

Full clinical cases submission template

<p>TITLE OF CASE <i>Do not include "a case report"</i></p> <p>Orbital mass secondary to infantile acute lymphoblastic leukaemia</p>
<p>SUMMARY <i>Up to 150 words summarising the case presentation and outcome (this will be freely available online)</i></p> <p>An 8-month-old Asian female infant was referred with a one-week history of left periorbital swelling on a background of a narrowed left palpebral aperture over the preceding 8 weeks. There was no history of chronic illness, fever or other systemic features. Examination revealed a tender and fluctuant medial canthal swelling with associated periorbital haematoma. There were no other ophthalmic findings and neurological examination was normal. A MRI scan of the brain and orbit demonstrated abnormal soft tissue with features of an aggressive tumour in the left orbital region with no globe invasion. Peripheral blood smear revealed blast cells, confirmed by bone marrow aspirate. A diagnosis of infant acute lymphoblastic leukaemia was made. The patient was started on risk-stratified chemotherapy according to the <i>Interfant-06 Protocol</i>. The periorbital swelling resolved by day eight following a course of prednisolone, the patient continues on chemotherapy and is currently in molecular remission.</p>
<p>BACKGROUND <i>Why you think this case is important – why did you write it up?</i></p> <p>Orbital masses secondary to acute lymphoblastic leukaemia (ALL) are a rare entity, with only seven cases reported in the literature, five of which were known to already have a systemic diagnosis.(1) Only 10% of orbital tumours in childhood are due to leukaemias and lymphomas, with granulocytic sarcomas secondary to acute myelogenous leukaemia (AML) being the most prevalent.(2) This patient was misdiagnosed with unilateral conjunctivitis, revised to dacryocystitis, and finally referred to our tertiary referral centre with an extensive dacryocele. ALL was found to be infiltrating the orbit as the sole presenting feature. Due to the misdiagnosis and delay in referral, it is important to highlight more sinister cases of orbital swelling as a potential differential diagnosis.</p>
<p>CASE PRESENTATION <i>Presenting features, medical/social/family history</i></p> <p>An 8-month-old Asian female infant was referred to the Ophthalmology department at Great Ormond Street Hospital (UK) with a one-week history of left periorbital swelling, preceded by an eight-week history of a narrowed left palpebral aperture. This was initially treated as conjunctivitis and then dacryocystitis. There was no fever, weight loss or other systemic features reported. There was no significant medical or family history and the baby was previously healthy with normal development.</p> <p>On examination, the patient was afebrile and appeared comfortable, alert and interactive. External examination revealed extensive swelling around the left medial canthus extending into the periorbital region with evidence of haematoma (Fig 1A). The palpebral aperture in the left eye was smaller than the right. The patient was able to fix and follow, and using forced choice preferential looking Teller acuity cards, the visual acuity was 6 cpd in both eyes (6/45), and there was no strabismus. Pupils were equally reactive to light with no relative afferent pupillary defect. Slit lamp examination revealed no anterior segment abnormalities, and fundus examination was normal with healthy optic disc, macula and peripheral retina. Regional examination of the lymph nodes revealed a 1 cm enlarged, firm, mobile occipital node on the left. On auscultation of the chest, there was diffuse bilateral wheeze. Tonsils were also enlarged. Abdomen was distended but soft and non-tender. Liver and spleen were 4 cm and 3 cm below the costal margin, respectively. Neurological and cardiovascular examinations were normal.</p>

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INVESTIGATIONS *If relevant*

An urgent MRI of the brain and orbit was performed (Fig 1C, D). This revealed abnormal soft tissue in the left orbital region with radiological features of an aggressive tumour such as neuroblastoma or rhabdomyosarcoma. The tumour was found to invade the left medial aspect of the orbit with extension into the extraconal fat, muscle orbicularis, anterior ethmoidal cells, radix of the nose, and the subcutaneous infraorbital fat tissue reaching the superior alveolar process of the mandible (highlighted by white arrows). There was minimal mass effect on the left globe with no invasion or intracranial extension noted.

