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Case Report

Surveillance and Treatment of Malignancy in Bloom Syndrome

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ABSTRACT:
We report a patient with Bloom syndrome, a rare autosomal recessive condition characterised by chromosomal instability leading to a high risk of cancer at an early age. The diagnosis should be considered in patients with any cancer of significantly early onset, short stature and a photosensitive lupus-like rash on the face. Diagnostic confirmation is obtained from chromosome studies that show significantly increased numbers of sister chromatid exchanges. There are important management implications, including minimising the use of ionising radiation in surveillance and treatment. Thomas, E. R. A. *et al*. (2008). *Clinical Oncology* 20, 375–379

Key words: Bloom syndrome, cancer genetics, DNA repair defect

Introduction

Bloom syndrome is a rare autosomal recessive condition occurring more commonly in the Ashkenazi Jewish population, due to a high carrier frequency arising from a founder effect. The main features are growth retardation of prenatal onset, with final height generally remaining below 148 cm, a photosensitive rash in a butterfly distribution over the cheeks, similar clinically and histologically to the rash seen in systemic lupus erythematosus, and an increased risk of cancer at an early age. Clinical characteristics include dolichocephaly, prominent ears, micrognathia, malar hypoplasia and a high-pitched voice [1].

The condition is caused by mutations in the *BLM* gene on chromosome 15, which encodes a protein with homology to the RecQ helicases. The absence of BLM activity leads to a DNA repair defect, which causes genomic instability with increased rates of somatic recombination, chromosomal breakage and gene mutation [2]. The diagnostic feature on investigation is significantly increased sister chromatid exchanges.

The profile of cancers seen in Bloom syndrome seems to resemble the spectrum of cancers within the general population (but occurring at a much younger age and higher frequency than expected), which makes it unusual among the cancer-predisposing genetic syndromes, which usually have a well-defined pattern of neoplasia with respect to site and histology. The increased cancer risk is lifelong in patients with Bloom syndrome, although their absolute risk of developing cancer increases significantly in the third and fourth decades. In the first decade, the most common malignancies are rare tumours such as Wilms tumour and osteosarcoma. In the teens and twenties, leukaemias and lymphomas become more common, and the risk of developing a carcinoma at any site (most commonly breast, gastrointestinal tract and skin) is high from the twenties onwards. Second and even third and fourth primary cancers are not uncommon. This increased risk of malignancy leads to a shortened life expectancy, and no patient with Bloom syndrome has yet been reported to have survived into their fifties [3].

Other medical problems frequently seen in Bloom syndrome include type 2 diabetes mellitus, chronic lung disease and immune deficiency, which can lead to life-threatening infections. Male patients are usually sterile, and females have a shortened fertile period, although successful pregnancy has been reported in a number of cases [4]. Abnormal liver function tests have been noted quite frequently, and one patient was found to have sclerosing hyaline necrosis of the liver [5]. A number of ophthalmological complications have been reported, including retinal drusen in childhood, an interesting manifestation of premature aging in this population [6].

It has been suggested that heterozygosity for a Bloom syndrome mutation may lead to an increased risk of developing colon cancer [7]. However, chromosome abnormalities have not been identified in carriers, and other studies have shown no increased risk of cancer in carriers [8].

Case Report

This 41-year-old woman is the youngest of three children of non-consanguineous Ashkenazi Jewish parents. She was

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originally referred to the Growth Clinic at Great Ormond Street Hospital in 1968 at the age of 2 years. She had a birth weight of 1.87 kg (less than 0.4th centile), and she remained small with a bone age delayed by 2 years. Her growth hormone was measured and was normal. She had decreased subcutaneous tissue and some dysmorphic features, including a beaked nose and micrognathia (Fig. 1), as well as dystrophic nails (Fig. 2). She developed very few secondary teeth, a feature shared with her mother, maternal aunt and grandmother and great-grandmother. Her intellectual development was above average, and her general health as a child was good, apart from some minor infections such as chicken pox, infected bites, herpes around her nose, and chronic fungal infection of her toenails. The diagnosis of Bloom syndrome was made in 1978, and confirmed by finding significantly increased sister chromatid exchanges on chromosome examination. She has had a long-standing photosensitive rash on her face, and routinely uses high factor sunscreens. She also has several café au lait macules in the gluteal region. Her final adult height is 129 cm (18 cm below 0.4th centile); her father's height is on the third centile and her mother's on the 10th centile.

