PROBLEM SOLVING IN CLINICAL PRACTICE

THE COST OF CURE

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Rachel was diagnosed with acute lymphoblastic leukaemia (ALL) at 6 years of age, and treated on the UKALL XI protocol[1] with randomisation to high dose methotrexate plus third intensification. She relapsed 22 months after the initial diagnosis and received further chemotherapy and a matched unrelated donor bone marrow transplant (BMT). Her conditioning for the BMT included cyclophosphamide and total body irradiation (TBI) (eight fractions of 180 cGy each). She developed graft versus host disease post-transplant and was treated with high dose methylprednisolone for five weeks and oral prednisolone for several weeks thereafter. One year after BMT she continued to be in remission from her leukaemia.

COMMENT

- Bone marrow transplant, especially when TBI is part of the conditioning regimen, is associated with both endocrine and non-endocrine co-morbidity (table1).[2] Dividing the total dose of irradiation into smaller fractions (fractionation) is used to minimise these late effects of treatment. High dose corticosteroids, used to treat graft versus host disease, heighten the risk of iatrogenic adrenal suppression. Recovery of adrenal function usually occurs with time but this is not universal and steroid replacement therapy is sometimes needed. Therefore, after stopping steroid treatment the pituitary–adrenal axis should be assessed with a Synacthen test in all children treated with steroids for graft versus host disease, and replacement steroid therapy given if appropriate.

At 9 years of age Rachel is referred to the BMT follow up clinic for ongoing monitoring for evolving sequelae of treatment. It is now just over one year after her transplant. Routine blood tests taken as part of her annual review included thyroid function tests. The results were: free thyroxine (FT_4) 8.8 pmol/l (normal range: 10.8–18.7 pmol/l); thyroid stimulating hormone (TSH) 12 mlu/l (normal range: 0.5–4.5 mlu/l).

Although Rachel has no clinical features of hypothyroidism, the abnormal thyroid function results come as no surprise since peripheral hypothyroidism (high TSH and low FT_4) caused by radiation damage to the thyroid gland is a recognised complication of TBI (table 2). Thyroxine replacement therapy is commenced.

COMMENT

- There are concerns, supported by animal work, that a persistently raised TSH may increase the risk of thyroid neoplasia in a predisposed gland.[3] Thyroxine replacement therapy should therefore be instituted if the TSH is persistently raised with an aim of keeping the TSH suppressed. There is also an increased risk of thyroid carcinoma caused by irradiation of the gland.[4] Annual thyroid function tests and neck palpation should therefore be part of ongoing surveillance in all survivors of BMT regardless of the conditioning regimen.

Three months later, during a routine appointment, Rachel complains of worsening respiratory symptoms. In particular she has an intermittent cough that is sometimes exercise induced and occasionally nocturnal. In spite of this she remains very active and takes part in physical exercise at school and swims regularly. On examination there is no chest deformity and no clubbing. There are scattered crackles and wheeze, particularly over the left lung.

The consultant is aware that a transfer of atopy from the donor to the recipient of a BMT is well described[5] and considers asthma in the differential diagnosis. Yet she is also conscious that radiation and chemotherapy induced lung damage can cause respiratory symptoms in survivors of BMT and a range of other childhood cancers. Her differential diagnosis therefore also includes post-radiation fibrosis, bronchiolitis obliterans, and (least likely) chronic graft versus host disease. She prescribes a pulse of oral steroids and inhaled beclomethasone, and arranges lung function tests.

