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Case Report

Leukostasis in Leukaemia: A Child with Sky-high White Cell Count

DCY ***Au***, NC ***Fong***, SC ***Ling***

Abstract Acute leukaemia is the most common malignancy in childhood, and could be associated with life-threatening complications at presentation such as tumour-lysis syndrome. Hyperleukocytosis with leukostasis is less commonly recognised. Clinical presentation could be confusingly overlapping with tumour-lysis. High vigilance and early initiation of medical cytoreduction therapy remain as the key to minimising early mortality and morbidity.

Key words *Acute leukaemia; Hyperleukocytosis; Leukostasis; Paediatric intensive care*

Case Description

An 8-year-old Nepalese boy with good past health presented with unexplained fever for 2 weeks and bilateral parotid swelling. Four days prior to admission he also developed gross haematuria with generalised oedema over face and four limbs. He had reduced appetite and subjective weight loss. On admission, physical examination showed a tired looking boy with pallor. There were bilateral non-tender parotid swelling, and generalised non-tender lymphadenopathies involving cervical, axillary, inguinal lymph nodes. There were also petechiae over his lower limbs. Abdominal examination revealed hepatosplenomegaly of liver 5 cm and spleen 3 cm below costal margin. Urgent blood tests showed white blood cell (WBC) count of $538x10^9$/L with 97% blasts up to $522x10^9$/L. Haemoglobin was 7.0 g/dL and platelet count was $28x10^9$/L. Flow cytometric analysis showed findings suggestive of pre-cursor B-cell lymphoblastic leukaemia. Tumour lysis syndrome was suspected in view of Hyperkalaemia of 6.3 mmol/L, raised serum urate of 0.55 mmol/L, hypocalcaemia of 1.87 mmol/L, a borderlinely elevated serum phosphate of 1.68 mmol/L and elevated lactate dehydrogenase (LDH) of 3145 unit/L. He had oliguria with raised creatinine up to 72 umol/L (eGFR = 65 ml/min/1.73 m^2) requiring intravenous frusemide. After rasburicase and hyperhydration, the urate level normalised. Hyperkalaemia normalised with nebulised salbutamol and one dose of per rectal resonium. He however remained oliguric. He was covered with empirical cefepime for possible sepsis.

He deteriorated around ten hours after admission with vomiting, right-sided weakness and unequal pupils with left mydriasis sluggish in response to light. Urgent computer tomography (CT) scan showed right frontal intracerebral and left pontine haemorrhage (Figure 1). He was transferred to our paediatric intensive care unit (PICU) for close monitoring as no surgical intervention was required after neurosurgical assessment. Haemoglobin dropped to 4.8 g/dL secondary to haemorrhage and haemodilution by hyperhydration, and his haemoglobin raised up to 6.3 g/dL after first transfusion and further to 8.9 g/dL after second transfusion. He was given platelet transfusions to top up his platelet count to above $100x10^9$/L in view of intracranial bleeding. His clotting profile was

Department of Paediatrics and Adolescent Medicine, Princess Margaret Hospital, 2-10 Princess Margaret Hospital Road, Lai Chi Kok, Kowloon, Hong Kong SAR

DCY **Au**（區子榆） *FHKCPaed, FHKAM(Paed)*
NC **Fong**（方乃聰） *FHKCPaed, FHKAM(Paed)*
SC **Ling**（凌紹祥） *FHKCPaed, FHKAM(Paed)*

Correspondence to: Dr DCY **Au**
Email: acy340@gmail.com

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serially normal with no need for fresh frozen plasma.

Twelve hours later (i.e. within 24 hours from admission), he developed drowsiness with decreased Glasgow Coma Scale (GCS) from 13 to 9. Urgent CT repeated showed static right frontal and left pontine haematoma, but with new right occipital haemorrhage. He was electively intubated for airway protection in view of decreased GCS. Subsequently, his respiratory condition deteriorated with arterial blood gas showing impaired gaseous exchange with both hypoxia and hypercapnia despite optimising ventilator settings. Partial pressure of oxygen (PaO_2) remained around 7-10 kPa despite fraction of inspired oxygen (FiO_2) of 0.8-1 with peak end-expiratory pressure (PEEP) of 7-9 mmHg, mean airway pressure (MAP) of 10-12 mmHg, peak inspiratory pressure (PIP) of 17-20 mmHg, with adequate tidal volume (TV) up to 8-10 ml/kg. Oxygen Index (OI) was around 11.5. CO_2 retention was also evident with partial pressure of carbon dioxide ($PaCO_2$) up to 7-8 kPa despite optimising TV, respiratory rate and I:E ratio. Serial chest radiographies (CXR) showed increasing generalised infiltrates (Figure 2). Endotracheal suction yielded blood-stained aspirate suspicious of pulmonary haemorrhage. Upon early initiation of dexamethasone within 24 hours from admission for induction and cytoreduction according to CCCG-ALL 2015 protocol, his WBC count responded well dropping from above $500x10^9$/L to below $300x10^9$/L within 24 hours after dexamethasone. However, he developed hypotension with bedside echocardiogram revealing moderate mitral regurgitation (MR) with poor contractility of shortening fraction (SF) of 19% and ejection fraction (EF) of 40%, which improved to SF 30% and EF 58% after commencement of 8 microgram/kg/min dopamine. High sensitive Troponin-I was raised to maximum of 7604 ng/L evident of myocardial injuries. Electrocardiogram (ECG) did not show any changes suggestive of genuine myocardial infarction. He remained frusemide-dependent to maintain satisfactory urine output, with serum creatinine elevated to a maximum of 78 umol/l (eGFR = 60 ml/min/1.73 m^2).

