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Childhood leukaemia: relapse in the anterior segment of the eye

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SUMMARY A proved first relapse occurred in the anterior segment of eight children with acute leukaemia, two of whom had concurrent central nervous system or bone marrow relapse. A further child developed uveitis after remission was induced, but in this patient no causal relationship with leukaemia was established. Uveitis in children who have had acute leukaemia should be regarded as evidence of relapse, and anterior chamber aspiration and iris biopsy are essential procedures in their evaluation. The outlook for children with anterior segment relapse remains poor despite intensive local and systemic treatment.

The clinical and pathological features of leukaemic infiltration of the anterior segment are well established.[1] Anterior segment changes may be the first manifestation of leukaemia or may reflect the ocular toxicity of antileukaemic therapy.[2] The anterior segment is an uncommon site of extramedullary relapse, accounting for between 0·5% and 2·6% of all relapses in large published series[1 3–5] and is seen most frequently in acute lymphoblastic leukaemia (ALL). Two large post-mortem studies of patients with ALL revealed a similar incidence of anterior segment involvement.[6 7] Anterior segment disease is rare in patients with acute non-lymphoblastic leukaemia[8 9] and is very rare in the chronic leukaemias.

The presenting symptoms of anterior segment relapse are generally non-specific, and post-mortem studies show that anterior segment change may occur in asymptomatic eyes.[6] Symptoms include redness, epiphora, and photophobia, and parents may observe changes in the shape and reactions of the pupils or in the colour and appearance of the iris. Ocular pain and rarely visual loss also occur.

The clinical findings are very varied, with iritis and hypopyon being the most common. Ciliary injection, fine keratic precipitates with anterior chamber cells, flare,[10–12] posterior synechiae,[13] or a greyish white[14] or bloody[15] hypopyon are found on slit-lamp examination.

Secondary glaucoma with corneal oedema is common.[9] These signs are not pathognomic of leukaemic uveitis, but the diagnosis is suggested by iris thickening, either nodular or diffuse, iris masses, iris colour changes, loss of iris crypts, and rubeosis.[4 8 16 17]

Iris nodules complicated by hyphaema and secondary glaucoma also occur in juvenile xanthogranuloma (JXG). Other causes of spontaneous hyphaema in childhood[13] include retinoblastoma, retrolental fibroplasia, persistent hyperplastic primary vitreous, iridoschisis, unsuspected trauma, iris vascular malformations,[18] rubeosis iridis, and other blood dyscrasias.

There is often uncertainty about the diagnosis that can only be resolved by histological or cytological examination.

Heterochromia and iris discoloration, a JXG-like syndrome,[19] and endophthalmitis[9] have also been the first presentations of leukaemia. In the rare event of leukaemia presenting in the eye[19] it is the failure of response to standard uveitis therapy or progression of the disease with intraocular mass formation which alerts the ophthalmologist to the underlying leukaemia.[9] The diagnosis can be established from histopathological investigations of a peripheral iridectomy specimen[20] or cytological examination of an anterior chamber paracentesis aspirate.[9–11 21 22]

Pathological studies show tumour infiltration of the iris and trabecular meshwork.[6 23] The hypopyon consists of leukaemic cells, necrotic tissue,[9] and proteinaceous exudate.[24] Leukaemic infiltration of or haemorrhage into the iris stroma causes discoloration or heterochromia. Patients with glaucoma have histological evidence of leukaemic obstruction of the outflow channels, including the episcleral vessels,[25]

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but there is no specific pattern of vascular involvement in the anterior segment.[1,23]

Materials and methods

Eleven cases of anterior segment relapse of acute leukaemia in childhood have been referred to the Ophthalmology Department at the Hospital for Sick Children, Great Ormond Street, London, between May 1977 and January 1987. Two had insufficient clinical records to be presented as they were second opinions and not managed or followed up by us.

As part of the routine diagnostic investigations a combined paracentesis and iris biopsy technique is used. We make a partial-thickness 3 mm limbal corneal incision and aspirate some of the aqueous through a 25 gauge needle, which is used to complete the incision. The incision, which is made in the 12 o'clock position of the iris, is increased to full thickness and the iris is induced to prolapse or grasped with forceps. The wound is closed with one buried 10/0 nylon suture and subconjunctival steroids and antibiotics given, followed by topical antibiotics and mydriatics.