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Table 1 Important treatments responsible for late effects in acute lymphoblastic leukaemia (ALL) treatment and bone marrow conditioning (a number of other chemotherapy agents are given but are lower risk for late effects)

Treatment for ALL (UKALLXI)[1] includes:	Potential late effects include:
Anthracyclines (daunorubicin (180 mg/m^2)	Cardiomyopathy—risk increases with increasing dose
Steroids	Reduced bone density Obesity
High dose methotrexate	Reduced bone density
Etoposide	Secondary leukaemia
At relapse chemo included:	
Anthracyclines (additional 200 mg/m^2 epirubicin)	Increased risk of cardiomyopathy
Bone marrow conditioning	**Potential late effects**
Total body irradiation (TBI)	Second malignancy (particularly skin and thyroid) Thyroid nodules Cataracts Endocrine dysfunction (see table 2) Gonadal failure Sicca syndrome Restrictive lung defect Cardiac dysfunction
Cyclophosphamide	Potentiates cardiac effects of anthracyclines Pulmonary toxicity Gonadal dysfunction

Table 2 Endocrinopathy after bone marrow transplant

Endocrinopathy	Risk factors
Short stature	▶ Total body irradiation ▶ Previous cranial radiation ▶ Growth hormone deficiency ▶ Chronic graft versus host disease ▶ Poor nutrition/malabsorption
Growth hormone insufficiency	▶ Total body irradiation ▶ Previous cranial radiation
Thyroid dysfunction	Hypothyroidism ▶ Females ▶ Total body irradiation ▶ Busulphan/cyclophosphamide conditioning (lower risk than total body irradiation) Thyroid nodules ▶ Females ▶ Younger age at treatment Hyperthyroidism (rare) ▶ Total body irradiation Thyroid cancer ▶ Increased time from treatment ▶ Younger age at treatment ▶ Females
Gonadal dysfunction	Female ▶ Older age at treatment ▶ Total body irradiation ▶ Busulphan Male ▶ Radiation ⩾4 Gy—azoospermia very likely ▶ Radiation ⩾20 Gy—Leydig cell failure likely (testicular boost for testicular relapse is 24 Gy) ▶ Bulsuphan ▶ Effect of age unclear
Adrenal insufficiency	▶ Chronic graft versus host disease
Reduced BMD	▶ Hypogonadism ▶ Chronic graft versus host disease ▶ Inactivity ▶ Poor nutrition ▶ Growth hormone deficiency ▶ Previous chemotherapy/radiotherapy
Metabolic syndrome	▶ Risk factors unknown ▶ Total body irradiation probably important ▶ ?Role of growth hormone deficiency ▶ Hypothalamic dose ⩾51 Gy ▶ Physical inactivity (for example, neurological impairment) ▶ Endocrinopathy

BMD, bone mineral density.

The lung function tests show a restrictive lung defect with no significant reversibility with β2 agonists (fig 1, table 3 and fig 2, table 4). After consultation with a respiratory physician, a chest *x* ray and a high resolution computed tomographic (CT) scan of the chest are performed. These reveal no evidence of bronchiolitis obliterans and are consistent with a diagnosis of pulmonary fibrosis. No further treatment was prescribed.

COMMENT

- Chemotherapy and radiation therapy (alone or combined) are associated with clinically significant pulmonary toxicity. The incidence of drug induced pulmonary toxicity ranges from 3–30%. The antineoplastic drugs commonly responsible include BCNU (bischloroethylnitrosourea), CCNU (chloroethylcyclohexlnitrosourea), and busulphan and bleomycin (although there is less evidence for this in children than in adults). Radiotherapy to any field that includes the lungs can cause pulmonary toxicity. The pulmonary toxic effects of chemotherapy are usefully divided into early onset, resulting in interstitial lung injury, and late onset with pulmonary fibrosis.
- Post-BMT lung toxicity is usually related to TBI rather than chemotherapy. The risk and severity of pulmonary complications following irradiation are influenced by the total dose, dose fractionation, and irradiated lung volume. Acute irradiation injury (uncommon post-BMT) typically occurs two weeks to three months after treatment and is usually limited to the irradiated field. Spirometry is the first line investigation and provides an indication of whether the lung defect is obstructive or restrictive. Radiation induced lung damage classically causes a restrictive defect with small, stiff lungs.
- Bronchiolitis obliterans is a rare disease of small airways that results in progressive dyspnoea and airflow restriction.[6] It is well described after BMT as well as after lung, and heart–lung, transplantation. It can also occur as a complication of certain pulmonary infections, adverse drug reactions, toxic inhalation, and autoimmune disorders. In transplant related bronchiolitis obliterans, the diagnosis is suggested by obstructive changes (not reversible with β2 agonists) on lung function tests. Hypoxia with exertion is also common. High resolution CT is valuable in diagnosing and assessing the severity of bronchiolitis obliterans. Prompt diagnosis is important since early treatment with high dose steroid is indicated.

