Case Report

Drug resistant epilepsy with mesial temporal sclerosis as possible late neurological complication in two AML survivors after stem cell transplantation

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1. Introduction

Drug resistant epilepsy with mesial temporal sclerosis (MTS) has previously been reported as a late complication of hematological malignancies, mainly acute lymphoblastic leukaemia (ALL) and lymphoma with or without stem cell transplantation (SCT) [1,2]. Most cases had no prior central nervous system inflammation or infection. It has been suggested that brain irradiation or intrathecal use of cytosine or methotrexate were possible causes [1]. Here we report two cases of MTS in survivors of childhood acute myeloid leukaemia (AML) who had also received SCT, and review the literature of the reported cases of late onset drug resistant epilepsy with MTS in childhood haematological malignancies.

2. Material and methods

We reviewed two patients with history of AML having received SCT who developed medically resistant epilepsies several years after completing treatment. Both developed MTS and required epilepsy surgery to become seizure-free. Literature review was performed through OVID/EMBASE using the keywords Leukemia, hematological cancers, mesial temporal sclerosis, childhood, epilepsy and seizure. Articles published in English from 1990 to 2016 with MTS as a late complication for hematological cancers were identified and reviewed.

3. Results

3.1. Case summaries

3.1.1. Patient 1

A 24-year-old lady initially presented to our hospital with pallor at age six in 1997. She was diagnosed with AML and was treated with Hong Kong Pediatric Hematology and Oncology Study Group (HKPHOSG) 1996 protocol. Three courses of chemotherapy were given. Intravenous chemotherapy included daunorubicin, cytarabine, etoposide and amsacrine. Three doses of triple intrathecal chemotherapy (methotrexate, cytarabine and hydrocortisone) were given during the treatment course. Cerebrospinal fluid did not show abnormal cells and no craniospinal irradiation was prescribed. She received one ant igen mismatch peripheral blood SCT in 1998. Conditioning agents included busulfan and cyclophosphamide. There was good engraftment and subsequent recovery. Another six doses of triple intrathecal chemotherapy were given during the post-transplantation period as central nervous system prophylaxis. She suffered from grade II graft-versus-host disease and was treated with steroids and cyclosporine. There was no central nervous system infection or inflammation during intensive chemotherapy and SCT.

She was first noted to have seizures in 2005 at age 14 (8 years after initial diagnosis and 7 years after transplantation). She developed recurrent focal seizures with impaired awareness associated with temporal lobe epilepsy. She had daily brief attacks of incoherent speech, forced head turning to left side with eye staring or tonic limb posturing. There was no prior history of febrile convulsion or family history of epilepsy. Physical examination did not reveal any focal neurological signs. First magnetic resonance imaging (MRI) of the brain was performed in 2006 which did not reveal any abnormalities. Intercital electroencephalogram (EEG) in 2006 showed isolated right temporal sharp waves. She was managed as temporal lobe epilepsy with anti-seizure medication. She failed multiple medication including sodium valproate, carbamazepine, oxcarbazepine, levetiracetam and clobazam. She still had approximately 10 seizures per month and her schooling was severely affected. Repeated MRI...
brain in 2008 showed subtle decrease in volume in right hippocampus. Positron emission tomography (PET) showed a right hypometabolic temporal lobe. Ictal EEG was concordant with right side seizure onset (Fig. A.1). Surgery was performed in 2009 at age 18 with right anterior temporal lobectomy and amygdaloid hippocampectomy. Pathology showed mild loss of neurons and gliosis involving the right hippocampus. After the surgery, she was seizure-free and all medications were weaned. She made good neurological recovery, finished her education and now enjoys gainful employment.

3.1.2. Patient 2
A 16-year-old boy was diagnosed with AML at eight months of age in year 2002. He had favourable cytogenetics inversion 16. He was treated according to the HKPHOSG 1996 protocol with four courses of chemotherapy including intravenous daunorubicin, cytarabine, etoposide, amsacrine and mitoxantrone. Intrathecal chemotherapy during the induction course was withheld due to fever. He developed a brief seizure manifest as lip smacking and staring during the induction course. Cerebrospinal fluids were normal with no atypical cells, bacteria or viruses identified. EEG was unremarkable. CT brain at that time showed small hypodense foci in the posterior limb of the internal capsule extending to left corona radiata which could represent small bleed or leukemic infiltration. He was begun on phenobarbital for six months and there was no further seizure recurrence. Subsequent MRI brain showed resolution of the suspicious lesions. Two doses of triple intrathecal chemotherapy (methotrexate, cytarabine and hydrocortisone) were subsequently given. He completed treatment in November 2002.

