CASE REPORT

Treatment with cyclosporin A in a patient with Omenn's syndrome

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Unless treated with haematopoetic stem cell transplantation, Omenn's syndrome, a rare variant of severe combined immunodeficiency, is associated with a fatal outcome. We describe a male infant showing all the typical features of Omenn's syndrome, who was successfully treated with cyclosporin A to improve clinical condition prior to haematopoetic stem cell transplantation.

Omenn's syndrome, a rare autosomal recessive severe combined immunodeficiency, was first described in 1965.[1] Except for recurrent infections, clinical manifestation is variable. The syndrome is characterised by the occurrence of diffuse erythrodermia, hepatosplenomegaly, generalised lymphadenopathy, and protracted diarrhoea, causing failure to thrive and evolving within the first weeks of life. Laboratory investigations typically show notable eosinophilia and highly increased serum IgE.[1] Activated, autoreactive T lymphocytes infiltrate skin, liver, spleen, and intestine, and lead to autologous graft versus host disease-like reaction. The T cell repertoire shows a restricted heterogeneity. Recently, it has been shown that a mutation in either RAG-1 or RAG-2 involved in the creation of T cell variety may be one cause of Omenn's syndrome.[2]

Unless treated with allogenic haematopoetic stem cell transplantation (SCT), prognosis of Omenn's syndrome is fatal.[3] However, poor clinical status before SCT results in a high transplantation related mortality. Control of T cell activation and proliferation as well as nutritional support before SCT has been shown to reduce the risk of fatal complications.

In the patient described here, treatment with cyclosporin A (CsA) in addition to anti-infectious therapy led to considerable improvement of clinical status, disappearance of erythrodermia, and a constant weight gain, while an unrelated SCT was procured.

CASE REPORT

The male infant was the second child of healthy non-consanguineous parents with an older healthy daughter. Pregnancy and delivery were uncomplicated. Birth weight was 3170 g (25th to 50th centile).

At about 3 weeks of age he presented with generalised exanthema, which was ichthyosiform, itching, and scaling, and an upper respiratory infection proceeding to pneumonia. He subsequently developed disseminated marked lymph node enlargement of up to 40 mm and hepatomegaly up to 6 cm below costal margin. He suffered from protracted diarrhoea resulting in failure to thrive.

Laboratory evaluation showed eosinophilia (up to 25%) and increased concentrations of serum IgE (up to 984 kU/l). Immunoglobulins A, G, and M in serum were normal. There was a marked leucocytosis of up to 50 000/µl with a lymphocytosis of 66%. In vitro, T cell proliferation in response to mitogens was decreased and absent to several antigens including candida antigens. All specific antibody titres of child origin were negative. Chromosomal analysis of peripheral blood cells revealed 46 XY in all 13 metaphases.

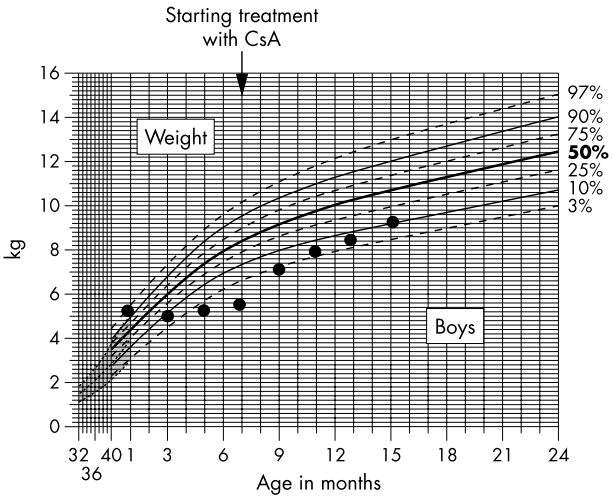

Figure 1 Weight curve of the patient.

In skin biopsy specimens, keratinocytic necrosis was present, imitating graft versus host disease. Analysis of the T cell repertoire by spectratyping of the CDR3 of the T cell receptor β chain showed abnormal variability in most BV chain families.

