

Extensive intracranial haemorrhage as a complication of acute lymphoblastic leukaemia with hyperleukocytosis



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ABSTRACT

We report a rare case of distinctive extensive punctate intracranial haemorrhage associated with acute lymphoblastic leukaemia with hyperleukocytosis. A 7-year-old girl presented with hyperleukocytosis (white cell count $788.7 \times 10^9/L$; 94% peripheral blasts) and laboratory tumour lysis syndrome. The diagnosis of T-cell acute lymphoblastic leukaemia was established and confirmed by immunophenotyping of peripheral blood and chemotherapy was commenced promptly. On day 3 of treatment, she developed progressive encephalopathy, left sided hemiparesis with left 6th and upper motor neuron 7th cranial nerve palsy. Brain MRI scan showed extensive punctate haemorrhages with perilesional oedema over the frontal, parietal, occipital, temporal, brainstem and cerebellar regions. The lesions were predominantly over the juxtacortical grey matter. She made a full neurological recovery after 3 months. Our report widens the neuroradiological features of intracranial haemorrhage associated with hyperleukocytosis and highlights the importance of prompt chemotherapy in these patients.

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1. Introduction

Acute leukaemia is the commonest childhood malignancy worldwide with an age-standardised incidence rate of 46.4 per million person-years [1]. One of its complications is hyperleukocytosis which is defined as total white blood cell count $>100 \times 10^9/L$. A distinctive extensive punctate intracranial haemorrhage is a rare but significant central nervous system complication of acute childhood leukaemia associated with hyperleukocytosis.

We report a case of a 7-year old girl with extensive punctate intracranial haemorrhage due to hyperleukocytosis in acute lymphoblastic leukaemia (ALL). She made a full neurological recovery and achieved disease remission following prompt commencement of systemic chemotherapy and supportive measures. We also reviewed the current literature of the reported cases of intracranial haemorrhage associated with hyperleukocytosis in ALL.

2. Case report

A 7-year-old girl presented to her local hospital with two weeks history of fever, lethargy, progressive abdominal distension and spontaneous bruising. Initial physical examination revealed pallor, tachypnoea, and massive hepatosplenomegaly. Her chest and upper limbs were covered with multiple petechiae. Baseline blood investigations showed hyperleukocytosis (total white cell count $788.7 \times 10^9/L$), with 94% peripheral blasts, anaemia (haemoglobin 4.7 g/dL), and thrombocytopenia (platelet count $114 \times 10^9/L$) without coagulopathy. She was referred to our tertiary hospital for further management.

Intravenous hyperhydration fluid was commenced immediately. Immunophenotyping of peripheral blood confirmed the diagnosis of acute T-cell lymphoblastic leukaemia and oral prednisolone with induction chemotherapy was initiated. Her disease responded to the treatment with a reduction of white cell count to $398.3 \times 10^9/L$ after 48 h of treatment without evidence of laboratory or clinical tumour lysis syndrome. An acute neurological

deterioration on day 3 of treatment was noted as she became agitated with reduced consciousness. Neurological examination showed a left 6th nerve palsy, left upper motor neuron 7th nerve palsy, weak gag reflex and a left sided hemiparesis. She had no clinical signs to suggest raised intracranial pressure.

Urgent brain CT brain showed multiple symmetrical widespread hyperdense punctate lesions involving bilateral frontal, parietal, occipital and thalamic regions. Further evaluation by brain MRI (Fig. 1) demonstrated similar findings of extensive symmetrical punctate circular subacute haemorrhagic lesions at the brainstem, thalamic, frontal, parietal, temporal, occipital lobes and cerebellum. The haemorrhagic lesions were primarily in the juxtacortical grey matter with perilesional oedema. Mass effect on the thalamus and the third ventricles were also seen. There was no evidence of vasculopathy and thrombosis on MRA and MRV. Her cerebrospinal fluid was normal with no evidence of leukemic cell infiltration. She recovered fully over 3 months with no residual neurological deficits. Her repeat brain MRI 10 months after presentation (Fig. 1) showed resolution of perilesional oedema with some residual intracranial haemorrhage and no further evidence of mass effect to the thalamus. Her disease remained in remission at 16 months follow-up.

