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Syndrome 'X' in adult female recipients of bone marrow transplantation for haematological malignancies

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New transplant techniques and improvement in supportive care in patients with haematological malignancies have resulted in an increased number of long-term survivors of bone marrow transplantation (BMT). Approximately 30 000–40 000 bone marrow transplants take place annually worldwide and there is a trend for the number to increase by 10–20% per year.[1] As more patients survive and possibly remain disease free, this has led to an awareness of late effects such as multiple endocrinopathy, especially hypogonadism with premature ovarian failure (POF) and consequences such as infertility, osteoporosis and sexual dysfunction.[2] In the recent years, emphasis has also been given to late morbidity and mortality in long-term survivors of various malignancies treated by multimodal chemotherapy (CT) and/or radiotherapy (RT). Although this may be attributed to a second malignancy,[3] metabolic disturbances are well-recognised complications predisposing to increased mortality in patients with testicular[4] or brain tumours[5] treated with conventional CT and RT regimens. The metabolic disturbances in these studies resemble the components of metabolic syndrome 'X' which may act as a precursor for atherosclerosis and cardiovascular disease with its consequent morbidity and mortality.[6] The core signs of syndrome 'X' include hyperlipidaemia, impaired glucose tolerance or type II diabetes and hypertension.[7] Other associations or components of syndrome 'X' include obesity, hyperuricaemia, hyperleptinaemia and microalbuminuria.[8] The exact incidence and pathophysiology of metabolic syndrome in cancer survivors is unknown. Furthermore, clarity exists about the future development of cardiovascular disease (CVD) and syndrome 'X' in cancer survivors. If however, syndrome 'X' is a forerunner of CVD, this syndrome would be a major target for intervention strategies during follow-up of cancer patients. Dyslipidaemia and impaired glucose tolerance (IGT) are also described recently as late complications of BMT in recipients in childhood cancer.[9] However, no data are available on metabolic syndrome in adult BMT recipients for haematological malignancy. Here, in a 7-year longitudinal observational study (median time 4 years) we report five female adult recipients of BMT for haemato logical malignancies who presented with features of ovarian failure post BMT to the reproductive medicine unit, and were treated with sex hormone replacement therapy for hypogonadism. They presented with some of the core signs of syndrome 'X' 3–5 years post BMT. Table 1 summarises patients' characteristics. The median age at the transplant was 27 years (18–41), where the median age at syndrome 'X' was 33 years (18–41). Four patients received an allogeneic transplant and one patient an autologous one. The conditioning consisted of high-dose chemotherapy and total-body irradiation (TBI) for four patients and high-dose chemotherapy alone for one patient. All patients were on cyclical HRT for POF since BMT. Patients 3 and 4 were on oral antihypertensive drugs (atenolol 25 mg daily) and simvastatin 20 mg daily. Patients 1 and 4 were on 100 μg L-thyroxine daily orally for hypothyroidism. Patients 1 and 2 were on oral metformin hydrochloride 500 mg twice daily for IGTT/DM. At the time of diagnosis of the syndrome 'X', all patients had hypertension ($\geqslant$90 mmHg on two or more occasions 3 months apart) and hyperlipidaemia, 2/5 had hypothyroidism (patients 1 and 4), one had frank diabetes mellitus (DM) (patient 1) and one had IGT (patient 2, data not shown). All had POF and were on HRT since BMT without clinical and radiologic evidence of osteoporosis. BMI was normal in all patients and did not change at the onset of syndrome 'X'. Table 2 summarises the metabolic and endocrine data of patients with syndrome 'X'. To the best of our knowledge, this is the first study where we report five adult recipients of BMT presenting with core signs of metabolic syndrome. However, dyslipidaemia with impaired glucose tolerance and hypertension has been recently reported in 23 long-term survivors who had BMT in childhood.[9] The cause of syndrome 'X' remains obscure in patients with various types of cancer,[4,5,9] however, the actual culprit is likely to be CT/RT which can inflict metabolic, neurogenic and vascular injury. Nuver *et al*[6] suggested the following factors to contribute to syndrome 'X' in cancer survivors which may also be applicable to our population: Firstly, CT/RT can induce endocrine and metabolic problems. Hypothalamic–pituitary–gonadal (H–P–G) dysfunction including growth hormone deficiency is an important factor. In fact, all the five patients in this study had primary hypogonadism with premature ovarian failure (POF). Although, it is very unlikely that these patients had hypopituitarism, it cannot be totally excluded, as we did not undertake comprehensive assessment for H–P dysfunction. TBI containing transplant regimens especially in the allogeneic setting are extremely damaging to the entire H–P–G axis compared to chemotherapy alone.[2] In our series, 4/5 patients had an allogeneic transplant and 4/5 had TBI. This is also in accordance with the data by Taskinen *et al*,[9] who found allogeneic transplant to be associated with syndrome 'X'. In the same study, there was a suggestion that GVHD may be a contributing factor, as 10/23 patients had signs of limited chronic GVHD. In our study, three patients developed Grade I acute GVHD and one limited chronic in the skin. Secondly, Nuver's theory of vasculogenic and endothelial damage has well been demonstrated in cancer patients.[9] This may apply to our patients who had high-dose therapy with or without TBI.

