

Uveitis masquerade syndrome as an early manifestation of precursor B-cell acute lymphoblastic leukaemia: a case report

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Abstract

Background: To report a case of paediatric precursor B-cell acute lymphoblastic leukaemia (ALL) presenting as uveitis masquerade syndrome.

Case presentation: A 3-year-old girl with neutropenic sepsis presented with poor fixation and right preferential gaze. Vision was light perception and counting fingers in right (OD) and left (OS) eyes with bilateral panuveitis, and OS Roth spots, retinal haemorrhages, and exudates. Vitreous biopsy was negative for organisms, malignant cells, and blasts. Bone marrow aspiration and trephine biopsy (BMAT) was inconclusive for leukaemia and orbital magnetic resonance imaging showed no infiltration. She improved with antimicrobials and steroids. However, during rehospitalization six months later for neutropenic sepsis, repeated BMAT showed 80% blasts confirming B-cell precursor ALL, requiring chemotherapy. OD vision remained poor with band keratopathy, keratoconjunctivitis sicca, seclusio pupillae, cataract, and vitreous haemorrhage. OS vision improved partially with a macular scar.

Conclusion: Paediatric precursor B-cell ALL may present as uveitis masquerade syndrome. Prompt diagnosis and treatment may increase survival and visual potential.

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Keywords: paediatric acute lymphoblastic leukaemia, uveitis, uveitis masquerade syndrome

Sindrom penyamaran uveitis sebagai manifestasi awal sel B pelopor leukemia limfoblastik akut laporan kes

Abstrak

Latar belakang: Melaporkan satu kes melibatkan kanak-kanak dengan sindrom penyamaran uveitis sebagai manifestasi awal sel B pelopor leukemia limfoblastik akut (ALL).

Persembahan kes: Seorang kanak-kanak perempuan berusia tiga tahun yang dijangkiti sepsis neutropenik mengalami tumpuan penglihatan yang lemah dan cenderung melihat ke arah kanan. Penglihatan mata kanannya (OD) adalah hanya persepsi kepada cahaya, sementara mata kiri (OS) hanya dapat mengira jari. Hasil dari pemeriksaan, kedua-dua mata mendapat radang panuveitis serta terdapat bintik Roth, pendarahan retina, dan eksudat pada OS. Biopsi dari vitres tidak menunjukkan kehadiran sebarang organisma, sel barah mahupun blas. Pemeriksaan sum-sum tulang dan biopsi (BMAT) serta pengimejan resonan magnetik bahagian orbit tidak menunjukkan penyusupan leukemia. Rawatan dengan ubat antibiotik dan steroid adalah berkesan pada peringkat ini. Malangnya, kanak-kanak ini dimasukkan semula ke hospital enam bulan kemudian untuk sepsis neutropenia. Hasil dari BMAT yang kedua menunjukkan kehadiran 80% sel blas yang mengesahkan sel B pelopor ALL. Kanak-kanak ini dirawat dengan kemoterapi, malangnya penglihatan OD tidak dapat dipulihkan dengan kewujudan keratopati jalur, keratoconjunktivitis sicca, seklusio anak mata, katarak, dan pendarahan vitreous. Manakala penglihatan OS pulih sebahagiannya dengan parut di bahagian titik peka.

Kesimpulan: Sindrom penyamaran uveitis mungkin merupakan tanda awal sel B pelopor ALL di kalangan kanak-kanak. Pengesanan awal dan rawatan segera mungkin boleh meningkatkan jangka hidup dan potensi penglihatan.

Kata kunci: leukemia limfoblastik akut (ALL), sindrom penyamaran uveitis, uveitis,

Introduction

Acute lymphoblastic leukaemia (ALL) is the commonest childhood malignancy of which precursor B-cell ALL is the commonest form.¹ The annual incidence is 35 per million children below 14 years.² Although ALL has a bimodal distribution affecting children and middle-aged adults, 80% of cases occur in children.³ It is due to abnormal proliferation and malignant transformation of lymphoid progenitor cells in the bone marrow, peripheral blood, and extramedullary sites.³ Patients present with constitutional symptoms and bone marrow failure due to leukemic infiltration.¹ Ocular infiltration in leukaemia accounts for only 5% of paediatric uveitis cases.⁴ Ocular manifestation as an initial presenting feature of ALL, especially those involving the anterior segment as well, is extremely rare with only three cases previously described to our knowledge.¹ We now present a case of a child with bilateral uveitis as a presenting feature of precursor B-cell ALL.