Laboratory studies included: Full blood count which discovered neutropenia, thrombocytopenia and anaemia with WBC $21 \times 10^9/L$ (high), platelets $10 \times 10^9/L$ (low) and haemoglobin 75 g/L (low). Total white cell count was increased for age when examined in the peripheral blood smear; showing a majority of total white blood cells (80%) with immature appearances consistent with lymphoid blasts. Bone marrow aspiration revealed ALL with blast rate representing 80% of total bone marrow events. Immunophenotypic markers (CD10-87%, CD19-100%, CD34-0%, CD38-100%, CD44-80%, and CD45-100%) were consistent with precursor B-cell ALL. Expression levels of CD45 and CD38 are typically observed in pre B-cell ALL, however the remaining phenotypic picture with CD10 expression on 87% of blasts would suggest common/pre B-cell ALL. Cytogenetic analysis of this patient's bone marrow cultures showed what appeared to be a normal karyotype (46,XX) with no identifiable abnormal clone in twenty-three metaphase spreads examined (sixteen metaphase spreads fully analysed and seven metaphases screened). Interphase FISH analysis identified a *KMT2A* rearrangement i.e. rearrangement of the mixed lineage leukemia (*MLL*) gene in 45.5% of nuclei. We have examined 202 interphase nuclei using an Abbott/Vysis dual-colour, break-apart probe set for the *KMT2A* (11q23, red/green fusion) region; 92/202 (45.5%) nuclei examined showed a positive signal pattern for a *KMT2A* rearrangement. Metaphase FISH identified a derived chromosome 11 in two metaphase spreads but due to poor chromosomal morphology, the *KMT2A* partner was unable to be reliably identified.

The cerebrospinal fluid obtained by lumbar puncture was clear of leukaemic blast cells.

DIFFERENTIAL DIAGNOSIS *If relevant*

There are age-specific trends in the incidence of disorders causing orbital swelling, which aid the diagnostic process. For children under 2 years of age, the major causes are infantile peri-ocular haemangiomas, lymphangiomas, and dermoid cysts, which tend to be slow growing. Acute onset signs may arise through a haemorrhage from a pre-existing vascular lesion, or an infective cause resulting in pre-septal or orbital cellulitis. Rapidly increasing proptosis with periorbital swelling and ecchymosis is suggestive of a rapid-growing tumour such as rhabdomyosarcoma or neuroblastoma. The main differential diagnoses to consider are:

1. Vascular: Venous-lymphatic malformations e.g. infantile peri-ocular haemangioma, lymphangioma
2. Infective: Dacryocystitis, orbital cellulitis, pre-septal cellulitis
3. Tumour: Neuroblastoma, rhabdomyosarcoma, retinoblastoma, granulocytic sarcoma (AML), optic nerve glioma, dermoid cyst

Infantile peri-ocular haemangiomas appear by 6 months of age, are characterised by a period of rapid growth in the first year, followed by regression over the proceeding years. Lymphangiomas infrequently present in early childhood, they do not regress and can be complicated by sudden haemorrhage with rapidly progressive enlargement. Characteristic cutaneous lesions can be diagnosed clinically, however, most will require ultrasound and CT/MRI to delineate the tumour with its intrinsic blood flow.

Children with pre-septal cellulitis present with fever, malaise, painful swollen inflamed lids, but no proptosis, normal eye movements and normal optic nerve function. This is in contrast to those with orbital cellulitis who do show proptosis, restricted eye movements, and potentially optic nerve compromise.

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Neuroblastoma accounts for most childhood orbital metastatic disease under the age of 3. Rhabdomyosarcoma and retinoblastoma are the most important sources of secondary orbital disease, although the latter is usually confined intraocularly but in advanced cases may extend into the orbit. Optic nerve gliomas and dermoid cysts are slow growing. There are a number of other rare tumours but as a group they are difficult to distinguish clinically and biopsy is recommended for confirmation.

TREATMENT *If relevant*

The patient was started on chemotherapy as per the *Interfant-06 Protocol*. This is the international collaborative treatment protocol for infants under the age of 1 with ALL. Patients are stratified into low, medium or high risk based upon age, white cell count/prednisolone response and *MLL* status. This patient was categorised into medium risk and urgently commenced on oral prednisolone 60 mg/m²/day according to the induction block of chemotherapy.

OUTCOME AND FOLLOW-UP

The periorbital swelling resolved by day eight (Fig 1B). The prednisolone response was good and subsequently the patient continued with chemotherapy treatment on the standard medium risk arm. At the end of the induction chemotherapy block our patient was in molecular remission. Providing the patient remains in complete remission at all follow-up time points, 5 blocks of chemotherapy will be completed in total.

In terms of prognosis, infants with ALL do far worse than older children. Interfant-99, the largest collaborative trial to date of infantile ALL reported 4-year event free survival (EFS) of 47% with considerable variation in outcome between different risk groups.(3) Infants with ALL defined as low risk had a 4-year EFS of 74%, medium risk 44.8%, and high risk 19.8%. Even though most treatment failures are related to relapse of disease, treatment-related mortality and life-limiting late effects in survivors are significant.