As part of the evaluation of her breathlessness, Rachel also had an echocardiogram. This showed slightly

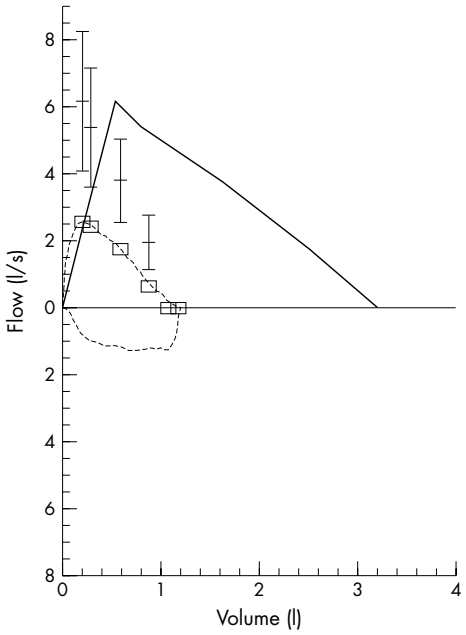

Figure 1 Lung spirometry showing a restrictive pattern. Note the normally shaped, but proportionately reduced, flow–volume loop. Flow is on the y axis, with expiratory flow in an upward direction. Volume is on the x axis, with full inspiration at 0, and full expiration at the right hand limit of the loop. Predicted loops for height, age, and sex are shown by the bold line, and error bars show the normal ranges for peak expiratory flow, and flow at 25%, 50%, and 75% of expired volumes.

Table 3 Figure 1 data: FEV_1/FVC is normal at 92%

	Actual	% predicted
FEV_1	1.09	40%
FVC	1.18	37%
$FEV_1/FVC\%$	91.9	109%
PEF	2.57	42%
FEF25	2.43	45%
FEF50	1.76	46%
FEF75	0.65	33%

Note similar reduction in volumes and flows when assessed by % predicted.
FEF, forced expiratory flow; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; PEF, peak expiratory flow.

reduced left ventricular contractility and a reduced fractional shortening (30% as compared with 36% on a previous scan). Mild septal hypokinesia was also noted.

Although the clinicians are aware of the cardiotoxic effects of Rachel's leukaemia treatment, they considered that the echocardiographic changes were not contributing to her respiratory symptoms and that continued surveillance only was necessary. It was decided to repeat her echocardiogram one year later.

COMMENT

- Anthracyclines at doses > 300 mg/m^2 are associated with an 11-fold increased risk of clinical heart failure, compared with a cumulative dose < 300 mg/m^2.[7] There is, however, no safe dose of anthracyclines although the higher the cumulative dose the greater the risk of cardiomyopathy, with younger age at treatment and female sex being independent risk factors.[8] They cause myocyte death and impede the return of the cardiac muscle to the resting state, thereby leading to hypertrophy of the remaining cells, interstitial fibrosis, and reduced wall thickness. In patients who have received anthracyclines, the risk of cardiotoxicity is increased by mediastinal radiation, uncontrolled hypertension, and exposure to other chemotherapeutic agents (especially cyclophosphamide, dactinomycin, mitomycin C, dacarbazine, vincristine, bleomycin, and methotrexate). It is also more common in females, younger children, and in those with electrolyte disturbances such as hypokalaemia and hypomagnesaemia. ECG abnormalities are also relatively common, especially prolonged QT interval.
- Survivors of childhood cancer represent one of the largest new groups at risk of premature cardiovascular disease, although cardiac complications may not become manifest for many years. Factors that may precipitate cardiac decompensation are pubertal growth spurt, growth hormone treatment related growth, pregnancy, sex steroid replacement, or weight lifting. Echocardiograms at 3–5 yearly intervals (more frequently if there is concern) are recommended. Where reduced left venticular function is demonstrated, treatment with angiotensin converting enzyme (ACE) inhibitors may be of benefit in slowing deterioration. Once end stage heart failure occurs cardiac transplantation is the only treatment option.[9]