He had relapse of AML in July 2003. He was given intravenous fludarabine, cytarabine, daunoxome and one dose of triple intrathecal chemotherapy. He received two antigen mismatched unrelated cord blood transplantation in Oct 2003 at 22 months of age. Conditioning agents included busulfan, cyclophosphamide, melphalan and lymphoglobulin. The transplant was uneventful. Six doses of triple intrathecal chemotherapy were given as CNS prophylaxis during posttransplant period. He had grade II graft versus-host disease which was improved with prednisolone and cyclosporin.

He developed focal seizures with impaired awareness at seven years of age (six years after initial AML diagnosis and five years after SCT). He had daily seizures which presented with tonic upper limb posturing while staring and/or irrelevant speech with purposeless movements preceded with aura. Initial interictal EEG showed no focal abnormalities or epileptiform discharges. His seizures were not well controlled when the culprit drug has been withheld or the underlying cause was treated. He also had comorbid attention deficit/hyperactivity and mood disorders.

Repeated MRI brain showed bilateral mesial temporal sclerosis with right sided hippocampal atrophy (Fig. B.1) [Fig. B1 legend: Left is FLAIR, Right is T2]. Ictal EEG showed right side onset seizures (Fig. B.2). Right anterior lobectomy and amygdaloid hippocampectomy was performed in July 2013 at age 11. Pathology showed atrophy and sclerosis of right hippocampus. After the surgery, he was seizure-free in the subsequent four years and is in the process of weaning off anti-seizure medications. Among the twelve reported cases, patients were diagnosed childhood leukemia from eight months to 13 years of age with a median age of four and a mean age of five. Among all, four of them were females and eight of them were males. 11 patients had the primary diagnosis of ALL and one patient was diagnosed to have non-Hodgkin lymphoma. CNS leukemia was not identified in most cases. Only one patient had an infiltrative lesion in the brain, which subsequently resolved with courses of chemotherapy. Intrathecal chemotherapy with methotrexate were given in all cases except one case with no treatment details regarding intrathecal chemotherapy. Five of them received craniospinal irradiation. None had received SCT.

Eight patients had documented brain insults during treatment period including methotrexate induced encephalopathy, intracranial bleeding or acute symptomatic seizure. They remained well for an average of 6.7 years from the initial diagnosis. The other four had no documented CNS infection or inflammation at all. Focal impaired awareness seizure (FIAS) (91%) was the predominant seizure type. MRI findings or EEG findings were suggestive of MTS in eight patients (67%). Among these patients, Leng et al. described presence of temporal-plus epilepsy rather than the conventional temporal lobe epilepsy [6]. But in common, seizures were mostly drug resistant and four out of eight patients (50%) received epilepsy surgery and subsequently achieved seizure freedom.

In our two reported patients, both of them had diagnosis of AML. They had received intrathecal chemotherapy with no brain irradiation. No overt CNS infection or inflammation has been documented. They developed FIAS six to eight years later which were resistant to medical treatment. Epilepsy surgery was performed and had rendered them seizure free.

4. Discussion
Seizures are seen in 8–13% of patients in ALL [8]. Most seizures occur during the induction and consolidation phases. For AML, there is no data on seizure incidence in the current literature. However, it is believed to be much lower than in ALL. These seizures are usually precipitated by intracranial infections, electrolyte disturbances and immediate side effects from chemotherapy. Seizures are relatively easy to control when the culprit drug has been withheld or the underlying causes have been managed [9]. Few cases had persistent seizures since then and developed MTS [10]. Late onset seizures were relatively uncommon.

With the advancement of various chemotherapy and supportive treatment, the curative rate of childhood leukemia has improved. According to the data from American Cancer Society, overall 5-year survival rate increased from more than 85% in childhood ALL and 60%–70% in childhood AML, disregarding the different subtypes. Since 2003, there were several articles describing survivors from childhood lymphoblastic leukemias and lymphomas developing drug resistant epilepsies years after remission from their hematological malignancies.