In adult life, the patient's first problems arose in her mid-twenties, when she entered an extremely early menopause, and started treatment with hormone replacement therapy. She then went on to develop fibroids, and had a total abdominal hysterectomy and bilateral salpingo-oophorectomy at the age of 35 years.

In her early thirties, the patient developed a number of medical problems, including type 2 diabetes mellitus, a fibroadenoma of the left breast, raised cholesterol, osteoporosis and intermittent viral labyrinthitis. She has lost the sight in her right eye due to diabetic complications. She has been diagnosed with cirrhosis of the liver, having had fluctuating liver enzymes over many years, but further investigations have not established the cause of this. An abdominal ultrasound also showed a left-sided pelvic kidney and probable bilateral small renal angiomyolipomata. She has no evidence of lung disease, and apart from fungal toenail infections, she has not had any problems related to immunodeficiency in adulthood. However, she has had several episodes of urticaria, one thought to be caused by a hogweed allergy and one attributed to penicillin allergy. She has taken regular vitamin C and multivitamin supplements from her mid-twenties, and more recently supplements of vitamins A, C and E for their antioxidant properties, in an attempt to reduce her risk of future neoplasms. She has had influenza and pneumococcal vaccinations with no side-effects, although their efficacy in this condition is not established.

The patient developed her first cancer at the age of 38 years — a basal cell carcinoma on her right upper lip. This was treated successfully by excision. Her second cancer was found on screening colonoscopy at the age of 39 years. She had had six 2—3 mm polyps removed from the transverse colon 2 years previously, with histology showing tubular adenomas with low-grade dysplasia. At repeat colonoscopy, a 10 cm pedunculated polyp was excised from the sigmoid colon and found to have a focus of intramucosal carcinoma, but the ascending and transverse colon could not be visualised due to anatomical problems. Computed tomography of her chest, abdomen and pelvis and magnetic resonance imaging of the pelvis were normal. Proctocolectomy with an ileal pouch was suggested because of the difficulties with colonoscopy and the high risk of further

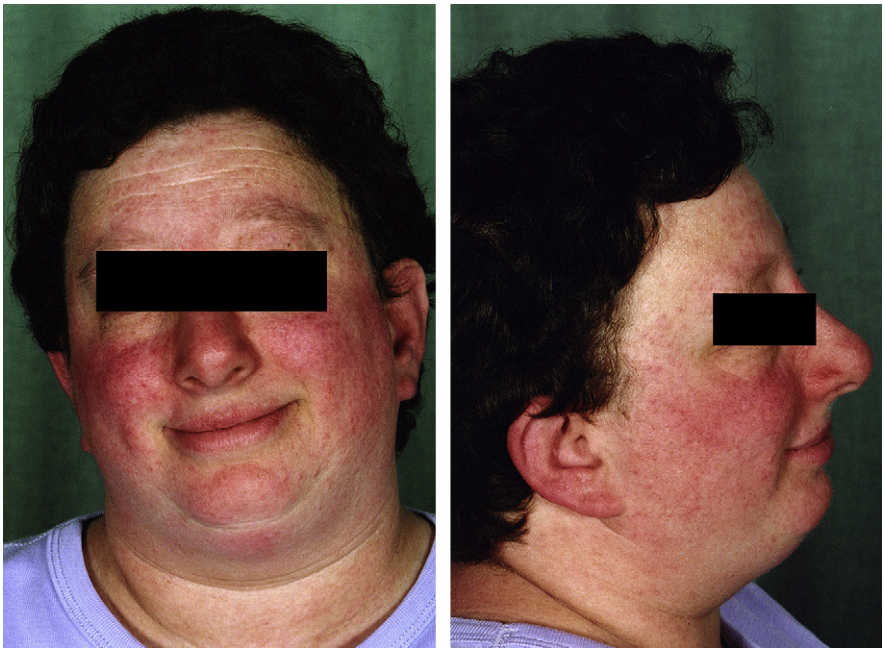

Fig. 1 — Facial features of Bloom syndrome: rash in a butterfly distribution, malar hypoplasia, beaked nose, micrognathia, dolichocephaly.