Although lifestyle changes and smoking may act as permissive factors in the aetiology in syndrome 'X', in our population is seems unlikely, as our patients were

Table 1 Clinical characteristics, blood pressure and lipid profile of patients with syndrome 'X'

Patient	1	2	3	4	5
Disease	MM	ALL	AML	AML	AML
Age at BMT (years)	37	21	27	41	18
Conditioning regimen	Melph/TBI	Eto/TBI	Bu/Cy	Cy/TBI	Cy/TBI
Type of transplant	Autograft	Allograft	Allograft	Allograft	Allograft
GVHD	N/A	Grade I	Grade I	Grade I, limited chronic	None
Age at syndrome 'X'	42	24	33	45	22
BMI at BMT (g/cm^2)	20	23	30	23	18
BMI at syndrome 'X' (g/cm^2)	19	23	32	23	18
BP at first visit (mmHg)	110/70	100/70	100/70	100/70	100/60
BP at syndrome 'X' (mmHg)	160/100	140/110	140/90	150/100	130/90
Cholesterol at first visit (2.3–5.2 mmol/l)	4.9	2.8	1.0	6.8	6.1
Cholesterol at syndrome 'X' (2.3–5.2 mmol/l)	6.2	9.1	6.8	7.8	6.3
Triglycerides at first visit (0.41–1.8 mmol/l)	1.1	2.2	1.0	1.8	1.1
Triglycerides at syndrome 'X' (0.41–1.8 mmol/l)	2.0	8.0	1.2	4.0	0.6

AML = acute myeloid leukaemia; ALL = acute lymphoblastic leukaemia; Melph = melphalan; TBI = total-body irradiation; Eto = etoposide; Bu = busulphan; Cy = cyclophosphamide; N/A = nonapplicable; BMI = body mass index; BP = blood pressure.
First visit refers to the time when patients were referred to the reproductive medicine unit post BMT.

Table 2 Endocrine profile in patients with syndrome 'X'

Pt no	*Fasting glucose at FV (3.9–6.0 mmol/l)*	*Fasting glucose at syndrome 'X'*	*FSH at FV (4–15 U/l)*	*FSH at syndrome 'X' 4–15 U/l)*	*LH at FV (3–22 U/l)*	*LH at syndrome 'X' (3–22 U/l)*	*TSH at FV (0.35–5 mU/l)*	*TSH at syndrome 'X' (0.35–5 mU/l)*	*FT3 at FV (9–19 pmol/l)*	*FT3 at syndrome 'X' (9–19 pmol/l)*
1	5.2	27	87.3	19.1	60.9	18.8	1.1	8.1	15.1	10.8
2	4.5	10.1	7.28	39.4	87.4	46.3	1.4	1.65	13.0	15.0
3	5.0	6.1	12.8	49.5	5.1	27.5	1.2	1.8	11.2	10.8
4	4.5	6.9	13.2	3.3	53.9	0.4	6.5	48.84	11.5	7.9
5	5.3	6.2	92.8	48.5	18.8	56.7	2.0	3.05	12.9	14.5

FV = first visit; FSH = follicle-stimulating hormone; LH = luteinising hormone; TSH = thyroid-stimulating hormone; FT3 = free triiodothyronine.

nonsmokers and were on a normal healthy diet. We appreciate that our patient number is small and the incidence and the pathogenesis of syndrome 'X' in adult BMT survivors is less clearly understood. Also we have no data to predict whether syndrome 'X' in these patients will eventually lead to CVD with the same degree of cardiac morbidity and mortality as observed in older patients. However, it has significant health implications and we propose that primary and secondary intervention strategies should be undertaken for prevention and treatment of syndrome 'X'. Life-long follow-up of endocrine and metabolic screening tests in transplant patients might lead to early therapy and prevention of death from coronary heart disease.

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