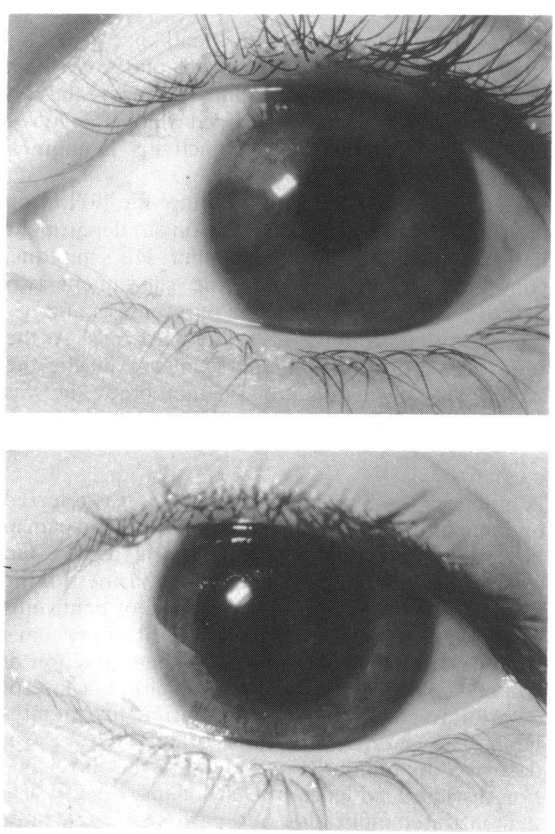

Fig. 1 *Patient 1. Upper figure shows iris thickening, vascularity, discoloration, and pupillary distension. This appearance was also seen in patients 2, 3, 5, and 7.*

Case reports

We present the clinical and pathological data on patients whose first haematological remission was terminated by a recurrence of leukaemia in the anterior segment or was complicated by uveitis.

CASE 1

A boy of 3 years 4 months was found to have ALL without evidence of central nervous system (CNS) involvement. Remission was successfully induced and maintained on the UKALL V regimen.[26] All treatment was discontinued after 26 months. Four months later he presented with sudden onset of pain in his right eye. On examination iritis with hypopyon and a diffusely thickened iris were seen (Fig. 1). Anterior chamber paracentesis and iris biopsy confirmed infiltration by leukaemic lymphoblasts. Local radiotherapy resulted in his anterior chamber appearances returning to normal.

CASE 2

A girl of 2 years 1 month presented with recurrent infections, pallor and fever. Laboratory data included a leucocyte count of $22{\cdot}0\times10^9$/l with 31% lymphoblasts. Bone marrow examination confirmed the diagnosis of ALL. Examination of the cerebrospinal fluid (CFS) was normal. Remission was induced with a modified UKALL IV regimen,[27] and continuation therapy was stopped 31 months after diagnosis. Relapse in the anterior chamber (AC) was diagnosed one month later during investigation of recurrent unilateral left conjunctivitis. On examination a solid white mass in the anterior chamber was noted together with multiple deposits throughout the iris. A diagnosis of ALL infiltration was made by an anterior chamber paracentesis. Local radiotherapy resulted in a rapid improvement apart from the appearance of a small lens opacity.

CASE 3

This patient first presented at age 3 years with fever and malaise. Laboratory findings included leucocytes $30{\cdot}2\times10^9$/l with 80% blasts. Bone marrow examination confirmed the diagnosis of ALL. She had no evidence of CNS involvement. She was treated with vincristine, prednisolone, asparaginase, and daunorubicin induction, craniocervical irradiation (1800 cGy) and intermittent vincristine, prednisolone methotrexate and 6-mercaptopurine continuation chemotherapy for a total of 26 months. One month later she was noted to have anisosocoria.