Case presentation

A 3-year-old girl with no comorbidities presented with 1 week of fever, cough, and lethargy associated with 1 day of vomiting and reduced consciousness. On examination, she was in septic shock and had hepatosplenomegaly, skin bruises, and generalized lymphadenopathy. She required inotropes and intubation for airway protection. Full blood picture (FBP) showed severe anaemia (haemoglobin 2.1 g/dL) with leucocytosis (13.8 K/ μ L), neutropenia (absolute neutrophil count 0.73 K/ μ L), and thrombocytopenia (5 K/ μ L) with an absence of blasts. She was treated with broad-spectrum antibiotics and antifungals following a diagnosis of febrile neutropenic bicytopenia with liver and splenic microabscesses. Blood, urine, tracheal aspirate, and cerebrospinal fluid cultures were negative. She improved hemodynamically with treatment. However, she required intravenous dexamethasone 9 mg and nebulized budesonide 1 mg BD for 1 day for stridor after extubation. Subsequently, she underwent a bone marrow aspiration and trephine (BMAT) biopsy that showed a borderline B-cell precursor blast count of 4–5%, which was insufficient to diagnose leukaemia. BMAT was not repeated as she improved clinically and repeated FBP showed normalizing counts.

Three weeks later, she was referred for poor fixation with a right preferential gaze. There was no eye redness, swelling, discharge, or pain. She had no previous visual problems. Vision was light perception in the right eye (OD) and counting fingers in the left eye (OS). Red reflex was poor bilaterally (OU) without leukocoria or relative afferent pupillary defect. There were fine keratic precipitates with occasional anterior chamber cells without hypopyon OU. Fundus OD showed dense vitritis whereas OS showed inferior vitritis, submacular haemorrhage, Roth spots, and retinal haemorrhages with exudates. There was no vasculitis or optic

