Reversible Posterior Leukoencephalopathy Syndrome Complicating Therapy of Hodgkin Disease in A Child with Familial Mediterranean Fever: A Case Report

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Abstract
Introduction: Reversible posterior leukoencephalopathy syndrome (RPLS) is characterized clinically by headache, abnormalities of mental status and visual perception, and seizures. Despite its diverse causes, common precipitating factors are defined as abrupt elevations of blood pressure, renal decompensation, fluid retention, and immunosuppressive therapy.

Presentation of Case: We report a case of a child, aged five and half years old, having symptomatic FMF confirmed by genetic studies, who developed Hodgkin lymphoma while on colchicine therapy. The association between MEFV gene mutations, the gene responsible for familial Mediterranean fever (FMF), and hematolymphoid neoplasms has been recently suggested. Initiation of chemotherapy was complicated by development of RPLS. After initial good response to chemotherapy, the patient developed progressive Hodgkin disease with evidence of secondary amyloidosis despite regular colchicine therapy.

Conclusion: The causes of RPLS in our case could be multifactorial, that could stem from the abrupt elevation of blood pressure, high-dose chemotherapy, Hodgkin disease or the FMF.

Keywords: Hodgkin disease; Familial Mediterranean fever; Reversible Posterior Leukoencephalopathy Syndrome

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Introduction
Reversible posterior leukoencephalopathy syndrome (RPLS) was a term first used by Hinchey et al [1] in 1996 to describe a distinct clinico-radiological entity comprising headache,
seizures, visual disturbance, and altered mental function associated with symmetrical posterior cerebral white matter oedema [2]. RPLS is an uncommon but distinctive clinicoradiological entity comprising of headache, seizures, visual disturbance, and altered mental function. RPLS has been previously reported in association with immunosuppressive therapy [3, 4]. Previous study described RPLS in FMF patients during attacks associated with hypertension [5].

Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrent attacks of fever and serositis affecting mainly Mediterranean populations (Jews, Armenians, Arabs, and Turks). Most patients begin to suffer during childhood, 60% before 10 years of age and 90% before the age of 20 years. The disease is characterized mainly by fever with abdominal pain and/or arthritis [6]. FMF is caused by mutations in MEFV gene, which encodes pyrin and results in uncontrolled inflammation [7]. The prevalence of Hodgkin lymphoma in patients with FMF is rare and its association is equivocal [8].

Specific magnetic resonance (MR) techniques, such as FLAIR (fluid attenuated inversion recovery) and DWI (diffusion weighted images) sequences, have improved the ability to detect subcortical/cortical lesions and helped to clarify the underlying pathophysiological mechanism of cerebrovascular involvement, which results important for an appropriate therapeutic decision [9]. We report the case of a child with FMF and Hodgkin lymphoma, mixed cellularity subtype, complicated with post-chemotherapy RPLS.

Case Presentation

A five and half years old male patient, second in order of birth of first cousin parents, diagnosed at the age of 4 years as a case of familial Mediterranean fever (FMF). The diagnosis was suggested by recurrent attacks of fever, arthralgia, and infrequent attacks of abdominal pain without organomegaly, and proved by molecular genetic analysis of having combined heterozygous state for M694V and M694I mutations in MEFV gene. The patient was on regular colchicine therapy (1 mg /day) and had partial clinical response. While on treatment for eight months, he developed progressive abdominal enlargement, recurrent fever, and his clinical condition was re-evaluated.

By examination, the patient looked toxic and ill, his weight was 20 kg (75th centile for age), height was 115cm (95th centiles for age), temperature was 39°C, blood pressure was 100/70 mm Hg (90th /75th centile for age). Abdominal examination revealed hepatomegaly, the right lobe of the liver was palpable 4cm below the costal margin and the span was 12cm, the spleen was palpable 2 cm along its long axis, and he had generalized lymphadenopathy.

Investigations revealed normocytic normochromic anemia, low serum iron and normal total iron binding capacity, repeatedly elevated ESR and CRP, elevated cytomegalovirus IgG titre while other viral markers were negative, normal kidney and liver function tests, and normal serum amyloid A. Results were negative for lupus anticoagulant, anti-DNA and antinuclear antibodies, and antcardiolipin IgM and IgG.

CT scan revealed multiple enlarged mediastinal, pretreacheal, retrocaval, right paratracheal, azygo-oesophageal, subcarinal and hilar enlarged lymph nodes, the largest measuring 1.5x2.5 cm as well as multiple enlarged lymph nodes in the portahepatis, peripancreatic, celiac and paraaortic regions, the largest measuring 2.5 cm in diameter, and multiple bilateral confluent infiltrative lung lesions. The liver and the spleen were enlarged showing multiple heterogenous hypodense areas.