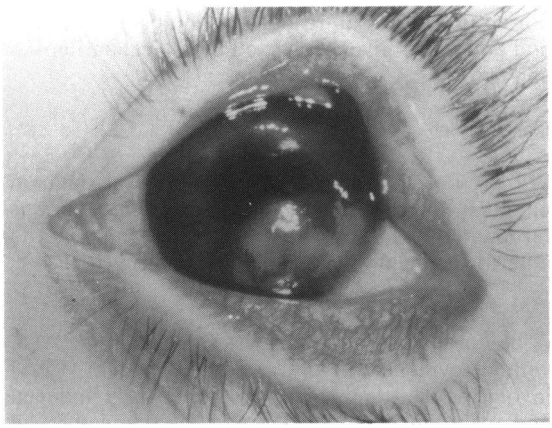

Fig. 2 *Patient 4. This child had an ocular relapse with a solid mass. Patient 8 had a similar appearance.*

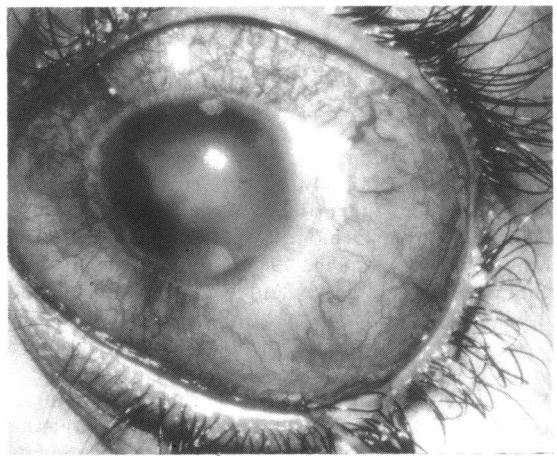

Fig. 3 *Patient 6 had an ocular relapse treated initially with topical and systemic steroids, later with 150 cGy. This appearance, with the eye destroyed by recurrent tumour was seen five months later.*

Examination revealed a few cells in the left anterior chamber and some iris irregularities. Anterior chamber paracentesis revealed the cause of the iritis to be recurrent ALL. She was given a total of 2300 cGy radiotherapy to her left eye, with complete resolution of her ocular signs. Five months later she was diagnosed as having moderately severe bilateral iritis, again assumed to be due to ALL.

Anterior chamber paracentesis did not reveal the cause of the iritis, which responded well to topical steroids and mydriatics. A further five months later she suffered another episode of bilateral iritis. She was given a total of 2500 cGy radiation to each eye, with good resolution. She is developing a small left lens opacity but remains free of recurrent leukaemia.

CASE 4

This patient presented at age 10 months with a leucocyte count of $3{\cdot}0\times10^9$/l with 12% lymphoblasts. Bone marrow examination revealed ALL. There was no evidence of CNS involvement. She received similar treatment to patient 3, although cranio-cervical irradiation (1500 cGy) was deferred until after age 2 years. Treatment was continued for 25 months. Her presentation with a red left eye coincided with the elective discontinuation of therapy. Examination showed an oedematous cornea, raised intraocular pressure, and iris infiltration with a solid mass (Fig. 2). Anterior chamber paracentesis revealed blast cells. Radiotherapy of 2500 cGy resulted in a return to a near normal anterior segment, apart from a slightly peaked pupil due to peripheral anterior synechiae superiorly.

CASE 5

This 3½-year-old boy was found to have ALL following presentation with fever and knee pain, and leucocyte count of $2{\cdot}4\times10^9$/l with 9% blasts. No blast cells were seen on CSF cytospin. He was treated on the UKALL X regimen.[28] He first developed features of a left sided unilateral conjunctivitis 17 months after diagnosis of ALL.

His symptoms fluctuated during the following month, and when he was first seen on our department he had cells in the anterior chamber. His symptoms continued to fluctuate over the subsequent two months. An anterior chamber paracentesis and iris biopsy were performed, revealing blast cells. At the time of anterior chamber paracentesis, during the second year of continuation chemotherapy, he was found to have a bone marrow relapse.

CASE 6

A boy from the Middle East with ALL was referred one year after diagnosis with photophobia and pain in his left eye radiating to the temporal region. On examination conjunctival congestion, haziness of the cornea, slight proptosis, and evidence of panuveitis were noted. He was treated with topical and systemic steroids without improvement. A single fraction of 150 cGy was given at his local hospital because of deteriorating vision. He was referred five months later. The internal structures of his left eye was destroyed by tumour (Fig. 3), and further investigation disclosed evidence of CNS relapse. A CT scan demonstrated infiltration of the whole eye and optic nerve. He was treated with palliative radiotherapy to his lefe eye. However, he experienced bone marrow and CNS and bilateral ocular relapses and died.