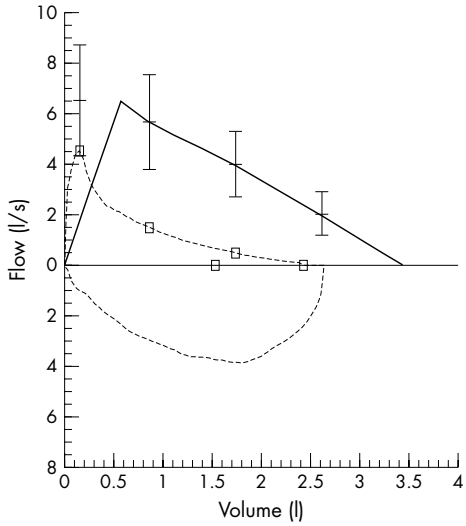

Figure 2 Lung spirometry showing an obstructive flow volume loop. Note the concave shape of expiratory flow, and disproportionate reduction in flow compared to volume.

Table 4 Figure 2 data: FEV_1/FVC is reduced to 63%

	Actual	% predicted
FEV_1	1.53	53%
FVC	2.43	70%
$FEV_1/FVC\%$	63.2	75%
PEF	4.53	69%
FEF25	1.48	26%
FEF50	0.49	12%
FEF75	Unrecordable	

At the next outpatient appointment Rachel, who is now nearly 10.5 years of age, is upset and depressed. It transpires that she is being teased at school for being short and fat. Her growth chart shows that she is on the 25th centile for height, 50th centile for weight,

with a median parental height (MPH) on the 75th centile. Her height velocity during the previous six months is below the 25th centile. On examination she is relatively overweight with increased abdominal girth. Her pubertal staging is Tanner stage B1, PH1 (pre-pubertal). Since her height velocity is below normal, anterior pituitary function testing is arranged.

Clonidine stimulation results in a peak growth hormone concentration of 9.2 mIU/l (< 10 mIU/l: severe growth hormone deficiency; 10–20 mIU/l: partial deficiency). Her luteinising hormone (LH) concentration was 2.3 iu/l and follicle stimulating hormone (FSH) 1.8 iu/l (pre-pubertal values). After discussion of the pros and cons of growth hormone therapy, Rachel is commenced on daily growth hormone injections.

COMMENT

- Impaired growth during and after BMT has a multifactorial aetiology—disturbed puberty, the direct action of chemotherapeutic drugs and irradiation on the growth plates, growth hormone deficiency, graft versus host disease and its treatment, and nutritional factors all play a role. The relative importance of TBI and chemotherapy is the subject of debate but it is likely that both are important. Spinal growth is impaired because of the effect of radiation on spinal growth plates. Cranial irradiation before BMT, reserved for those children with central nervous system leukaemia at diagnosis or relapse, increases the risk of growth hormone deficiency. Regular and accurate auxology including sitting height is essential. When there is a persistent reduction in height velocity (despite appropriate thyroid and/or sex steroid replacement) provocative growth hormone testing should be undertaken. Optimisation of nutrition is also important.
- If growth hormone deficiency is confirmed, replacement therapy should be considered on an individual basis not only to optimise growth but also because of the importance of growth hormone for bone health, quality of life, and cardiovascular wellbeing. The evidence suggests that the risk of relapse or secondary cancer is not significantly increased by growth hormone replacement therapy.[8] IGF-1 should be monitored and maintained within the normal age related range.