Despite intensified antibiotic treatment, severe bronchopulmonary infection persisted for more than two months. Bronchoscopy was performed and malformations were excluded. Bronchoalveolar lavage revealed candida species and treatment with amphotericin B was started. Thereafter, fungal infections did not recur. Because of severe obstructive bronchitis the patient received theophylline, salbutamol, and ipratropium bromide by inhalation as well as systemic corticosteroids. Protracted diarrhoea necessitated prolonged parenteral nutrition. However, weight gain was poor (fig 1). At 7 months of age his weight was only 5500 g (500 g below 3rd centile).

Exanthema proceeded to generalised itching erythrodermia with loss of hair resulting in total alopecia including the eyebrows and eyelashes (fig 2A). Topical corticosteroids and intensive symptomatic treatment led to slight improvement of skin efflorescences. Erosio corneae was diagnosed and treated symptomatically. Because of loss of water by erythrodermia

Abbreviations: CsA, cyclosporin A; SCT, stem cell transplantation

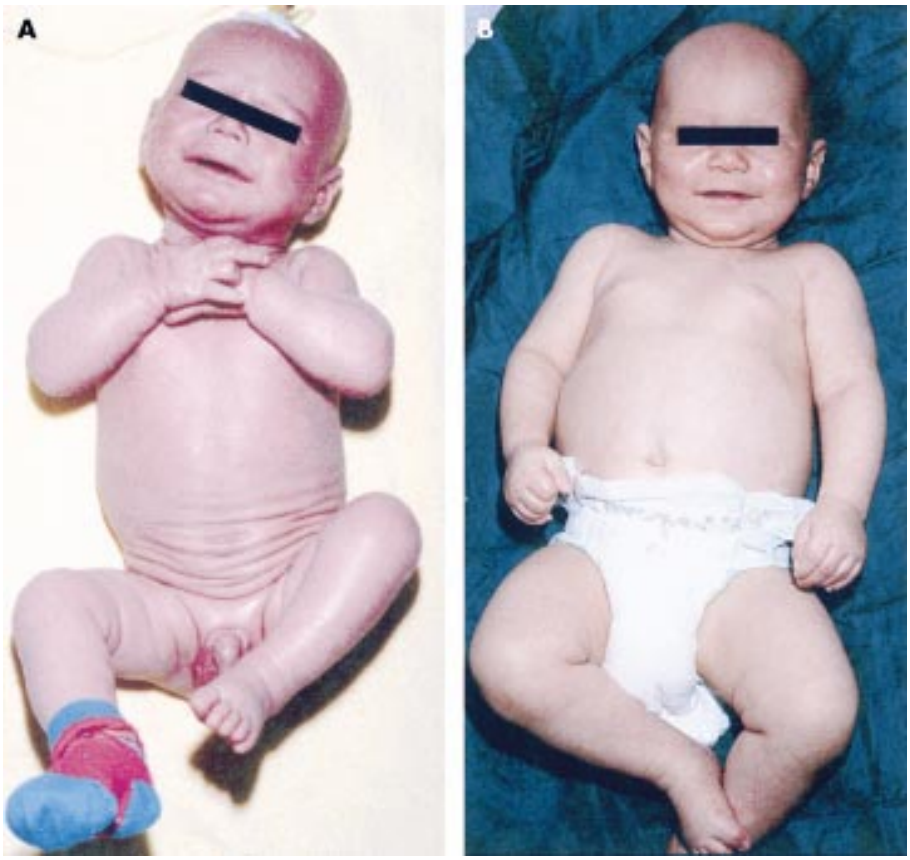

Figure 2 (A) The patient aged 5 months, showing a generalised scaling and itching erythrodermia, total alopecia, and a poor nutritional status. (B) The patient aged 15 months under treatment with CsA. Erythrodermia has disappeared and the patient had a constant gain of weight.

and diarrhoea, repeated exsiccation with marked hypernatraemia developed at the time of highest lymphocytosis and lymphadenopathy.

