone marrow aspiration demonstrated 6% myeloblasts and erythroid hyperplasia with multinucleated erythroblasts. Of 20 bone marrow metaphases analyzed, 10 showed a karyotype of 46,XY,-7,-13,+der(13)t(1;13)(q11;p11.1)+mar and the other 10 a normal karyotype. A urine sample contained 300 mg/dl of sugar and the blood glucose was 220 mg/dl. The serum IgG was 780 mg/dl, IgA 440 mg/dl, and IgM 70 mg/dl. Proliferative responses of lymphocytes to phytohemagglutinin and concanavalin A were decreased. A purified-protein-derivative skin test was nonreactive. Serological tests for syphilis, hepatitis B and C viruses, HTLV-I, and HIV-I were all negative.

The patient was diagnosed as having BS, diabetes mellitus, and myelodysplastic syndrome (refractory anemia with excess blasts). Treatment consisted of periodic blood transfusions and control of diabetes mellitus and infections. From that time, he had to be readmitted on several occasions for episodes of pneumonia and progression of pancytopenia. In November 1986, chromosome analysis was repeated on bone marrow cells and all 20 metaphases analyzed had a karyotype of 46,XY,del(5)(q22q33),del(7)(q11.2q22.1),-11,+der(11)t(11;11)(p15;q13),-13,+der(13)t(1;13)(q11;p11.1), indicating that additional chromosome changes had taken place (Fig. 2). In June 1988, biopsy of a crusted lesion of the lower lip showed solar keratosis. In March 1989, while being treated for recurrent otorrhea, a granuloma-like tissue was removed from the left auditory meatus and was found to be a well-differentiated squamous cell carcinoma (Fig. 3). This was successfully treated by radiation therapy with a total dose of 46 Gy. In May 1989, the patient began to have bloody diarrhea and radiographic examination demonstrated a tumor involving the sigmoid colon. Fiberscopic biopsy revealed a moderately differentiated adenocarcinoma. The tumor was resected (Fig. 4) and end-to-end anastomosis was performed. In March 1990, he developed painful swelling of the right cervical lymph nodes and biopsy of the lower pole of the enlarged right tonsil demonstrated a poorly differentiated squamous cell carcinoma (Fig. 5). Due to marked deterioration, however, he was treated symptomatically with morphine sulfate. A repeat bone marrow aspirate showed an increase (20%) of blasts. The total volume of blood transfused over the five years amounted to 32.6 l and the color of the skin had turned to dark gray. The patient died of pneumonia in August 1990.

Autopsy revealed neither residual carcinoma of the external auditory meatus nor relapse or metastasis of the colon cancer. There was a poly (2.8 × 1.7 × 1.0 cm) in the duodenum and several polyps less than 1 cm were found in the colon. Histologically, they were all tubular adenomas. The tonsillar carcinoma directly invaded the tongue and metastasized to the cervical lymph nodes. In addition, massive hemosiderosis was seen in most organs including the liver, spleen, bone marrow, lymph nodes, skin, heart, thyroid, adrenals, and pancreas. The Langerhans' islets were scarcely preserved. The testes were atrophic and lacked spermatogenesis.

**Fig. 2.** Karyotype of a bone marrow cell demonstrating 46,XY,del(5)(q22q33),del(7)(q11.2q22.1),-11,+der(11)t(11;11)(p15;q13),-13,+der(13)t(1;13)(q11;p11.1).
Discussion

The patient reported in this paper exhibited typical clinical and cytogenetic features of BS, but it was not until the age of 33 that the diagnosis of BS was made. Amazingly, family history disclosed parental consanguinity between first cousins in three successive generations down to his parents, although no other family members are known to have had BS. Such a high degree of consanguinity must be exceedingly rare in Japan. The present case is the 11th cytogenetically verified Japanese BS patient and has been accessioned as 132 (HiOka) in the Bloom’s Syndrome Registry (6). The parents of the 11 Japanese cases are consanguineous in four families.

Diabetes mellitus has been diagnosed in 11 of the 130 BS persons in the Bloom’s Syndrome Registry (7). In our patient, diabetes mellitus was diagnosed at the age of 19, long before the first blood transfusion was given at the age of 33. It is likely that frequent blood transfusions over the next five years aggravated the preexisting diabetes mellitus and contributed to the manifestation of hemochromatosis. This is in accord with the clinical course that he was treated initially with sulfonylurea but later became insulin-dependent. Considering the young age, the pathogenesis of diabetes mellitus in BS appears to be BS-related and needs to be clarified.

BS individuals are at increased risk of developing a variety of malignancies, notably leukemias, lymphomas, and carcinomas of various sites. According to the report from the Bloom’s Syndrome Registry, 57 malignant neoplasms were detected in the 130 persons at the mean age at diagnosis of 24.8 years (7). Some of them suffered from multiple primary cancers. The Bloom’s Syndrome Registry includes 15 cases of acute leukemia (seven lymphocytic, six nonlymphocytic, and one biphenotypic), but no cases of myelodysplastic syndrome, although mild or unexplained anemia has been occasionally recorded. It is noteworthy that our patient developed several premalignant and malignant conditions, namely, solar keratosis (precancer) of the lip, refractory anemia with excess blasts (preleukemia), squamous cell carcinomas of the external auditory meatus and tonsil, and adenocarcinoma and benign polyps of the gut. These two squamous cell cancers were histologically distinct and the possibility of one primary with metastasis to another is unlikely. A similar observation of adenocarcinoma and benign polyps of the colon in BS case, 4 (GeHo) (8), suggests that the risk of malignant transformation of intestinal polyposis may be high in BS. Squamous cell carcinomas of the external auditory meatus and tonsil have not been previously listed among BS-associated malignancies.

BS patients are thought to have a defective capacity in DNA repair as shown by chromosome instability and increased sister chromatid exchange. Accumulation of these processes will lead to the development of abnormal karyotypes and cancers of various types. In myelodysplastic syndrome including refractory anemia with excess blasts, chromosome abnormalities such as 5q− and −7/7q− are frequently observed and are regarded as poor prognostic indicators (9, 10). Bone marrow cells from our patient displayed karyotypic evolution from less
complex to complex defects, when studied on two occasions with an interval of 11 months, although no chemotherapy or radiotherapy was given prior to or during this period. The absence of leukemic infiltration in organs studied by autopsy confirmed that there was no progression to an overt leukemia.

Acknowledgments: We thank Dr. Tatsuo Abe, Kyoto Prefectural University of Medicine, for help with chromosome analysis.

References