Rachel grows very well during the next two years on growth hormone replacement therapy. However, when reviewed at the age of 12 years 9 months, she is noted to have had a reduced height velocity during the preceding six months. The general examination is normal, and pubertal staging is B1 and PH 1. There is no family history of pubertal delay. Measurement of LH, FSH, and oestradiol show menopausal gonadotrophin concentrations (LH 55 iu/l, FSH 105 iu/l, oestradiol < 75 pmol/l).

Since Rachel is almost 13 years of age with no clinical signs of puberty and no family history of pubertal delay, the paediatrician is concerned that she may have ovarian failure and this is confirmed by the investigations. It is therefore decided that oestrogen replacement therapy should be started.

Normally, investigations are indicated only where there are no signs of puberty by 14 years of age, but in this case Rachel has clear risk factors for ovarian failure.

COMMENT

- The risk of gonadal dysfunction after BMT is high following TBI or busulphan/cyclophosphamide conditioning.[10] In females, older age at transplantation increases the risk of ovarian failure and reduces the likelihood of ovarian recovery. Regular monitoring (3–6 monthly) of physical signs and gonadotrophin concentrations (annually) is required around the age of puberty.
- In primary and secondary gonadal failure appropriate sex steroid replacement therapy is necessary. Ovarian failure may be temporary, particularly in younger children and with lower doses of radiation, so discontinuation of oestrogen replacement for 6–8 weeks every two years should be considered to determine whether ovarian function has recovered. Ovarian failure after TBI (14.4 Gy) is unlikely to be reversible[11] Pregnancy after BMT is well described but there is an increased risk of second trimester miscarriage and fetal growth restriction, probably because of radiation induced impairment of uterine blood flow and elasticity.
- In males, TBI affects germ cells more than Leydig cells.[8] Thus, although oligospermia or azoospermia (and hence infertility) are common post-BMT, preservation of Leydig

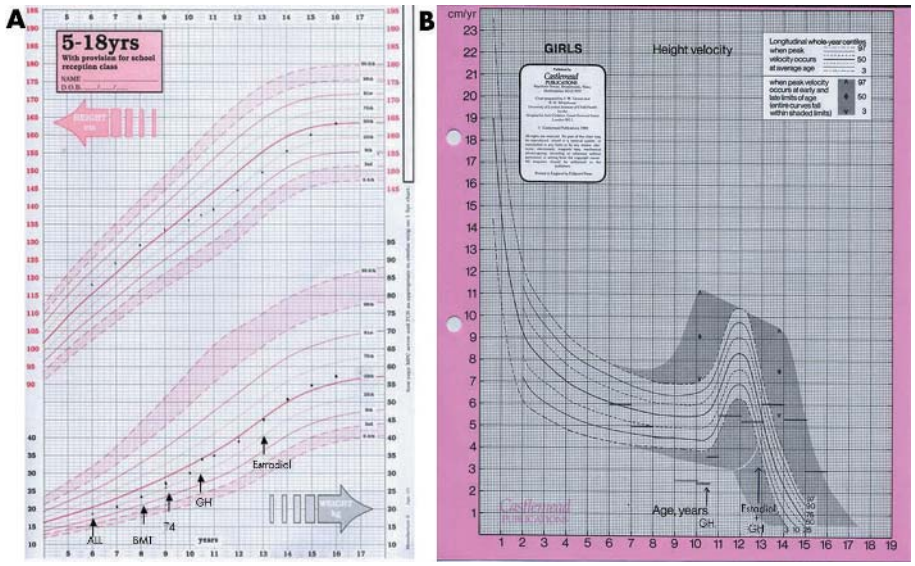

Figure 3 (A) Rachel's growth chart showing her final height at 16 years on the 50th centile and weight between the 50th and 75th centile. (B) Rachel's height velocity chart depicting the points where she started her growth hormone (GH) treatment and her oestrogen (Estradiol) replacement added on at 12 years and 9 months. After addition of both treatments her height velocity improved. ALL, acute lymphoblastic leukaemia; BMT, bone marrow transplant; GH, growth hormone; T4, thyroxine.

