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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

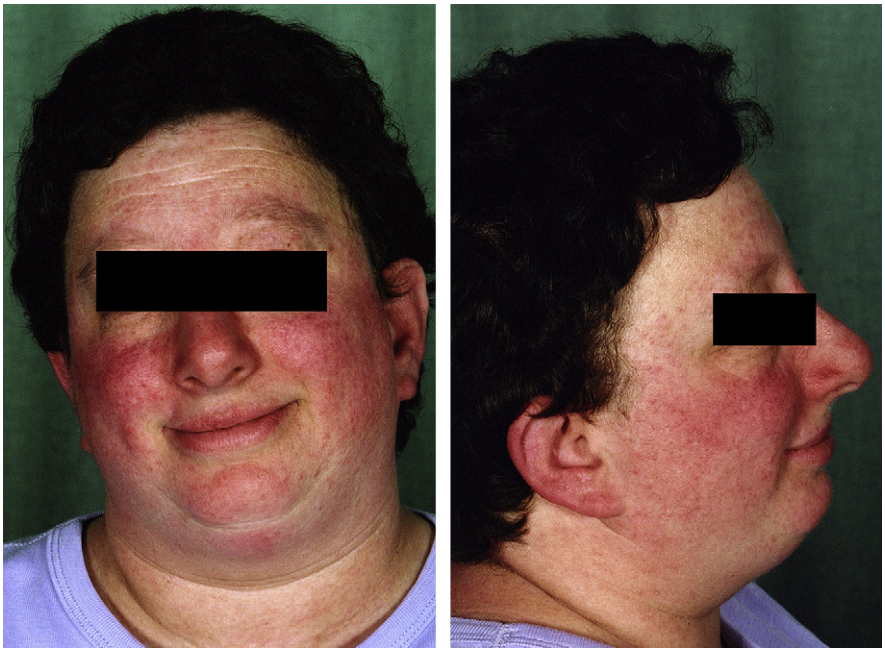

Fig. 1 — Facial features of Bloom syndrome: rash in a butterfly distribution, malar hypoplasia, beaked nose, micrognathia, dolichocephaly.

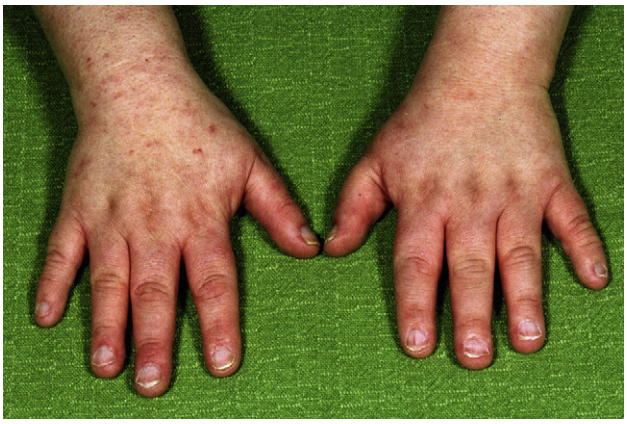

Fig. 2 — Hands of the patient: dystrophic nails.

colonic neoplasms. However, the patient reported a prolonged recovery period of several years after her hysterectomy and was therefore reluctant to undergo further major surgery. She is now being screened with a paediatric colonoscope, which has allowed visualisation of the entire colon. In addition, upper gastrointestinal endoscopy is due to be carried out in the future. Her current screening programme includes annual breast examinations and magnetic resonance imaging, with ultrasound scanning of any abnormal areas identified, annual skin examinations in the dermatology clinic, and annual colonoscopy and upper gastrointestinal endoscopy.

Discussion

The most significant implication of a diagnosis of Bloom syndrome from the patient's point of view is the high risk of developing cancer — so high that the oldest patients in the Bloom syndrome registry (a collection of data on 168 patients diagnosed between 1960 and 1991, collated by Professor German) died at the ages of 46 and 49 years. In many cases the diagnosis is made in childhood during the investigation of growth retardation and dysmorphic features, but a significant minority present for the first time with a malignancy and the diagnosis is made at this stage [3]. The possibility of Bloom syndrome should therefore be considered in all patients with a malignancy of unusually early onset, short stature and a photosensitive lupus-like rash on the face. Cytogenetic analysis looking for increased sister chromatid exchanges can then confirm or refute the diagnosis. Making the diagnosis has important management implications due to the increased risk of malignancy, probable hypersensitivity to chemotherapy and radiotherapy, and also the possibility that patients with Bloom syndrome are more likely to suffer from a range of complications of all treatments due to the other features of the condition, such as immunodeficiency.

The management of patients with Bloom syndrome poses a number of problems. First, due to the rarity of the condition, it is unlikely that any one specialist will be closely involved in the treatment of more than one patient, and there is therefore a lack of an individual with a body of experience in dealing with these patients and their management. Second, the large range of cancers that can occur in the condition (as the spectrum of cancers in Bloom syndrome is similar to that in the general population) makes it difficult to design an effective screening programme, and the need to avoid X-ray screening methods exacerbates this problem. Third, there is a body of anecdotal and molecular evidence (discussed further below) that suggests that patients with Bloom syndrome are hypersensitive to a range of chemotherapeutic agents as well as radiotherapy, and that treatment outcomes are frequently unsatisfactory in these patients, although patient numbers are too small to allow any prospective trials in individual cancers, and therefore there is a poor evidence base to use in designing treatment programmes. For all of the above reasons, there is no consensus regarding the most appropriate screening or treatment protocols in these patients.