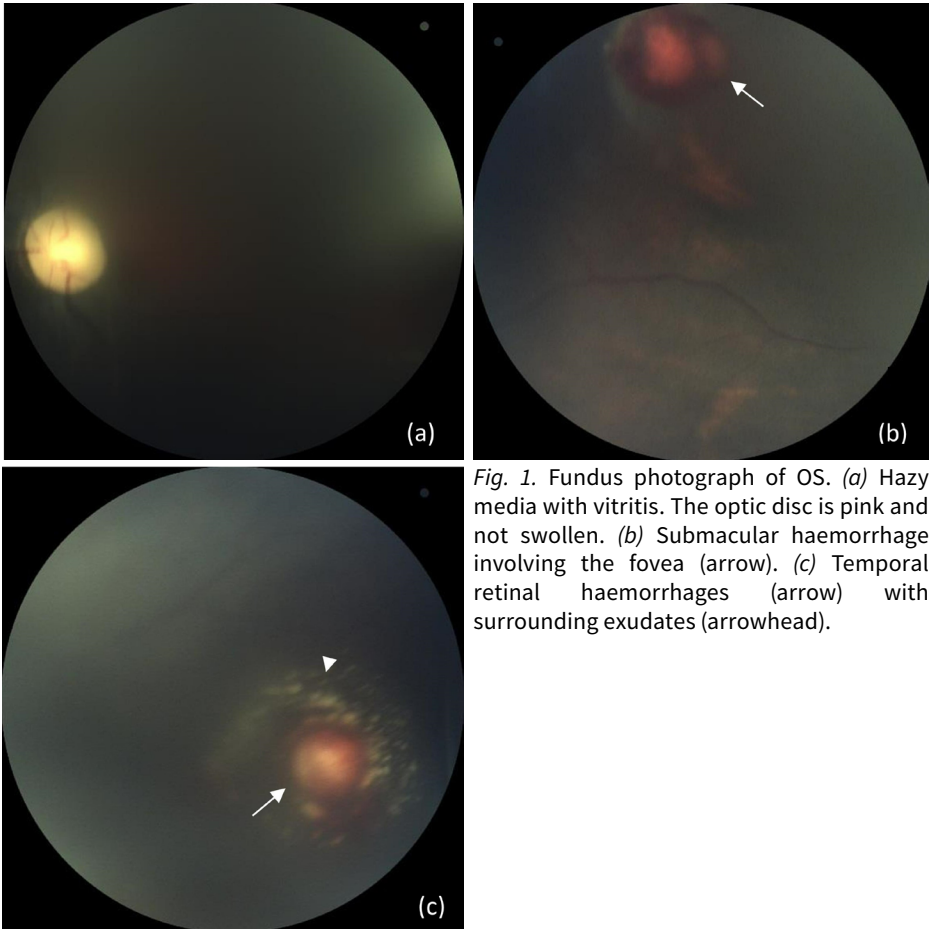


Fig. 1. Fundus photograph of OS. (a) Hazy media with vitritis. The optic disc is pink and not swollen. (b) Submacular haemorrhage involving the fovea (arrow). (c) Temporal retinal haemorrhages (arrow) with surrounding exudates (arrowhead).

disc swelling (Fig. 1). The intraocular pressure (IOP) was normal bilaterally. B-scan OD showed a flat retina with vitritis without loculation. The child was started on intensive empirical topical antibiotics and steroids. Magnetic resonance imaging (MRI) of the orbits showed hyperintense irregular intraocular lesions at the posterior aspect of both globes, suggestive of haemorrhage. However, there were no enhancing lesions that might indicate leukemic infiltration.

At this juncture, in the presence of dense vitritis OD, there was a diagnostic dilemma between leukemic infiltration and endogenous endophthalmitis secondary to immunosuppression, or both. Hence, she underwent right 23-G diagnostic and therapeutic pars plana vitrectomy. Intraoperatively, there was dense vitreous haemorrhage with pre- and submacular haemorrhage. Vitreous biopsy showed few pus cells with no bacteria or fungi on direct smear. Cytology

showed neutrophils admixed with a few atypical lymphocytes, which were likely reactive, consistent with a chronic inflammatory process. However, no malignant cells or blasts were seen. Vitreous culture and cytomegalovirus polymerase chain reaction (PCR) were negative. In view of normalizing FBP, clinical improvement after antimicrobial treatment, and inconclusive ocular investigations for malignancy, her uveitis was attributed to infective endogenous endophthalmitis, likely related to the liver and splenic abscesses.

Two months later, her vision remained light perception OD, whereas OS improved to 3/60. Fundus OD showed persistent diffuse organized vitreous haemorrhage with a flat retina on B-scan. Fundus OS showed a vitreous opacity overlying the macula with retinal fibrosis at the inferotemporal arcade without retinal traction and resolution of retinal haemorrhages.

Six months after the initial presentation, she was readmitted for 2 days of fever, cough, lethargy, and poor oral intake. The FBP showed bicytopenia and leucocytosis with 65% blasts. A repeated BMAT showed 80% blasts consistent with B-cell precursor ALL. Bone marrow cytogenetics revealed a t(12; 21)(p13; q22) translocation and *ETV6-RUNX1* gene fusion. There was no central nervous system involvement. Although her vision had improved to 6/9.5 OS, OD vision remained light perception only. OD examination showed a quiet anterior chamber, seclusio pupillae, white cataract, and contracting vitreous haemorrhage via B-scan. OS examination was unremarkable except for a vitreous band overlying the inferior macula. The OD was treated with topical steroid and cycloplegic agents.

The patient responded well to chemotherapy. Unfortunately, she developed band keratopathy and keratoconjunctivitis sicca OD and was given lubricants. She also developed transient raised IOP OU, which responded to a short course of single IOP-lowering agent and discontinuation of topical steroid. During the last review, OD vision remained status quo with light perception, whereas OS vision was 6/24 with a macular scar.