Echocardiography was normal. Bone marrow aspirate and biopsy were negative for neoplastic infiltration and/or fibrosis. CT-guided true cut biopsy from the abdominal lymph nodes, examined pathologically was reported as Hodgkin lymphoma, mixed cellularity subtype. The tumour cells were positive for CD 15 and CD 30 and negative for CD20.

The patient was diagnosed as Hodgkin lymphoma stage IVB, and the patient was scheduled to receive 8 ABVD cycles (Doxorubicin, Bleomycin, Vinblastine and Dacarbazine given on days 0 and 14 of each cycle) [10].

Seven days after the 1st chemotherapy session (ABVD 1a) had been given, the patient developed right sided focal convulsions with secondary generalization. One day following the onset of convulsions, he experienced sudden transient bilateral blindness that lasted few minutes. He developed acute
hypertension (170/120 mm Hg), fundus examination revealed bilateral pale optic disc. Serum electrolytes, CSF examination and CT brain were normal.

MRI brain (Figure 1) revealed moderate sized lesions mostly cortical and subcortical in left temporoparietal and to less extent occipital regions with bright signal on FLAIR and T2-Weighted MRI (T2-WI). It also showed gyral like pattern of post contrast enhancement. There was a mid pontine small lesion which was identified with high signal on FLAIR and T2-WI MRI, while low signal on T1-WI MRI and which was not enhancing on the enclosed images.

![Figure 1 MRI brain: Moderate sized lesions mostly cortical and subcortical in temporo-parietal and occipital lobes bilaterally](image1.png)

After four days, MRI brain was repeated (Figure 2), showed progressive course, particularly as regards the occipital lobes bilaterally, with new several bilateral cerebral hemispheric moderate sized zones of signal abnormality mostly cortical and subcortical but also with deep white matter involvement. MR Spectroscopy (Figure 3) showed inflammatory nature of the lesions. Magnetic resonance perfusion study (Figure 4) revealed that the lesions showed hypoperfusion, whereas MRA was normal. Renal ultrasonography and duplex were normal.

![Figure 2 Follow up MRI brain: Progressive course, particularly the occipital lobes bilaterally, with new several](image2.png)
The patient was initially diagnosed as possible multiple subacute infarctions versus viral encephalitis. Accordingly, he was started anticonvulsant therapy (intravenous phenytoin), low molecular weight heparin, intravenous acyclovir and immunoglobulin therapy. Blood pressure was controlled by oral antihypertensive drugs in the form of ACE inhibitor (captopril 12.5 mg /8h), calcium channel blocker (amlodipine 50mg/day) and diuretic (furosemide 0.5 mg tab in the morning), this treatment had been gradually withdrawn after stabilization and patient was maintained only on amlodipine). Heparin was stopped after a few days. After 5 days, the patient markedly improved with control of convulsions and hypertension. After stabilization, the patient resumed ABVD chemotherapy cycle Ib on day 20 with 6 days delay. MRI brain was repeated six months later and was normal; suggesting the diagnosis of reversible posterior leukoencephalopathy syndrome (RPLS).
After completion of chemotherapy, whole body PET/CT was done and revealed residual pathological metabolically active single focal lesion in the spleen and low grade active focal foci in mid-abdomen consistent with suspected residual activity in celiac lymph nodes. Whether these lesions were related to Hodgkin disease or FMF itself or related to the developing amyloidosis could not be decided as no sites were available for biopsy. Splenomegaly has been reported in as many as 57% of the cases of FMF in various series and lymphadenopathy, with biopsy of the glands, showing non-specific hyperplasia [11]. On the other hand, PET positive lesions simulating malignancy were previously described in patients with amyloidosis in various sites including the lungs and bones [11, 12]. Because malignancy could not be excluded, the possibility of residual Hodgkin disease was considered.

Unfortunately, the patient was refractory to initial chemotherapy. Salvage therapy was started as DHAP (cytosine arabinoside-cisplatin-dexamethasone) protocol [13], and the patient was scheduled for autologous bone marrow transplantation as he had no HLA matched donor. While on salvage therapy, the disease progressed rapidly with numerous pulmonary, osseous and nodal (pretracheal, retrocaval, subcarinal, paraaortic) lesions and biopsy confirmed relapsed Hodgkin disease. Serum Amyloid A protein was assessed for suspected amyloidosis, and its value was high for the reference age range (410 mg/l). Bone biopsy was done from the active lesion in the femur, pathology and immunohistochemistry confirmed Hodgkin lymphoma relapse, unfortunately the patient died while on salvage therapy.