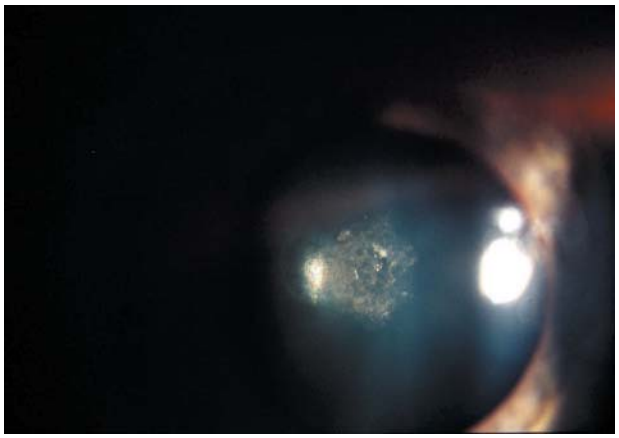

Figure 4 Cataract following total body irradiation.

cell function may maintain testosterone secretion within the normal range despite raised LH and FSH concentrations. The testes post-BMT are often inappropriately small and soft (because of radiation and/or chemotherapy damage to germ cells) and hence testicular enlargement should not be used to monitor pubertal progression.

Table 5 Bone marrow transplant follow up protocol

Auxology including sitting height	3–6 monthly Plot BMI
Bone age	Annually
Discussion points	Schooling/employment—statementing? Psychology assessment Weight Diarrhoea? Eyes and mouth—?Sicca syndrome (Consider faecal elastase/trial of Creon if loose stools/poor weight gain) Hip pain/knee pain: consider MRI—?osteonecrosis Fertility—if relevant/appropriate age
Special points on examination	Pubertal assessment at each visit (testicular volume not a useful indicator of pubertal progression) Palpation of thyroid Check moles Neurological examination Fundoscopy (cataracts) Blood pressure
Echocardiogram	All patients who have had anthracyclines Echocardiogram at end of treatment (Request FS, LV function, septal motility) ECG annually (QT interval) 3 yearly if FS ⩾30%, annually if <30%
Growth hormone status	Evaluate if persistent poor growth
Glucose:insulin ratio	Annually—as increased risk of metabolic syndrome GTT if abnormal
Lipids	Fasting lipids annually
Thyroid function	T4 and TSH annually Replace thyroxine if TSH persistently elevated
Gonadotrophins	LH, FSH, oestradiol/testosterone annually after 10 years of age Consider pelvic USS in females; uterine size, endometrial thickness, Doppler studies Semen studies in males as requested by patient Ovarian failure may be reversible—trial off oestrogen for 6–8 weeks every 2 years recommended
Evaluation of BMD	Annual PTH and vitamin D DEXA at 2 years, then 3 yearly if concern (must correct for size)

BMD, bone marrow density; BMI, body mass index; DEXA, dual energy x ray absorptiometry; ECG, electrocardiogram; FS, fractional shortening; FSH, follicle stimulating hormone; GTT, glucose tolerance test; LH, luteinising hormone; LV, left ventricle; MRI, magnetic resonance imaging; PTH, parathyroid hormone; TSH, thyroid stimulating hormone; USS, ultrasound scanning.

Rachel is now 15.5 years and recently had her first oestrogen withdrawal bleed. Oestrogen replacement therapy has resulted in breast stage 4. She is pleased with her height, which is between the 25th and 50th centile (fig 3) and has settled well in school. Examination is normal other than small cataracts that are not impairing her vision (fig 4). Nevertheless, she has been referred to an ophthalmologist for a formal assessment. She continues to be monitored annually in respect of the late effects of her leukaemia and its treatment.