CASE 7

This boy was diagnosed as having ALL at the age of 9 months. Remission was induced with vincristine, prednisolone, and L-asparaginase. He received triple intrathecal chemotherapy but no cranial irradiation because of his young age. At the age of 2 years and 1 month he presented with an acutely inflamed right eye, which proved to be due to leukaemic infiltration on anterior chamber paracentesis and iris biopsy. He received further induction chemotherapy, cranial and local radiotherapy, and has remained disease free.

CASE 8

At 5 months this child presented with acute monocytic leukaemia. Remission was induced with intensive chemotherapy, complicated by septicaemia and was associated with bacterial colonisation of her central venous line. At 9 months of age, during her third course of chemotherapy, she developed a red left eye with uveitis. An iris biopsy and anterior chamber paracentesis confirmed the presence of leukaemic blasts. Local ocular radiotherapy was begun but was complicated by iris prolapse, which was repaired, however. She died aged 10 months of septicaemia from Gram-negative organisms.

CASE 9

This 5-year-old boy had been seen by an ophthalmologist at age 3 years for a pseudo squint, with no abnormality detected. He developed ALL in May 1984, and treatment was stopped electively in July 1986. His mother sought the advice of an ophthalmologist because he failed a school eye test. The only significant abnormality found on examination was cells in both anterior chambers and a fine keratic precipitate. An iris biopsy and AC paracentesis revealed inflammatory cells. He was treated with subconjunctival depot steroids and has been free of symptoms and abnormal signs for nine months.

Discussion

The mechanism of anterior segment relapse is not clear. Migration of leukaemia lymphoblasts along the posterior ciliary vessels in the subarachnoid space surrounding the optic nerve had been proposed as a mechanism linking the central nervous system and the anterior segment.[10] Although the pathogenesis of anterior segment disease is unknown, the infrequency of concurrent CNS relapse and anterior segment relapse suggests that seeding from the CNS is unlikely to be an important mechanism. The frequency of isolated anterior segment relapse supports the sanctuary concept of the anterior chamber.[11] Care is taken to exclude the anterior chamber from 'prophylactic' central nervous system irradiation.

Extensive ocular leukaemic infiltration is exceptionally rare and easily recognised, but the diagnosis in children with intermittent iritis, as in case 5, or refractory iritis, as in case 3, is less obvious. Examination of an anterior chamber aspirate has been the most widely used technique for establishing a diagnosis, but we would not support this as a sole means of obtaining an accurate diagnosis because of the difficulty in interpreting the significance of the few abnormal cells on cytospin of fluid obtained by aspiration. Cytochemistry, surface immunological markers, cytogenetics, or possibly molecular studies might change this, but at the moment we use a combination of iris biopsy and paracentesis. The technique of aspiration or paracentesis is important because the child may be debilitated and immunosuppressed, and healing may be further delayed by radiotherapy. In addition the intraocular pressure is likely to be severely raised from time to time by crying.

Six of our cases had iris biopsy, which revealed the exact cause of the iritis, enabling more accurate characterisation of the infiltrating cells. Iris biopsy has a very low surgical complication rate and is indicated in the leukaemic child with iritis, when there is even the least doubt about the diagnosis. In case 7, for instance, the clinical certainty was so high, and the therapeutic alternatives so few, that neither biopsy nor aspiration were indicated. In contrast, in patient 9 the result was that no leukaemic cells were found and the uveitis responded to topical steroid treatment only, with no recurrence of leukaemia over nine months. In case 3, although there was some difficulty with the interpretation of the second iris biopsy and AC aspirate, radiotherapy and reinduction chemotherapy brought about a prolonged period of freedom from uveitis.

That the uveitis is not necessarily related to leukaemic ocular relapse, as in case 9, emphasises the need for accurate diagnosis. In view of the rarity of childhood uveitis it is also puzzling that a non-leukaemic uveitis should occur so closely related to the cessation of chemotherapy. Perhaps in this instance the uveitis was not related to the leukaemia so much as the treatment, or the associated immunosuppression, as occurs in patients receiving bone marrow transplants.