As his WBC count further dropped to below $100x10^9$/L three days after start of dexamethasone, his overall condition collectively improved. Arterial blood gas normalised with ventilatory support weaned and he was extubated to nasal cannula four days after start of dexamethasone. CXR cleared up. Dopamine was weaned off on the same day with repeated echocardiogram showing moderate MR with borderline but improved contractility of SF 25% and EF 50%. Good urine output returned with no further need for frusemide, and serum creatinine normalised. Parotid swelling subsided in keeping with our initial suspicion of leukaemic infiltration, therefore no further biopsy or imaging was required. Fever subsided and sepsis workup including blood culture, endotracheal aspirate and C-reactive protein were all negative.

He remained stable and was transferred out to general ward two days later for further chemotherapy. Bone marrow

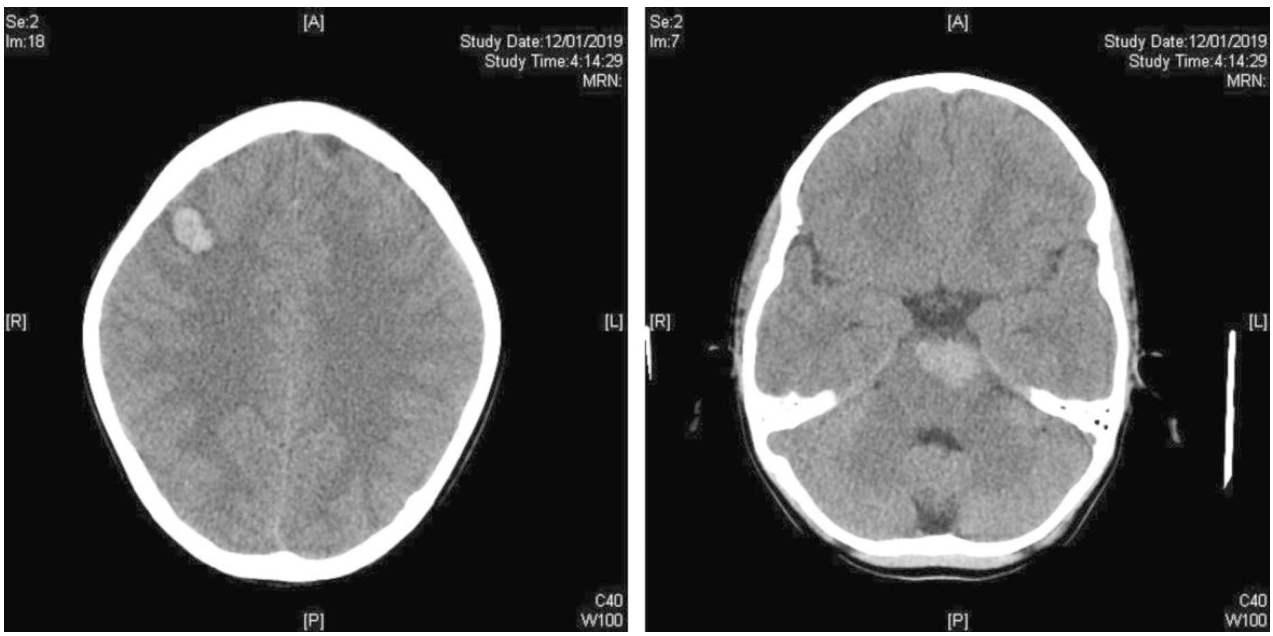

Figure 1 (Left) Right intracerebral haemorrhage; (Right) Left pontine haemorrhage.

biopsy confirmed findings consistent with B lymphoblastic leukaemia, with cytogenetics positive for t(9;22)(q34.1; q11.2), and BCR-ABL1 fusion detected by molecular test. One day after PICU discharge, he was transferred to a local hospital with paediatric oncology centre for further care.