COMMENT

- Cataracts may occur following TBI and although they may be present for many years without visual impairment, surgery is occasionally required. They are one of many initially asymptomatic complications that mean that lifelong surveillance is required for all BMT survivors.
- A vital component of follow up, often delivered by nurse specialists, is health promotion. Particular issues include dietary and lifestyle promotion of bone health (because of an increased risk of osteopenia and osteoporosis) and sun protection (because of increased risk of skin cancer). Counselling in relation to smoking is also important, especially where there is already established lung disease such as pulmonary fibrosis. Table 5 provides a suggested follow up protocol for bone marrow survivors. As additional late effects become evident such protocols will need to be modified. For example, there is growing evidence of an increased risk of insulin resistance and metabolic syndrome following BMT.[12] Monitoring of the glucose:insulin ratio and blood lipid values, with an oral glucose tolerance test if the glucose:insulin ratio is abnormal, has therefore been added to our follow up protocol.
- This case shows the wide ranging nature of the late sequelae of childhood cancer treatment. Almost any system can be affected, with cardiac, respiratory, and particularly endocrine sequelae being common.[2 13 14] It also demonstrates that, despite considerable late morbidity, many patients have good quality of life. In addition, historically very few patients with relapsed leukaemia like Rachel would have achieved long term cure, highlighting the massive improvement in survival for childhood leukaemia that has been seen in the last 30 years.

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IMAGES IN PAEDIATRICS

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Starry sky: multiple neurocysticercosis

A 5 year old developmentally normal girl, with seizure disorder for one year, presented with altered sensorium and quadriparesis. Magnetic resonance imaging of the brain showed a starry sky pattern with multiple rounded calcific lesions. Both serum and cerebrospinal fluid were positive for cysticercus serology. Work up for tuberculosis was negative. The girl was treated with albendazole and steroids, and the seizures were controlled with anticonvulsants.

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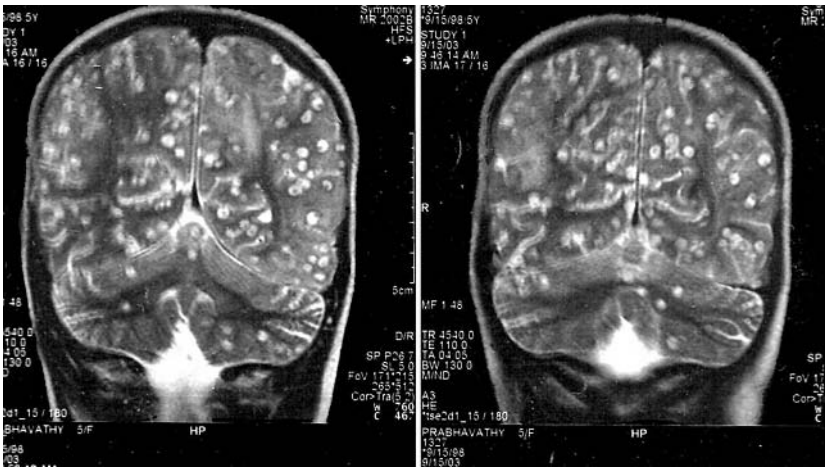

CORRECTION

doi: 10.1136/adc.2004.050237corr1

C Flohr and H C Williams. Evidence based management of atopic eczema. *Arch Dis Child Ed Pract* 2004;**89**:ep35–9. Due to a production error Figure 1 was missing from the print version of this article. The illustration and caption are reproduced below. A corrected version of the article can be downloaded from the website http://ep.bmjjournals.com/cgi/reprint/89/2/ep35.

The error is regretted.

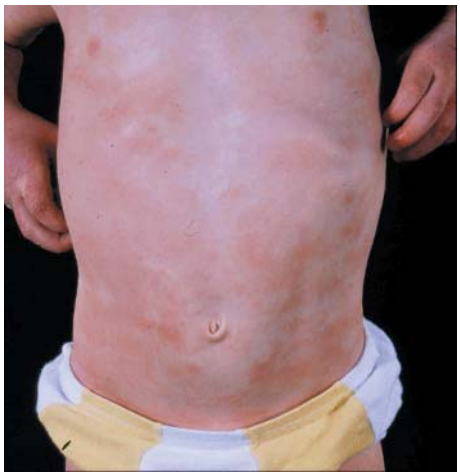

Figure 1 Widespread, poorly demarcated redness with associated surface dryness typical of atopic eczema in a young child.