PRIMARY OCULAR RELAPSE IN ACUTE LYMPHOBLASTIC LEUKAEMIA

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SUMMARY

Relapse of acute lymphoblastic leukaemia (ALL) occurred in the anterior segment of four children. All cases had been treated according to the Medical Research Council's UK Acute Lymphoblastic Leukaemia trial protocol (UKALL) including 2 years of continuation chemotherapy. In three cases the diagnosis was confirmed by anterior chamber aspirate while in one case the diagnosis was presumed on clinical grounds alone. All four cases experienced isolated leukaemic relapse in the anterior segment within 2 months of stopping therapy. The months immediately following cessation of continuation chemotherapy as part of the UKALL regime appear to represent a 'high-risk' period for primary anterior segment relapse of ALL. Children with ALL presenting with uveitis should be regarded as having leukaemic relapse and anterior chamber taps with or without an iris biopsy should be considered to confirm this diagnosis. Early diagnosis and treatment of ocular leukaemic relapse is likely to give these children the best chance of ultimate cure.

Acute leukaemia is the commonest malignancy in children, affecting 1 in 30 000 below the age of 14 years. Acute lymphoblastic leukaemia (ALL) is the commonest variety, accounting for 90%. ALL is characterised by uncontrolled proliferation of primitive white cells (blasts) in the bone marrow (Fig. 1). The accumulation of blast cells displaces the normal marrow and leads to anaemia, neutropenia and thrombocytopenia. Without treatment, death from haemorrhage and intercurrent infection rapidly follows. Treatment regimes for ALL have been standardised using the MRC Leukaemia Trial Protocols (UKALL I–XI, 1960s to present day) and survival rates of 70% are achieved.[1] Anterior segment relapse is rare, accounting for 0.2–2% of cases.[2–5] The clinical features of leukaemic infiltration of the anterior segment are well established.[2,6] Symptoms include redness, epiphora and photophobia and parents may notice changes in pupil shape or iris colour. Ocular pain and rarely visual loss also occur. Clinically, iritis with accompanying hypopyon, which may be streaked with blood, is common.[7,8] Secondary glaucoma with corneal oedema is also a frequent finding.[9] Iris changes include diffuse or nodular thickening, changes in colour, loss of iris crypts and rubeosis.[10]

CASE REPORTS

Four cases of anterior segment relapse of acute leukaemia in childhood were referred to the Ophthalmology Department of the Royal Victoria Infirmary, Newcastle upon Tyne, between 1988 and 1994.

Anterior chamber taps were performed on three patients using a 25 gauge needle. Cytospins of these

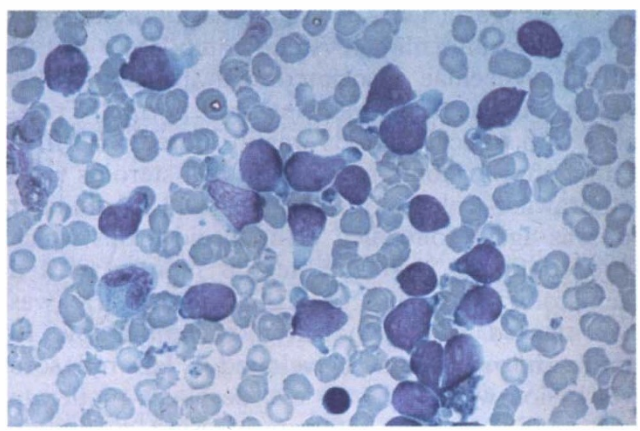

Fig. 1. *Bone marrow aspirates (from case 2) showing large purple-staining blast cells with scanty cytoplasm.*

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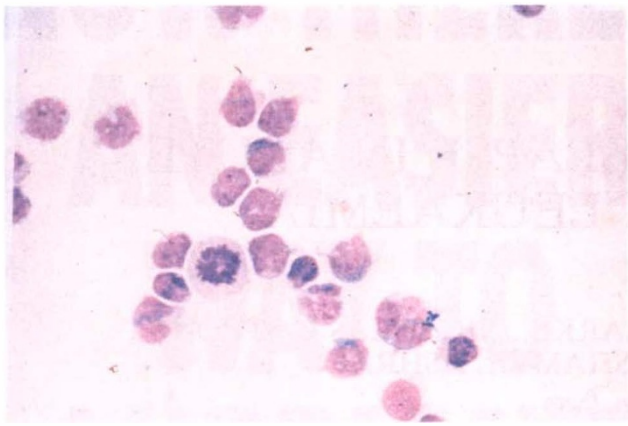