DISCUSSION *Include a very brief review of similar published cases*

Infantile acute lymphoblastic leukaemia is rare, contributing to ~2-4% of all childhood ALL.(4) It is biologically distinct from the disease in older children and associated with a poorer prognosis. Infants are more likely to present with high leucocyte counts, hepatosplenomegaly and overt neurological disease.(5) The vast majority (70-80%) of infants with ALL express cytogenetic abnormality by chromosomal translocations involving the *MLL* gene at chromosome 11q23.(6) Independent prognostic factors of outcome in infant ALL include status of the *MLL* gene, CD10 expression, age at diagnosis, white blood cell count at presentation, central nervous system involvement, co-expression of myeloid markers, and early response to prednisone.(7)

It is unclear if this infant girl presented with primary orbital or systemic ALL, as the initial focus was the periorbital swelling, causing a deflection from any systemic features, which were later found on presentation to our institution. A more careful consideration to the extra-ocular clinical data and blood counts may have hastened the diagnosis of this child. There is only one other report in the literature of an infant presenting with similar orbital involvement.(8) There are a further 6 cases reported of childhood orbital ALL, 5 with a confirmed systemic diagnosis, and only one in a 3 year old with primary orbital presentation.(9)(10)

Ophthalmic signs in patients suffering from leukaemia was first described as 'leukemic retinopathy' by Liebreich in 1863, and although reports of patients with ALL presenting with ophthalmic symptoms as the initial sign of the disease is rare, ocular changes during the disease is common.(11) Ophthalmic manifestations are due to the accumulation of blast cells secondary to bone marrow failure, and include extraocular muscle, optic nerve and intraocular infiltration. Ocular involvement is associated with a poor prognosis and increase

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risk of relapse. One study found that the five year survival rate was 21.4% in children with leukaemic ocular involvement compared to 45.7% in those that did not.(12) Many of these lesions are asymptomatic, therefore it is important to consider ophthalmic evaluation at the time of diagnosis of ALL as well as in monitoring relapse.

There was a lack of investigative rigour in treatments for infantile ALL. This is due to the rarity of the disease, making it hard to design clinical trials with sufficient numbers. For this reason, in 1999, 17 different study groups across 20 nations participated in an international collaborative clinical trial, Interfant-99, which was subsequently revised to Interfant-06 in 2006, to include early intensified regimens to reduce relapse. With multi-agent, risk-stratified regimens, 90-95% of infants with ALL can achieve remission after initial induction therapy.(13) Although the survival rate has improved, in the last decade it has remained stagnant and the longterm outcome for *MLL*-rearrangement infantile ALL, such as in our case, still remains suboptimal i.e. 4-year EFS of 44.8%. The future of infant ALL therapy will revolve around molecular targets, which focus on prognostic markers such as genetic factors. The challenge now is to identify the most appropriate target for future clinical trials. The FMS-like tyrosine kinase 3 (FLT3) inhibitor, CEP-701, is the first novel agent to be investigated in a large collaborative clinical trial for *MLL*-rearrangement infantile ALL and is currently underway.(14)

LEARNING POINTS/TAKE HOME MESSAGES 3 to 5 bullet points – this is a required field

- Infant acute leukaemia is a poor prognostic entity that should be considered as a rare differential diagnosis of persistent orbital swellings that otherwise appear to be caused by typical local infectious/inflammatory pathologies.
- A thorough physical examination and careful attention to the blood counts as well as early referral may help minimise diagnostic delay in these babies.
- Ocular involvement in patients with leukaemia is associated with a poorer prognosis and increased risk of relapse.

REFERENCES Vancouver style (Was the patient involved in a clinical trial? Please reference related articles)

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FIGURE/VIDEO CAPTIONS *figures should NOT be embedded in this document*

Figure 1 (A) Patient with extensive left medial canthal swelling at presentation, and (B) after 8-days on prednisolone the periorbital swelling resolved. (C) Axial MRI T2-weighted image demonstrating a tumour invading the left medial aspect of the orbit with extension to the extraconal fat, and (D) a coronal view showing invasion into the orbicularis oculi, anterior ethmoid cells, radix of the nose and subcutaneous infraorbital fat tissue reaching the superior alveolar process of the mandible.

PATIENT'S PERSPECTIVE *Optional but strongly encouraged – this has to be written by the patient or next of kin*

“It would be an understatement to say that I was shocked when I learnt that my baby had cancer. Initially, I was told by a number of services that it was an infection, but I knew something was wrong but felt no-one was listening. My daughter has leukaemia, I accept that, but I’m more frustrated at how long it took to find this out. I realise that her presentation was extremely rare, but even the basic tests such as a blood test was overlooked and not done in the initial phases. My message to doctors is to think outside the box, don’t always go by the textbooks, have a system in place to cover the 'what ifs' because one day you will come across something that doesn’t fit the picture, and you can’t afford to get it wrong”

- Patient's Mother

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