Discussion

ALL in children occurs typically between the ages of 2 and 5 years.⁵ This child fits the age group, being 4 years old at the point of diagnosis. The incidence of ocular manifestations in patients with leukaemia varies significantly from 9% to 90% due to the transient nature of findings that vary with the course of the disease.⁵ However, ocular manifestations are commoner in adults and in myeloid leukaemia than in lymphoid leukaemia.⁵

Ocular manifestations of leukaemia are divided into primary (direct infiltration) and secondary (indirect involvement). Direct infiltration, including uveal, retinal, orbital, and optic nerve infiltration, is rare and may present as uveitis, proptosis, and optic disc swelling.^{4,5} Ocular infiltration occurs most frequently in the choroid

due to its high vascularity. Uveitis due to direct infiltration of ocular tissues by leukemic cells is termed uveitis masquerade syndrome.⁶ The vitritis present in this patient could be due to uveal infiltration by leukemic cells causing intense inflammation. However, there was no radiological or cytological evidence of orbital, optic nerve, or vitreous infiltration.

Indirect ocular involvement may be due to haematological abnormalities (thrombocytopenia, anaemia, and hyperviscosity) that lead to leukemic retinopathy. This is the commonest ocular finding in ALL and may manifest as retinal and vitreous haemorrhage, Roth spots, and vascular occlusion.^{4,5} Ocular toxicity due to chemotherapy and the effects of immunosuppression may lead to secondary ocular manifestations such as infections, keratoconjunctivitis sicca, conjunctivitis, corneal opacity, glaucoma, and cataract.^{4,5}

Unfortunately, this child developed many of the ocular manifestations mentioned above. She displayed leukemic retinopathy evidenced by the presence of vitreous and retinal haemorrhages, Roth spots, and retinal exudates.⁵ The cause of IOP elevation was likely multifactorial, including steroid and chemotherapy administration. Leukemic infiltration of the trabecular meshwork by blasts should be considered as well. Severe inflammation as a cause is unlikely as both anterior chambers were quiet. She developed white cataract, keratoconjunctivitis sicca, and band keratopathy, which were likely sequelae of intense, prolonged ocular inflammation and chemotherapy.⁵ The cataract could also be attributed to the vitrectomy itself.

The diagnosis of uveitis masquerade syndromes was initially considered given her suspicious FBP and BMAT findings in addition to the unresolved bilateral vitritis. Furthermore, infection, as in her case, is a common presentation in the prodromal phase of leukaemia, where an initial BMAT may be negative in the presence of cytopenia.⁷ However, the vitreous tap and biopsy were inconclusive for malignant cells and did not yield any organisms. We postulate that the negative cytology results may be either due to the masking effect of topical and systemic steroids administered before sampling, or due to an insufficient vitreous sample or cell lysis caused by the vitreous cutter. Hence, the vitreous sample should be taken undiluted before turning the vitrectomy infusion on and with a low cut-rate setting. Her FBP had also normalized by then, leading to the possibility of spontaneous remission before vitreous sampling. Repeated vitreous sampling should be considered after discontinuation of topical steroids for 3 weeks in the interest of a conclusive diagnosis in the absence of one from BMAT, such as in this case.⁸

The poor ocular prognosis OD of this patient is multifactorial. Chronic severe intraocular inflammation, combined with leukemic retinopathy, vitrectomy sequelae, and toxicity of steroids and chemotherapy led to irreversible damage to the ocular structures and amblyopia. Hence, visual rehabilitation of the fellow eye is essential.

This patient had a t(12; 21)(p13; q22) translocation with *ETV6-RUNX1* gene fusion, the commonest molecular genetic aberration in childhood ALL, occurring in 25% of cases.⁹ Traditionally, patients with specific orbital or ocular lesions had poor prognosis, and short overall survival since eye involvement often denoted leukemic relapse.¹⁰ On the contrary, *ETV6-RUNX1* gene fusion has been associated with relatively low relapse rates and a favourable prognosis.⁹

Conclusion

A high index of suspicion for uveitis masquerade syndrome is required in cases of severe paediatric uveitis unresponsive to steroids. Early diagnosis may increase survival rates and visual prognosis in children with ALL. Children with persistent uveitis, whose investigations are inconclusive, should be closely monitored for new clinical manifestations which may aid the diagnosis.

Declarations

Consent for publication

The guardian provided informed consent for the use of the clinical images and information contained in this case report.

Competing interests

None to declare.

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