After diagnosis was established, anti-infectious prophylaxis with fluconazole, cotrimoxazole, and intravenous immunoglobulins was started. Treatment with topical corticosteroids was continued and oral CsA was instituted while searching for an HLA compatible stem cell/bone marrow donor. Treatment with CsA resulted in marked improvement of clinical symptoms. Receiving up to 9 mg/kg CsA orally, CsA blood concentrations were about 100 ng/ml. Erythrodermia disappeared and a significant reduction of lymph node and liver size was observed. Hypernatraemic dehydration did not recur. After several months, even hair growth restarted, beginning with the eyebrows. Diarrhoea stopped and the patient had a constant weight gain. At 15 months of age his weight was about 9000 g (3rd to 10th percentile) (fig 1 and 2B). Leucocyte and lymphocyte count normalised. However, eosinophilia and increased IgE remained unchanged and T lymphocyte proliferation was still decreased in response to mitogens and absent in response to antigens. Another infectious episode was successfully treated with antibiotics. Further severe infections were prevented by isolation of the patient in a laminar air flow unit and continuation of anti-infectious prophylaxis.

DISCUSSION

In 1965, Omenn presented an extraordinary kindred with 12 children suffering from skin eruption, followed by hepatosplenomegaly, generalised lymphadenopathy, eosinophilia, poor growth, and recurrent infection.[1] All children had fatal outcome within two to six months of life. Prognosis of these patients with Omenn's syndrome has been improved since SCT has been introduced, although the rate of complications is high because of poor clinical status prior to SCT in most patients.

Immunosuppressive therapy has been used in order to control activation of autoreactive T lymphocytes, which infiltrate skin, liver, spleen, and intestine, leading to autologous graft versus host disease-like reaction and causing the typical clinical signs.

Diverse immunosuppressive agents have been shown to be useful. Improvement of clinical symptoms by treatment with CsA, alone or in combination with topical or systemic steroids, has been reported by several authors.[3–5] Schandene *et al* reported treatment with interferon γ as an attempt to attenuate a T helper type 2 like cell response. Apart from improvement of clinical status, he observed a down regulation of interleukin 5 (IL-5) and IL-10, resulting in normalisation of the eosinophil count.[6] Etoposide alone or in combination with steroids was effective to control clinical symptoms in some patients.[3] In this report, a patient with the typical features of Omenn's syndrome is presented. Treatment with CsA and topical steroids, in combination with anti-infectious prophylaxis, resulted in a marked improvement of erythrodermia, hepatomegaly, and lymph node swelling as well as disappearance of diarrhoea. The number of leucocytes and T cells normalised. However, eosinophilia and elevation of IgE persisted.

As SCT in Omenn's syndrome is associated with an increased complication rate owing to poor general condition, severe infections, and malnutrition,[3] this observation underlines the value of treatment with CsA in combination with anti-infectious prophylaxis while waiting for allogenic SCT, which is so far the only curative therapy.

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POSTCARD FROM DOWN UNDER

Time off

"We'd like to offer you a consultant post. Before you accept, however, please note the terms and conditions of the post, and in particular the following stipulation: After ten years of continuous employment we insist that you take, in addition to your usual annual leave, a further three months of paid holiday . . .".

Most of us would wake up at this point and realise that it was all a dream. In fact, judging from the panic regarding senior posts amongst paediatric trainees in the UK, some would regard the offer of the job as the surprising part of the dream.

Long service leave is a quirk of Australian employment history. Like many other quirks, folk have become used to it, and any fundamental alteration to it would be political suicide. The original reasoning went, I think, something like this. Many Australians were European immigrants who had left family behind. The boat trip to Europe took a few weeks, and so for someone to maintain any ties with "back home" they needed enough holiday for the trip. This benefit is reasonably realised after ten years of continuous employment, and has to be applied across the workforce. With the arrival of cheap intercontinental flight, and the fact that nowhere in the world is further than 36 hours away from anywhere else, you can do a great deal more with your three months, but it has not altered the basic provision of this now fundamental right.

There are flaws of course. For example, many of the consultants employed in hospitals are visiting medical officers or VMOs; essentially private consultants, mostly self employed but contracted to the hospital for a number sessions per week. Their public sessions would be covered in the agreement, but of course their private practices would need to continue, or alternative staffing found. In addition, the cost to the employer is great. Every tenth year the employer needs to find an extra quarter of a year of wages, or work with one employee down.