3. Discussion

Children with acute leukaemia may present with hyperleukocytosis. One of the serious but rare complication of hyperleukocytosis is intracranial haemorrhage [2,3]. The feature of intracranial haemorrhage associated with hyperleukocytosis was described in 1960 by Freireich and colleagues [3]. They examined the central nervous system during the autopsies of patients with acute leukaemia who had fatal intracranial haemorrhage [3]. They discovered a unique pattern of intracranial bleeding in patients with leukocyte counts more than 300,000 per cubic millimeter. These lesions were described as multiple areas of symmetrical well circumscribed haemorrhagic lesions of different sizes that were primarily found in the brain white matter, and these lesions occasionally extend to the cortical and ventricular areas. Microscopically, the haemorrhagic lesions were characterized by coalescence of multiple smaller leukaemic leukocytes surrounded by fresh haemorrhage, as a result of leukostasis. The authors reported a mortality rate of 69%

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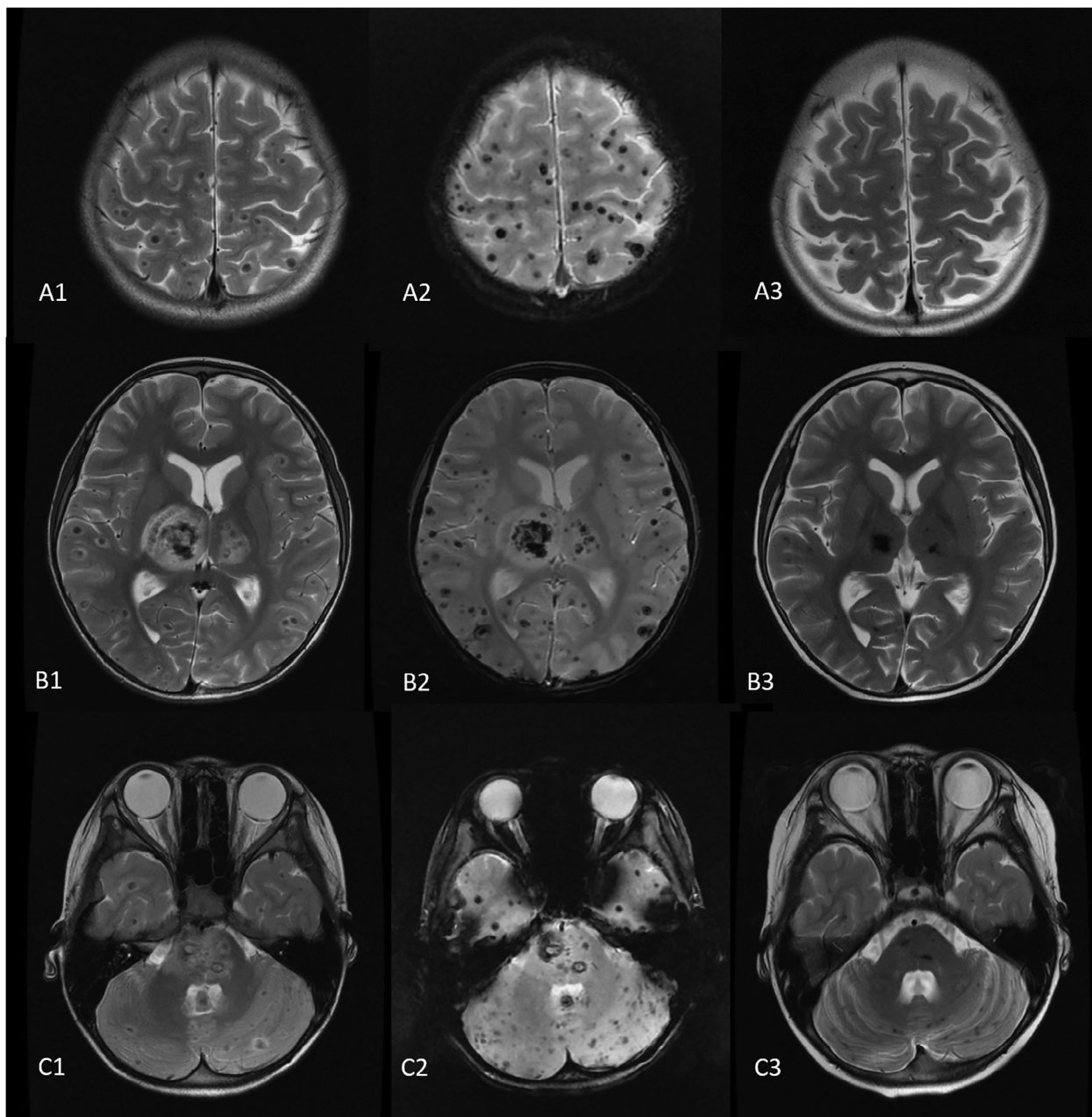