Fig. 2. *Cytospin of anterior chamber aspirate (from case 2) showing blast cells similar to those in Fig. 1. One cell is undergoing mitosis.*

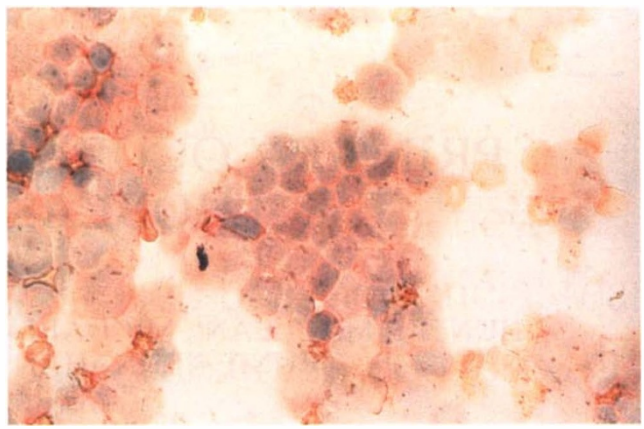

Fig. 3. *Cytospin of anterior chamber aspirate (from case 2) staining positive (brown) for common ALL antigen.*

aspirates were examined for leukaemic blast cells and stained for immunological markers (Figs. 2, 3). In addition, one case had an iris biopsy, which also confirmed leukaemic infiltration of the anterior chamber. In one case the diagnosis was made on the grounds of rapid response to radiotherapy alone. Once the diagnosis of anterior segment relapse has been made, local radiotherapy is successful in eradicating local disease. A search is then made in the bone marrow for haematological relapse and the patient repeats systemic chemotherapy in an attempt to eradicate any occult disease.

Case 1

A boy of 9 months of age was found to have ALL without central nervous system involvement. Remission was induced using the UKALL X C protocol,[1] including 18 Gy of cranial irradiation (delayed until after his second birthday) and 24 months of maintenance chemotherapy. He developed a sore red left eye concurrently with the cessation of maintenance treatment and was seen in the Casualty Department. Due to his age an accurate vision was not established; however, examination revealed a moderate uveitis without synechiae associated with prominent iris vessels. Fundal detail was clear and normal. Treatment with topical steroids was instituted. The iritis settled after 1 month's treatment and steroids were withdrawn. A relapse of iritis occurred 1 month later but was again controlled with steroid drops which were continued over the next 8 months until a haematological relapse of ALL occurred. He was then treated with reinduction chemotherapy, 10 months into which he developed a left red sore eye. Vision was 6/9 in the eye despite a moderate uveitis and an iris infiltrate causing a muddy discoloration and anisocoria. This responded well to 18 Gy of radiotherapy. Twelve months later he developed a second haematological relapse and died shortly afterwards.

Case 2

A girl of 4 years and 6 months was diagnosed with ALL. Cerebrospinal fluid examination was normal and she was treated using the UKALL X A protocol including 18 Gy of cranial irradiation and 24 months of maintenance chemotherapy. Maintenance therapy was discontinued after 24 months. Two months later she complained of photophobia and epiphora and was noticed to have a red left eye. Vision was reduced to 6/24. Examination showed an irregular heterochromic pupil with iritis and a blood-stained hypopyon. The diagnosis of leukaemia infiltration was confirmed on examination of anterior chamber cytospins and iris biopsy material. Local radiotherapy brought about rapid improvement with clearing of the eye changes and restoration of 6/6 vision. Further systemic chemotherapy was started. Fifteen months later she had a haematological relapse and further reinduction chemotherapy. Treatment of this systemic relapse was unsuccessful and she died.

Case 3

A girl aged 2 years and 4 months was diagnosed with ALL. She was treated using the UKALL XI protocol including continuing high-dose methotrexate. Maintenance therapy was stopped after 24 months. Two months later she complained of epiphora and photophobia. Examination revealed a red eye with iritis and heterochromia of the iris. Vision was reduced to 6/18. An anterior chamber tap confirmed leukaemic infiltration. There was no evidence of haematological relapse and a rapid response was obtained with ocular radiotherapy, restoring vision to 6/6. Chemotherapy was reintroduced and continued for 2 years. Unfortunately she has had a haematological relapse 4 months after stopping treatment. Her eyes remain normal to examination.