4.1. Mesial temporal sclerosis as late complication in AML survivors
Prince of Wales Hospital is a tertiary hospital that has a specialised Children’s Cancer Center. We receive referrals from the territory for management of oncology patients. We are one of the two centers equipped with bone marrow transplantation unit in Hong Kong. From August 2006 till July 2017, there were 160 new cases of ALL and 74 new cases of AML. During the period, we have performed SCTs for 37 ALL patients and 41 AML patients. The current two cases accounts for 4.5% of the 41 AML patients.
Our report adds two cases of MTS as a late complication of AML survivors who had received SCT to the literature. Previous cases reported by Goyal et al. in 2003 had early epilepsy soon after SCT [3]. An 18-year-old gentleman was diagnosed to have AML at age 12 with no CNS involvement. He developed early FIAS two months after bone marrow transplantation associated with high serum cyclosporin level (three times the upper limit). Initial MRI brain was normal. He had second seizure five months later and gradually became more frequent with seizures up to two to three times per month. Repeated MRI brain (Two and a half year after initial study) showed left MTS.

4.2. Initial precipitant injury for mesial temporal sclerosis

MTS develops several years after an initial precipitant injury (IPI), leading to hippocampal lesions associated with the epileptogenic zone. Common IPIs identified are perinatal hypoxia, febrile seizures, CNS infection, and trauma etc. Suggested IPIs in oncology patients were hypertensive encephalopathy, posterior reversible encephalopathy syndrome (PRES) [10], recurrent seizures, limbic encephalitis, chemotherapy toxicities, intrathecal cytosine, intrathecal methotrexate and brain irradiation [1].

Our two AML patients developed drug resistant seizures six to eight years after the initial diagnosis, which was comparable to the average latent period of 6.7 years in reported cases in development of MTS. For all 14 patients (twelve reported cases in the literature and our two patients), five out of 14 patients (35.7%) had no prior seizures or encephalopathy during the treatment period, nine out of 14 patients (64.2%) had not received any intracranial radiation and 12 patients (85.7%) had not had SCT. Six out of 14 patients (42.8%) have received intrathecal cytosine. Among all, it had to be noted that intrathecal methotrexate was administered in all patients except one patient with no data on intrathecal chemotherapy. Epileptogenesis is complex and multifactorial but intrathecal methotrexate is believed to be one of the key factors leading to the development of MTS and late onset drug resistant seizures. Methotrexate is a dihydrofolate reductase inhibitor. Several mechanisms had been postulated to be the cause of MTS. Methotrexate leads to folate deficiency and elevated levels of homocysteine [11]. Homocysteine has been described in pathogenesis of methotrexate neurotoxicity with damage to vascular endothelial injury [12]. Homocysteine is also an endogenous NMDA receptor agonists, causing enhancement of glutamate release which is one of the excitatory neurotransmitters in the brain [13]. Excess glutamate is believed to be involved as one of the epileptogenic mechanisms.

Similar speculation for postulation was also described by Fasano et al. in 2008 [1] and Yoshida et al. in 2013 [7]. Yet there is no data available regarding the association of dose of intrathecal medication use and seizure activity.

4.3. Early surgical evaluation

Most seizures in the reported cases were resistant to medical treatment. Together with the two cases that we reported, ten out of fourteen (71.4%) had temporal lobe epilepsy and MTS as suggested on subsequent MRIs and interictal/ictal EEGs. Six out of ten (60%) had epilepsy surgery performed and all achieved seizure freedom. Therefore, early referral for epilepsy surgery workup would be beneficial. Early epilepsy surgery should be considered when the seizures are drug resistant.

5. Conclusion

MTS is a potential late complication of childhood leukemia, for both ALL and AML. Increased vigilance for epilepsy in survivors of childhood leukemia is required. Exact mechanisms are to be further investigated. These seizures are usually drug resistant and when seizures are disabling early surgical evaluation is warranted.

Declaration

No author has disclosed any conflicts of interest. The study was conducted in accordance with good clinical practice guidelines and the Declaration of Helsinki.