Fig. 1. Serial brain MRI of axial T2-weighted (A1, B1, C1) and GRE (A2, B2, C2) at presentation and axial T2-weighted (A3, B3) after month 10 of presentation. Multifocal bilateral extensive hypointense punctate haemorrhagic lesions associated with perilesional oedema over the frontal, parietal, temporal, pons and cerebellum (A1, B1, C1) with associated blooming artefact (A2, B2, C2). The largest lesion is found at the right thalamus causing midline shift to the left (A2). Follow-up MRI brain resolution of perilesional oedema and residual punctate haemorrhage (A3, B3, C3).

among these patients with intracranial haemorrhage associated with hyperleukocytosis.

To our knowledge, there are only 5 case reports (3 paediatric and 2 adult patients) that have described the neuroimaging findings in patients with intracranial haemorrhage associated ALL and hyperleukocytosis as summarised in Table 1 [4–7]. Only 2 of these case reports reported brain MRI findings. All the reported cases showed similar neuroimaging findings as reported by the autopsy findings of Freireich and colleagues with all 5 cases showing diffuse multiple haemorrhage in primarily the white matter with one case extending to the grey matter. Our case widens the neuroimaging features associated ALL hyperleukocytosis as the punctate haemorrhagic lesions

in our patient was seen primarily in the juxtacortical grey matter bilaterally and deep grey matter within the thalami.

There were variable outcomes reported of patients with intracranial haemorrhage due to hyperleukocytosis [4–7]. Favourable outcome with neurological recovery following the commencement of chemotherapy were reported in majority of these patients [4,5,7]. Nonetheless, one case report [6] described a patient with ALL and hyperleukocytosis who developed fatal intracranial bleed before the initiation of chemotherapy. This strengthens the findings of Freireich and colleagues that that this distinctive intracranial haemorrhage associated with hyperleukocytosis were primarily due to leukemic nodules followed by fresh haemorrhage

Table 1
Summary of case reports on intracranial haemorrhage due to acute lymphoblastic leukaemia with hyperleukocytosis.

Authors	Case Description	WBC × 10 ⁹ /L	Brain neuroimaging findings	Treatment	Outcome
Current case	7-year-old girl with T-cell ALL presented with 2 weeks' history of fever, lethargy and easy bruising. She developed left sided hemiparesis with reduced consciousness on day 3 of chemotherapy.	788.7 (94% blasts)	MRI: extensive T2 hypointense circular punctate haemorrhagic subacute lesions associated with perilesional oedema found in bilateral frontal, parietal, occipital, temporal, thalami, pons and cerebellum (mainly juxtacortical grey matter).	Intravenous hyperhydration therapy started immediately. Induction chemotherapy commenced within 48 h.	Full neurological recovery 3 months after the onset of the intracranial haemorrhage. ALL in remission.
Koenig et al., 2008 [4]	9-year-old boy with T-cell ALL had altered mental status at presentation then progressed to unresponsiveness.	1037 (96% blasts)	CT: multiple discrete areas of haemorrhage with multifocal oedema in the white matter and bilateral uncal herniation.	Patient admitted to intensive care unit for mechanical ventilation. Chemotherapy commenced within 48 h.	Recovered neurologically with residual blindness bilaterally. ALL in remission.
Koenig et al., 2008 [4]	2-year-old boy with pre-B ALL became agitated with left focal posturing movement on day 20 of treatment	412.5 (95% blasts)	MRI: multifocal areas of increased FLAIR T2 signal with perilesional oedema in the white matter and ventriculomegaly	VP shunt and brain biopsy showed macrophagic cellular infiltration in the white matter. Chemotherapy commenced within 24 h.	Recovered with no neurological deficits. ALL in remission.
Ruggiero et al., 2009 [5]	4-year-old boy with pre-B ALL presented with multiple vomiting episodes and fever followed by hypotonia and deep coma	858 (>80% blasts)	CT: multiple intracerebral haemorrhage in the left fronto-parietal-occipital regions (both gray and white matters) and in the basal ganglia	Admitted to PICU for ventilation and emergency leukapheresis within 24 h. Chemotherapy commenced on day 5.	Full neurological recovery. ALL in remission.
Shiber et al., 2008 [6]	19-year-old man with ALL presented with sudden onset of apnoea and unarousable	1210 (% blast not available)	CT: multiple areas of parenchymal haemorrhage in the white matter with intraventricular bleed and subdural hematoma	Declared brain dead on arrival at A&E department.	Dead
Munoz et al., 2012 [7]	26-year-old lady with B-cell ALL had lower limbs weakness and blurry vision.	989 (80% blasts)	MRI: scattered hyper-attenuating haemorrhagic foci in the white matter	High-dose chemotherapy was initiated (timing of the chemotherapy commencement not stated).	Complete resolution of symptoms. ALL in remission