Case 4

A boy aged 7 years and 2 months was diagnosed with ALL without central nervous system disease. Examination revealed an iritis with an irregular pupil, but without obvious infiltration. He was treated using the UKALL XI protocol including intrathecal methotrexate injections. Concurrent with the cessation of maintenance therapy, 24 months later he developed a red eye without visual disturbance. Examination revealed an iritis with an irregular pupil. An anterior chamber aspirate confirmed the diagnosis of leukaemic relapse and he was successfully treated with local radiotherapy. Chemotherapy was reintroduced, including repeated intrathecal injections of methotrexate. Unfortunately he developed a symptomless central nervous system relapse, for which he received 24 Gy craniospinal irradiation. Systemic chemotherapy continues.

DISCUSSION

The clinical signs of primary relapse in the anterior segment may be so compelling as to allow diagnosis without investigation, but the consequences of the diagnosis are mammoth. Local treatment is easily instituted but the patient also has to undergo reinduction with systemic chemotherapy for an extended period to eradicate any occult disease.[1] This has its own mortality as well as morbidity.[1] Moreover, the diagnosis of uveitis may not always represent leukaemic infiltration. Novakovic *et al.*[6] present one case of a child treated for ALL who proved to have negative anterior chamber tap and was diagnosed with 'straightforward iritis'. Opportunistic endophthalmitis has also been reported presenting with uveitis.[11] For these reasons we believe it is important to confirm a suspected diagnosis of primary ocular relapse of ALL with an anterior chamber tap with or without an iris biopsy. Many patients with anterior segment relapse have a manifest iritis or even a hypopyon and in these cases examination of aqueous cytospins with immune staining is reliable for diagnosis. Cases with only iris changes may need an iris biopsy to confirm leukaemic infiltration. These techniques are relatively simple and safe.

If, when relapse in the anterior segment occurs, the patient is receiving systemic chemotherapy due to a relapse at a different site (as in case 1), then the approach of treatment without investigation appears justified as no significant extra burden to the patient's treatment regime would be imposed.

In case 1 the importance of the uveitis was initially not understood, especially as the iritis responded to treatment with local steroid therapy. It should be stressed that leukaemic uveitis will settle with steroid treatment alone as in case 1, and this should not be taken as an indication of its benignity.

These cases demonstrate a similarity in the timing of relapse. Two cases relapsed concurrently with maintenance therapy withdrawal while the remaining two cases relapsed within 2 months of treatment withdrawal. Novakovic *et al.*[6] present eight cases of anterior segment leukaemic relapse. Five of these were treated following UKALL protocols (one patient with UKALL IV, one with UKALL V and three with UKALL X). The timing of ocular relapse in these cases is also similar. Two cases relapsed concurrently with treatment withdrawal, one case within 1 month, one case within 4 months and one case 17 months into his maintenance therapy regime. Despite these small numbers a clear pattern appears to emerge of a high-risk period for anterior chamber leukaemic relapse in the first few months following maintenance therapy withdrawal. Prognosis is thought to be poor in this group of patients[6] and it may be that these cases represent refractory cases of leukaemia. Certainly these cases illustrate the fact that extramedullary relapse often heralds haematological relapse and this was not prevented by reinstatement of aggressive treatment in three of these patients. Ninane *et al.*[12] has suggested that the eyes may remain a sanctuary site for leukaemic cells during treatment, as they are routinely shielded during central nervous system irradiation and chemotherapy agents do not penetrate the eye wall. Certainly, the timing of relapse would suggest that some leukaemic cells reside in the eyes of some patients during treatment but do not proliferate until the dampening effect of chemotherapy has been removed. Since by far the majority of children in the UK are treated using the standardised UKALL regime it is important that ophthalmologists are aware of this apparent 'high-risk' period for the comparatively rare primary anterior segment relapse of ALL.

Awareness of this high-risk period of anterior segment leukaemic relapse should lead to early diagnosis and treatment and give these children the best chance of ultimate cure in this traditionally poor prognostic category.

Key words: Acute lymphoblastic leukaemia, Eye, Uveitis.

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