Appendix A

**Fig. A.1.** Ictal EEG of patient 1 EEG is shown in bipolar montage (Top: leads on right side; Bottom: leads on left side) The arrow indicates right temporal onset of seizure.
**Fig. B.1.** MRI brain of patient 2 (Left: T2 coronal view; Right: FLAIR coronal view) It shows bilateral mesial temporal sclerosis with rights sided hippocampal atrophy.

**Fig. B.2.**

**Table C1**

Summary of demographics, diagnosis and treatment of leukaemia in patients.

| Article | Patient demographics | Disease status | Treatment for leukaemia | IT chemotherapy | Brain irradiation | SCT |
|---------|----------------------|----------------|-------------------------|-----------------|------------------|-----|
| 1       | Patient 1a 2 M – ALL – | GTC after given L-asparaginase during induction | VCR, Prednisone, L-asparaginase, Daunorubicin, Ara-c, Cyclophosphamide, Doxorubicin, 6MP, MTx | MTx | – | – |
| 2       | Patient 2a 5 M – ALL – | Methotrexate induced encephalopathy | VCR, Prednisone, L-asparaginase, arabinosyktosine, cyclophosphamide, 6MP, MTx | MTx, hydrocortisone | – | – |
| 3       | Patient 3a 2.5 M – ALL – | One Febrile seizure | VCR, Prednisone, Daunorubicin, Doxorubicin | MTx, Ara-C | 18 Grey | – |
| 3b      | Patient 3b 2.5 F – ALL – | – | VCR, Prednisone, L-asparaginase, methotrexate | MTx | 18 Grey | – |
| Article | Patient demographics | Disease status | Treatment for leukaemia |
|---------|----------------------|----------------|------------------------|
|         | Patient | Age at diagnosis (years) | Sex | Comorbidity | Type of leukaemia | CNS disease | History of encephalitis/encephalopathy during treatment | Chemotherapy (intravenous and oral) | IT chemotherapy | Brain irradiation | SCT |
| 3c      |          | 7 M – | ALL – | Status epilepticus during induction | VCR, Prednisone, L-asparaginase, Daunomycin | MTx, Ara-C | 18 Grey – |
| 3d      |          | 3 F – | ALL – | – | VCR, Prednisone, L-asparaginase, Daunorubicin | MTx | 18 Grey – |
| 3e      | 0.67     | M – | ALL – | Symptomatic seizure due to hyponatraemia | VCR, Prednisone, Daunorubicin | MTx | 18 Grey – |
| 4a      | 13 F –   | NHL – | – | – | VCR, Prednisone, L-asparaginase, Daunorubicin | MTx, Ara-C, hydrocortisone | – | – |
| 5a      | 10 M –   | ALL – | Left parietal–occipital lobe intracranial haemorrhage, left occipital epidural haemorrhage | VCR, Prednisone, L-asparaginase, Daunomycin, cyclophosphamide, VM26, Ara-C, methotrexate | MTx | – | – |
| 5b      | 3 M –    | ALL | Infiltrative lesion | Infiltrative brain lesion | VCR, Prednisone, L-asparaginase, Daunomycin, cyclophosphamide, VM26, Ara-C, methotrexate | N/A | N/A | – |
| 6a      | 6 F –    | ALL – | Methotrexate encephalopathy with seizure | VCR, Prednisone, L-asparaginase, Adriamycin, Ara-C, cyclophosphamide, 6MP, MTx | MTx, Ara-C, hydrocortisone | – | – |
| 6b      | 5 M –    | ALL – | – | – | VCR, Prednisone, L-asparaginase, Adriamycin, Ara-C, cyclophosphamide, 6MP, MTx | MTx, Ara-C, hydrocortisone | – | – |
| Our patients | Patient 1 | 6 F – | AML – | – | One episode of afebrile seizure during chemotherapy | MTx | Daunorubicin, Ara-c, etoposide, amsacrine | MTx, Ara-C, hydrocortisone | – | Yes |
|         | Patient 2 | 0.67 M – | AML | CT: small hyperdense foci, resolved subsequently | VCR, Prednisone, L-asparaginase, Daunorubicin, Ara-c, etoposide, amsacrine, mitoxantrone, fludarabine, daunoxome | MTx, Ara-C, hydrocortisone | MTx, Ara-C, hydrocortisone | – | Yes |

**Key:** ALL: Acute lymphoblastic leukaemia; AML: Acute myeloid leukaemia; APL: Acute promyelocytic leukaemia; NHL: Non-Hogkin lymphoblastic lymphoma; IT chemotherapy: intrathecal chemotherapy; BMT: Bone marrow transplantation. PRES: Posterior reversible encephalopathy syndrome. VCR: Vinristine, MTx: methotrexate; Ara-C: cytarabine; VM26: teniposide.