around these nodules reiterating the importance of prompt initiation of chemotherapy in these patients [3]. Our patient achieved full neurological recovery despite extensive intracranial haemorrhage following prompt initiation of chemotherapy.

4. Conclusion

Our case report expands on the neuroimaging findings of a rare distinctive diffuse intracranial haemorrhage associated with ALL hyperleukocytosis. Despite the extensive nature of the haemorrhagic lesions, our report highlights that prompt supportive and cytoreductive treatment can offer potentially full neurological recovery in these group of patients.

Conflict of interest/disclosures

The authors declare that they have no financial or other conflict of interest in relation to this research and its publication.

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Pharmacoresistant seizures in neurofibromatosis type 1 related to hippocampal sclerosis: Three case presentation and review



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ABSTRACT

Neurofibromatosis type 1 (NF1) is an autosomal dominantly inherited disorder, with an estimated prevalence of 1 in 3000–4000 people. Seizures occur 4–7% of individuals with NF1, mostly due to associated brain tumors or cortical malformations. Hippocampal sclerosis (HS) in the patients with NF1 has been reported very rarely and only 15 patients were found in review of English literature. We presented here 3 additional patients with NF1 and intractable seizures due to hippocampal sclerosis; in whom one of them underwent epilepsy surgery and he is seizure free for 5 years after right temporal lobectomy.

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1. Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder characterised by multiple “café-au-lait” macules, neurofibromas, intertriginous freckling and Lisch nodules. Previous reports have estimated that seizures occur in approximately 4–7% of individuals with NF1 [1–6]. It was found that epileptic seizures are related to various types of intracranial lesions in NF1 patients. Associated malformation types have been described as hemimegalencephaly, cerebellar leptomeningeal heterotopias, transmantle cortical dysplasia, a periventricular band of heterotopic grey matter, pachygyria, occipital encephalocele, and unilateral as well as bilateral polymicrogyria. In patients with NF1, seizures are often focal, and focal abnormalities are seen in EEGs. Seizure control is difficult with monotherapy, and drug resistant epilepsy rate is relatively high [7]. HS has been reported very rare in the patients with

NF1 [8,9]. Here we report additional 3 cases with hippocampal sclerosis and NF1 after detailed investigation, in whom one of them underwent temporal lobectomy and he is seizure free for 5 years after surgery.

1.1. Case 1

A sixteen year old right-handed male patient has epilepsy history since the age of five and admit to our Epilepsy Clinic because of increased seizure frequency such as once a week or one-four times a day. Ictal behavioral characteristics were described in the form of bilateral automatism (hand and oral automatism), loss of consciousness and postictal confusion. Seizures had been persisted despite several drugs such as valproic acid, levetiracetam and pregabalin. He was on carbamazepine and pregabalin combined treatment at the admission. On the physical examination, there were extensive café au lait stains in the whole body, axillary freckles more than 5 and greater than 1 cm on the flexor and extensor side of right arm, abdomen, back and thigh and soft nodules on the back and right thigh lateral as well as lisch nodules on iris on the ophthalmic examination. According to family history, his grandmother,

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