Discussions

Hyperleukocytosis and Leukostasis

Hyperleukocytosis is classically defined as a WBC count >100x10^9/L.[1] Its incidence is quoted to be 10-30% in acute lymphoblastic leukaemia (ALL) in the literature,[1,2] and it can occur in other forms of leukaemia such as acute myeloid (AML) or chronic myeloid leukaemia (CML) as well. In particular, hyperleukocytosis is found to be more common in ALL with t(4;11) and t(9;22), with the latter being confirmed in our patient.[1] While hyperleukocytosis is a laboratory abnormality, leukostasis represents a medical emergency with symptomatic hyperleukocytosis, bearing clinical significance with respiratory, neurological or renal compromise.[3] There is consistent data from the literature to suggest that leukostasis leads to poor prognosis with high morbidity and early mortality,[4,5] as well as risk of tumour lysis syndrome, disseminated intravascular coagulation (DIC).[3] Lowe et al[2] showed in a large pediatric ALL series that leukostasis was most prevalent in patients with WBC >400x10^9/L in ALL.

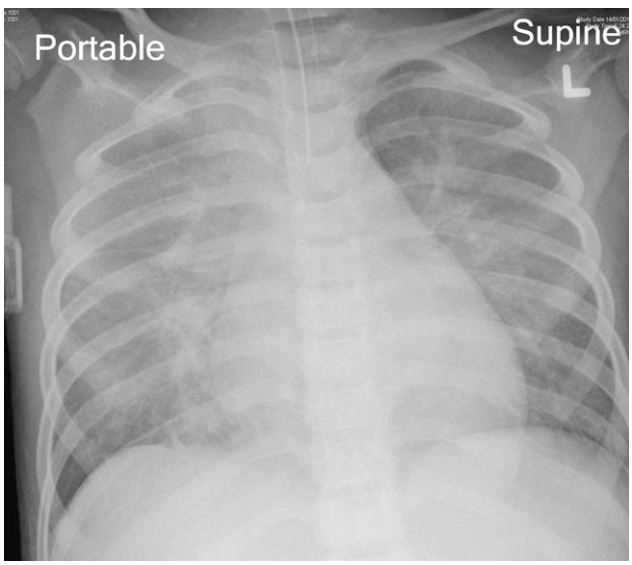

Figure 2 Interstitial infiltrates on chest radiographies.

Clinical Manifestations of Leukostasis

The clinical presentation of leukostasis is often under-recognised. The central nervous system (CNS) and the lungs are most commonly involved. Respiratory symptoms include dyspnoea, tachypnoea, hypoxia, diffuse alveolar haemorrhage and diffuse interstitial or alveolar infiltrates in CXR. Neurological involvement ranges from dizziness, headache, altered consciousness, to stroke or intracranial haemorrhage. Other rarer manifestations include acute leg ischaemia, renal vein thrombosis, myocardial ischaemia, bowel infarctions and priapism.[3,6] As many of these symptoms could also be directly explained by other complications of acute leukaemia such as acute lung injury, tumour lysis, severe symptomatic anaemia, bleeding tendency due to thrombocytopenia or DIC, leukostasis is often difficult to recognised unless physicians have high vigilance to pick up and interpret the multi-organ involvement as a whole picture.

Our patient had both evidence of leukostasis as well as tumour lysis syndrome, further adding up to the complexity of his clinical presentation. Multi-organ involvement including stroke with multifocal intracranial haemorrhage, impaired gaseous exchange with hypoxia and hypercapnia, pulmonary haemorrhage, diffuse infiltrates on CXR, and myocardial ischaemia with raised troponin and impaired contractility are evident of leukostasis and hyper-viscosity. Direct leukaemic infiltration may also have contributed. His renal impairment could also be explained by both leukostasis with impaired renal blood flow as well as tumour lysis evident biochemically by Hyperkalaemia, hyperphophatemia and hyperuricaemia. Improvement of all his clinical parameters correlating with the falling trend of WBC count further implicates hyperleukocytosis as one of the pathophysiological culprits.

The pathophysiology of leukostasis remains poorly understood, with the main theory centered around the less deformable blasts causing vascular obstruction leading to tissue hypoxia.[1,3,6] Packed cell transfusion has been associated with increased morbidity and mortality as it worsens hyperviscosity due to increased haematocrit.[7,8] Our patient only had fresh frozen plasma transfusion prior to deterioration, and packed cell transfusion was given after his deterioration with pontine and intracerebral haemorrhage. The need for intravenous frusemide to maintain urine output could not account for aggravation of leukostasis, as haematocrit was maintained stably at around 20% with concomitant hyperhydration.

Treatment of Leukostasis

To date, despite the lack of randomised controlled trials to provide clear recommendation on the preferred approach for cytoreduction,[3] it remains an expert consensus that early chemotherapy or steroid is usually effective and adequate in cytoreduction and alleviation of symptomatic organ involvements. As demonstrated in our case, medical cytoreduction with hyperhydration and rasburicase achieved successful management of leukostasis and concomitant tumour-lysis. Role of leukapheresis is probably limited and may only be reserved to rare cases where medical cytoreduction fails.

Conclusion

Acute leukaemia in children can present with leukostasis which is often clinically under-recognised. The CNS and lungs are most commonly involved. Timely medical cytoreduction by chemotherapy or steroid should be initiated early in attempt to prevent potential complications.

Declaration of Interest

The authors have no conflicts of interest to disclose.

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