**Article 1:** Monisha Goyal, Barbara A Bangert, Max Wiznitzer. Mesial Temporal sclerosis in Acute Childhood Leukaemias. Epilepsia 2003; 44: 131–134.

**Article 2:** Kouhei Hamamoto, Noboru Oriuchi, Takashi Kanazawa, Tetsuya Higuchi, Keigo Endo. Mesial temporal sclerosis associated with methotrexate induced leukoencephalopathy. *Paediatr Neurol* 2009; 40: 306–309.

**Article 3:** Rebecca E. Fasano, Donna C. Bergen. Intractable epilepsy in patients treated for childhood acute lymphocytic leukaemia. *Seizure* 2009; 18: 298–302. [DOI: https://doi.org/10.1016/j.seizure.2008.10.008]

**Article 4:** Rafael Sivera, Luis Bataller, Jesus Martinez, Vicente Villanueva. Mesial Temporal sclerosis as a complication of hematologic cancer. *J Neurol* 2009; 256: 1759–1761 [DOI: https://doi.org/10.1007/s00415-009-5108-5]

**Article 5:** Yun Leng, Tao Yu, Yongjie Li, Wenming Chen. Surgical treatment of refractory epilepsy after chemotherapy in two children with leukaemia. *Epilepsy and Behavior Case Reports* 1 2013: 32–34.

**Article 6:** Emi Kasai-Yoshida, Masaaki Oghira, Miwa Ozawa, Taiki Nozaki, Michiharu Horino, Atsushi Manabe, Ryota Hosoya. Temporal Lobe Epilepsy With Hippocampal Sclerosis in Acute Lymphoblastic Leukaemia. *Paediatrics* 2013; 132: 252–256.
### Table C2
Features of features of epilepsy and respective treatment in patients.