We have had one significant complication of iris biopsy: in patient 8 an iris prolapse occurred one week after biopsy during radiotherapy. It was closed without recurrence. We considered it was due to a combination of raised intraocular pressure from iritis and crying and a wound whose healing was compromised by chemotherapy and radiotherapy.

Table 1 *Clinical details of children with anterior segment relapse*

Patient	ASR on/off CT	Concurrent relapse	Duration of first remission† (months)	Further therapy		Duration of second remission (months)	Subsequent relapse (site)	Survival at Nov 1987 following initial ASR (months)
				Eye	Systemic			
1	Off	–	29	2400 cGy	UKALL V[25]	33	BM	76
2	Off	–	31	2400 cGy	UKALL V[25]	13	BM	14
3	Off	–	26	2300 cGy	UKALL X[27]	41+	–	45+
4	On	–	24	2500 cGy	Repeat initial therapy	18	BM	21
5	On	BM	16	1200 cGy	UKALL X[27] CPA TBI, ABMR	1	BM	6
6	On	CNS	10	2550 cGy	VCR 6MP MTX	2	BM, CNS, Bilateral ASR	12
7	On	–	13	2400 cGy	VCR Pred, Asp	12+	–	15+
8	On	–	4	2400 cGy	MAZE	–	–	1*

CT=continuation chemotherapy. BM=bone marrow. CNS=central nervous system. VCR=vincristine. 6MP=6 mercaptopurine. *Died from Gram-negative septicaemia. MTX=intrathecal methotrexate. RT=craniocervical radiotherapy. Pred=prednisolone. MAZE=M-AMSA, 5 azacytidine, etoposide. CPA=cyclophosphamide. TBI=total body irradiation. ABMR=autologous bone marrow rescue. Asp=asparaginase. †First remission terminated by AC relapse. ASR=anterior segment relapse.

Tumour regression and lowering of intraocular pressure have been the aims of ocular therapy. Topical steroids and periocular steroid injections have had variable success in reducing the severity of the iritis or arresting tumour infiltration. Irradiation yields more reliable results and is effective in most forms of anterior segment leukaemia both in inducing clinical tumour regression and in controlling the secondary glaucoma.[17] Initial doses administered have varied from 250 to 1500 cGy.[22] Case 7 had 250 cGy and this was followed by progression within the eye and around the optic nerve sheath and ultimately into the suprasellar cistern, from which death resulted despite treatment. The poor prognosis in our patients may be a reflection of the significance of sanctuary site relapse and emphasises the need for optimal local treatment. Despite our relatively high total doses of 2300 to 2500 cGy (Table 1), followed by complete clinical regression, long-term systemic prognosis is still poor and in two cases was followed by further ocular relapse. The ocular prognosis depends on the nature of the eye relapse: if there has been a solid recurrence there is usually structural eye damage, which may be irretrievable. All but one patient (6) retained useful vision in the involved eye.

When the biopsy and aspirate do not show leukaemic infiltration, it is important to consider the prior treatment that the child has received. Steroids may mask the real cause of the uveitis, and their preoperative use should be avoided.

Enucleation of an eye that is the site of recurrent isolated anterior segment relapse is rarely indicated. Jankovic *et al.*[23] reported an adolescent in prolonged second remission following enucleation. High-dose systemic chemotherapy has induced temporary remissions of anterior segment relapse.[29] However, this therapy alone appears to be ineffective in ensuring prolonged disease-free survival.

Patients with prolonged second remissions received intensive combination systemic chemotherapy, prolonged continuation therapy, and local irradiation. The prognosis for children with anterior segment relapse remains poor despite aggressive local and systemic treatment because of a substantial risk of subsequent bone marrow or CNS relapse. The timing of AC relapse is important in predicting which patients are at greatest risk of dying of recurrent leukaemia.[9 30 31]

We believe the goal of therapy in any child with AC relapse is cure and that every patient with uveitis within six years of achieving first remission in ALL should undergo iris biopsy and cytospin examination of AC aspirate followed by intensive retreatment.

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