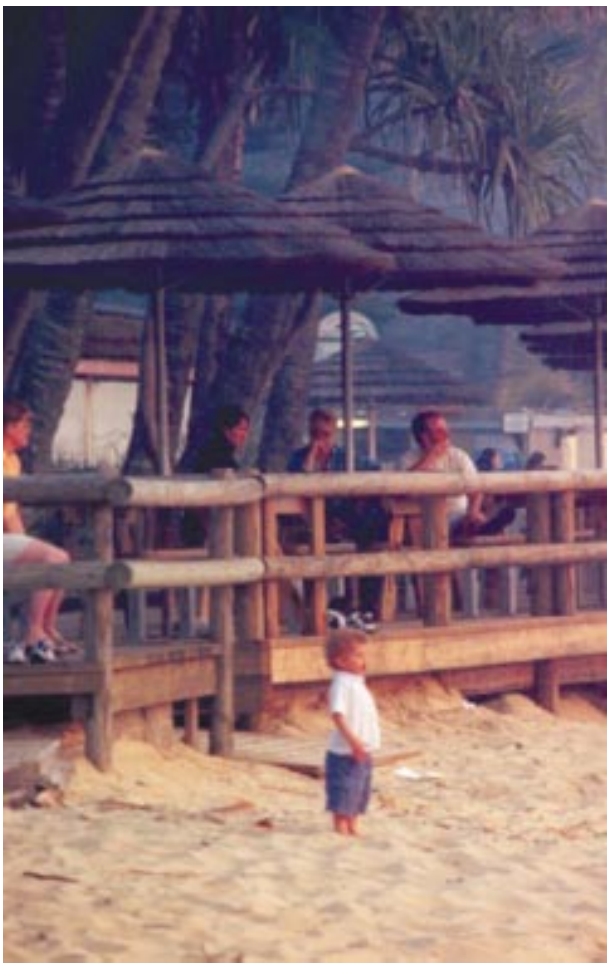
The pluses are obvious. After this leave the employer might find the employee rejuvenated, ready to apply themselves to their job with new vigour. At least, I imagine the employer would hope so. In addition, employee loyalty to a particular organisation should be bolstered, although in this increasingly flexible world this might be regarded as a negative feature.

There are some other differences in the area of annual leave. In the past in the UK, I have been used to taking my annual leave during each six month placement. However, in Queensland I accrue holiday at a fraction of the total year each pay period, and can spend it, with negotiation, when I wish. A recent directive from my employer here states that I can accrue a total of no more than two years' worth of annual leave—for health and safety reasons—but even this is at odds with the British system of "take it or lose it". Strangely, I'm paid an extra 15% while I'm on leave too. Again, I think that this is to help with the cost of travel "back home", although for junior doctors it also reflects that a significant proportion of the wages result from the penalties earned in overtime and out-of-hours work on top of the forty hour week.

The long service leave has an impact also on the length of normal annual leave. More than a couple of decades ago in the UK, taking a fortnight's leave was considered a bit racy, especially if you spent it all overseas. Although this attitude has altered, eyebrows are raised if you take three or more weeks, especially if you are actually holidaying for this whole period. Here you could happily take four, and easily take six. It brings to mind the hardworking and highly regarded senior colleague of mine in the UK who once told me that she was considering only taking one week off at a time in the future, because when she took two she found that she wound down too much—a revelation which I found both telling and a little sad.

Lastly, in the bottom right hand corner of my wage slip there are two numbers, one with A/L next to it, for annual leave, and one with S/L next to it. Watching it for a while, it goes up by about 80 a year, and it took me a while to figure out that this was in fact my sick leave allowance (in hours). An employee thus is granted two weeks of paid sick leave a year, and after that you are on your own. This seems harsh to me; we know that some people need more time off than others. It also has the effect of implying to some people that their sick leave is a special—supplementary—annual leave, supporting the Aussie tradition of "taking a sickie". However, some professions—for example, the police force—donate two days of accrued sick leave a year to a special fund, ready to help colleagues in dire need of extended leave, and there are other special arrangements for extended illness.

Now to get back to my dream. They are just getting to the part where I never have to work on a Friday afternoon or a Monday morning . . .



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I D Wacogne

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