| Article | Patient | Epilepsy | Age of onset | Time from diagnosis (years) | Time from SCT (years) | Seizure type | Frequency | MRI findings | EEG findings | Treatment | No of anticonvulsants tried | Non-drug trial/epileptic surgery | Neurological outcome | Cognitive impairment |
|---------|---------|----------|--------------|-----------------------------|-----------------------|--------------|-----------|--------------|-------------|-----------|---------------------------|-------------------------------|---------------------|---------------------|
| 1       | 1a      | FIAS     | 11           | 9                           | –                     | FIAS         | Frequent  (N/A) | Right MTS   | N/A         | 2         | –                         | Non-significant abnormality   | Fair (poor compliance) | N/A                 |
| 2       | 2a      | FIAS     | 12           | 7                           | –                     | FIAS +/- GTC | 1×/week  | Left MTS    | No significant abnormality | 1         | –                         | VNS                          | Good (6×/year) with valproate and lamotrigine | Impaired | Impaired |
| 3       | 3a      | FIAS     | 15           | 12.5                        | –                     | Absence, FIAS | 6×/day   | Unremarkable | Multifocal epileptiform discharges, 3 Hz spike-and-wave discharges left temporal epileptiform discharge | 4         | –                         | VNS                          | Refractory (1–2 seizure per month) with VNS, topiramate and carbamazepine | Impaired | Impaired |
| 3b      | 3b      | FIAS     | 14           | 11.5                        | –                     | FIAS +/- GTC | 1×/day   | Multiple areas of high T2 and FLAIR signal in bilateral cerebral white matter Unremarkable | Bilateral frontotemporal epileptiform discharges | 9         | –                         | VNS                          | Refractory (daily seizures) | Impaired | Impaired |
| 3c      | 3c      | FIAS     | 10           | 3                           | –                     | FIAS         | 3×/week  | Right MTS   | Ictal: right temporal theta activity | Several (not specified) | Right hippocampectomy | Seizure free | N/A                  |
| 3d      | 3d      | Absence, GTC, | 9             | 6                           | –                     | Absence, FIAS | ≥ 1×/day | Increased signal over left mesial temporal lobe High T2 and FLAIR signal in white matter | Multifocal epileptiform discharges/generalized spike-and-wave bifrontal epileptiform discharges | 8         | –                         | VNS                          | Refractory (daily seizures) | Impaired | Impaired |
| 3e      | 3e      | FIAS     | 9            | 8.33                        | –                     | FIAS +/- GTC | ≥ 1×/day | Right MTS and Right MTS and Right parietal–parietal lesion | Ictal: left temporal spikes | 6         | –                         | Seizure free (still on oxcarbamazepine after operation) | Seizure free | N/A |
| 4       | 4a      | FIAS     | 14           | 1; refractory in 6 years after stopping treatment | –                     | FIAS         | Frequent  | Right MTS   | Ictal: right temporal theta activity | Several (not specified) | Right hippocampectomy | Seizure free | N/A |
| 5       | 5a      | FIAS     | 5            | N/A                         | >4 (4 years after stopping treatment) | FIAS         | Several times/week | Left temporal occipital lobe | Left temporal occipital discharges | 6         | –                         | Surgical excision of epileptogenic tissue in left temporal parietal lobe, followed by left anterior temporal lobe excision | Seizure free (on carbamazepine and lamotrigine after operation) | N/A |
| 5b      | 5b      | FIAS     | 5            | 2                           | –                     | FIAS         | 20×/day  | Right MTS and Right MTS and Right parietal–parietal lesion | Right temporal parietal discharges | 4         | –                         | Seizure free (still on oxcarbamazepine after operation) | Seizure free | N/A |
| 6       | 6a      | FIAS     | 11           | 5                           | –                     | FIAS         | ≥ 1×/day  | Left MTS    | Ictal: left temporal spikes | 6         | –                         | Subpial transections of left mesial temporal lobe | Seizure free | N/A |
| 6b      | 6b      | FIAS     | 11           | 6                           | –                     | FIAS         | 1× per 2 months 10×/month | Left MTS | High voltage slow waves in left hemisphere | Right temporal sharp waves | 5         | –                         | Seizure free | Seizure free | N/A |

**Key:**
- GTC: generalised tonic–clonic seizure; FIAS: focal impaired awareness seizure
- MTS: mesial temporal sclerosis.
- VNS: vagal nerve stimulator.

Refractory seizure defined as ≥ 1 seizure per month.

Article 1: Monisha Goyal, Barbara A Bangert, Max Wiznitzer. Mesial Temporal Sclerosis in Acute Childhood Leukaemias. Epilepsia 2003; 44: 131–134.

Article 2: Kouhei Hamamoto, Noboru Oriuchi, Takashi Kanazawa, Tetsuya Higuchi, Keigo Endo. Mesial Temporal Sclerosis associated with methotrexate induced leukoencephalopathy. Paediatr Neurol 2009; 40: 306–309.

Article 3: Rebecca E. Fasano, Donna C. Bergen. Intractable epilepsy in patients treated for childhood acute lymphocytic leukaemia. Seizure 2009; 18: 298–302. [DOI: https://doi.org/10.1016/j.seizure.2008.10.008]

Article 4: Rafael Sivera, Luis Bataller, Jesus Martinez, Vicente Villanueva. Mesial Temporal Sclerosis as a complication of hematologic cancer. J Neurol 2009; 256: 1759–1761 [DOI https://doi.org/10.1007/s00415-009-5168-5]

Article 5: Yun Jiang, Tao Yu, Yongjie Li, Wenming Chen. Surgical treatment of refractory epilepsy after chemotherapy in two children with leukaemia. Epilepsy and Behavior Case Reports 2013; 1: 32–34.

Article 6: Emi Kasai-Yoshida, Masaaki Ogihara, Miwa Ozawa, Taiki Nozaki, Michiharu Horino, Atsushi Manabe, Ryota Hosoya. Temporal Lobe Epilepsy With Hippocampal Sclerosis in Acute Lymphoblastic Leukaemia. Paediatrics 2013; 132; 252–256.
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