The evidence available on which to base clinical decision-making falls into two categories: *in vitro* studies looking at various cell types from patients with Bloom syndrome, and case reports describing individuals with the condition, their presentation, treatment and clinical course. Several studies from the 1970s and 1980s compared the radiosensitivity of Bloom syndrome cells and normal controls, finding some evidence for increased sensitivity in S and G2 phases, but no difference in G1 [9—12]. More recently, inaccurate repair of double-strand breaks in DNA from Bloom syndrome patients has been reported [13], and it has been shown that 5-fluorouracil induces higher levels of DNA fragmentation in Bloom syndrome cells than in controls [14].

There are many case reports that mention treatment received by patients with malignancy related to Bloom syndrome, and most record increased sensitivity to chemotherapy, radiotherapy or both. Of 14 patients with acute leukaemia between the 1950s and 1970s reported by German from the registry, seven developed severe treatment reactions, including fatal bone marrow suppression, interstitial pneumonitis and hepatitis, mucositis leading to severe intestinal haemorrhage, candidiasis and neurological toxicity, some despite reduced doses of chemotherapy. The others were not reported to have any unusual reactions, although there are limited data for some patients, and only two survived their disease and treatment [15]. Another report described a patient with acute myelogenous leukaemia who was treated with reduced doses of cytarabine and doxorubicin but still suffered episodes of sepsis, bartholinitis, severe mucositis and massive gastrointestinal bleeding with prolonged bone marrow suppression. The authors commented that the treatment of acute myelogenous leukaemia in Bloom syndrome is particularly susceptible to failure due to the intensive chemotherapy regimen required to induce remission, which is poorly tolerated by the bone marrow in these patients [16]. The treatment of a patient for B-cell lymphoma of the larynx was more successful: despite bone marrow suppression during the first block of treatment, reduced doses for the remainder of her chemotherapy were well tolerated and she was discharged in good health a year after diagnosis [17]. Another paper

described a patient with an oesophageal stricture caused by radiotherapy for a lung cancer. The mediastinum received a dose of 30.6 Gy, but the stricture was severe enough to require tube and intravenous feeding and the patient died 18 months after treatment despite complete resolution of the tumour [18].

More recently, the treatment of a squamous cell carcinoma of the oropharynx in a young woman with Bloom syndrome was reported. The team planned to assay her lymphocytes before treatment to assess how sensitive she might be to radiotherapy — a process described in a second paper — but this was abandoned as her condition worsened [19]. She tolerated the initial course of radiotherapy with some patchy mucositis, but once concurrent 5-fluorouracil and cisplatin were added she developed severe bone marrow suppression, large areas of moist desquamation, ulcerating oropharyngeal mucositis and severe diarrhoea. Her recovery from these reactions was slow — her skin took 3 months to heal, and the mucositis resolved to patchy mucositis over 4 months. Four months after treatment she developed aggressive recurrence and died 4 weeks later. This is an interesting example of a recent case report in which the treating physicians were well aware of the potential problems with treating malignancy in a patient with Bloom syndrome, but the patient still suffered severe side-effects of treatment and died rapidly of her disease [20].

The difficulty in interpreting all of the above evidence is that the degree of publication bias is impossible to assess. One report mentions in passing that a patient was treated for an epipharyngeal tumour with chemotherapy and radiotherapy, and that the tumour responded well, with no mention of adverse effects [21], and some of the patients German reported are not known to have had treatment reactions [15], but the number of patients with Bloom syndrome who have been successfully and uneventfully treated for cancer around the world without having been reported is unknown. However, the fact that the underlying problem in Bloom syndrome is a defect in DNA repair, and there is *in vitro* evidence of sensitivity to ionising radiation and chemical mutagens, as well as a number of case reports detailing striking side-effects of treatment, leads to the conclusion that these patients should have their treatment designed with the possibility of hypersensitivity in mind.

The other notable trend to come out of the case reports is the incidence of other complications of disease and treatment in these patients. Even those who are successfully treated for malignancy frequently succumb to pneumonia or other pulmonary complications, hepatic disease or sepsis. This is not altogether surprising as Bloom syndrome causes diabetes, lung and liver problems and immunodeficiency independently of any malignancy or its treatment. A number of the patients discussed above have had stormy in-patient courses and have finally opted for palliative treatment.

One aspect of the management of a patient with Bloom syndrome that is discussed very little is the most appropriate screening regimen. German recommends avoiding regular haematological examination of children because there is no evidence that an early diagnosis of leukaemia improves prognosis, and there is a risk of psychological morbidity [15]. He does however comment that the situation with adults is different because the treatment of carcinomas by surgical resection at an early stage is the best curative option, and he recommends at least annual examinations for carcinoma of the breast, cervix and colon as well as rapid and thorough investigation of any new symptoms [3]. It would seem sensible, however, to try to achieve this programme with no or minimal use of X-rays where resources allow, for example by using magnetic resonance imaging if possible instead of mammograms for breast screening, and ultrasound to characterise any abnormalities.

Conclusion

Patients with Bloom syndrome are at severely increased risk of developing many tumour types at a young age, and a screening programme should therefore be offered, particularly for the more common cancers such as carcinomas of the breast and colon. There is evidence that patients with Bloom syndrome may exhibit clinical hypersensitivity to ionising radiation and chemical mutagens as well as *in vitro* cellular sensitivity. It is therefore important to recognise the condition as early as possible in order to diagnose any cancers at an early stage and tailor the treatment regimen to try to avoid severe side-effects.

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