Discussion

Reversible posterior leukoencephalopathy syndrome (RPLS) is an uncommon but distinctive clinicoradiological entity characterized by the development of headache, seizures, visual disturbance, and altered mental function, in association with posterior cerebral white matter oedema. With appropriate management, RPLS is reversible in the majority of cases [14]. Previous reported associations of RPLS include hypertension, eclampsia, renal failure, malignancy, use of immunosuppressive drugs, systemic lupus erythematosus, FMF [4, 15]. Typically, RPLS lesions in MRI occur predominantly in the posterior white matter of subcortical region and some involvement of the cortex can also exist [16].

Familial Mediterranean fever (FMF) is caused by mutations in the MEFV gene, which encodes for the pyrin protein, involved in the regulation of apoptosis and inflammation. Its N-terminal pyrin domain regulates caspase-1 activation and consequently, interleukin-1β production. Mutations interfere with the role of the pyrin domain, allowing an uninterrupted inflammatory cascade [6, 7]. So far, more than 60 FMF-associated mutations have been detected [3]. Molecular genetic testing revealed our patient to have combined heterozygosity for M694V and M694I mutation in MEFV gene; both have been described as the commonest mutations in Egyptian FMF patients [17]. A previous study [6] reported that M694I and A744S mutations were specific to Arab populations, and although M694V mutation is the most frequent mutation in various ethnic groups, it is less common among Arabs and, when present, occurs almost only in heterozygous form.

The association between FMF and malignancy has been under investigation. A recent study [8] determined the rate of the five most common MEFV gene mutations in 46 patients with hematolymphoid neoplasm, and found a high frequency of carriers in patients with multiple myeloma (60%), acute lymphocytic leukemia (33.3%), least in non-Hodgkin lymphoma (5%), and no MEFV gene mutations in patients with Hodgkin lymphoma. The prevalence of Hodgkin lymphoma in patients with FMF is rare and its association is equivocal [8]. Strong heterozygous mutations such as M694V and M680I were predominating in their patients with hematolymphoid neoplasm. Similarly, high prevalence of MEFV gene mutations in patients with myeloid neoplasms has been recently described [18].

Our patient, 6 days after receiving the 1st course of ABVD, developed convulsions and sudden onset of blindness. CNS infection was excluded by the normal CSF. CNS involvement of Hodgkin disease is reported to be rare. Gerstner et al., 2008 [19] stated that Hodgkin lymphoma, unlike non-Hodgkin lymphoma, rarely involves the central nervous system with the incidence reported as 0.2% to 0.5%
of all HL cases. So, the possibility of CNS disease was a remote diagnosis.

CNS disease developing in FMF patient has been described with three possible etiologies: demyelinating lesions and cerebrovascular disease being the most common [20], however Reversible posterior leukoencephalopathy syndrome (RPLS) has been rarely described in FMF especially in association with hypertension [5].

Neuroimaging of RPLS is typically associated with high signal intensity on T2-WI predominantly in the posterior regions, which is caused by subcortical white matter vasogenic edema [21]. The parietal and occipital lobes are most commonly affected, followed by the frontal lobes, the inferior temporal-occipital junction, and the cerebellum [22]. MR diffusion-WI was instrumental in establishing and consistently demonstrating that the areas of abnormality represent vasogenic edema [23, 24]. Complete reversibility is generally regarded as a defining feature of RPLS. The ideal timing of repeated brain imaging to document recovery is unclear and resolution of RPLS neuroimaging abnormalities probably occurs in the range of several days to weeks [25]. Focal areas of restricted diffusion (likely representing infarction or tissue injury with cytotoxic edema) are uncommon (11%–26%) and may be associated with an adverse outcome [26]. Hemorrhage (focal hematoma, isolated sulcal/subarachnoid blood, or protein) is seen in approximately 15% of patients [23, 27].

The typical clinical picture, the MRI abnormalities, MR Spectroscopy (minimal increase of choline, mild to moderate increase of myoinositol, glutamine, aminoacid, lipid and lactate and reduction of normal neuronal marker NAA) and the reversibility of the neurological manifestations favoured the diagnosis of Reversible posterior leukoencephalopathy syndrome (RPLS) which could be explained in our case by the sudden elevation of blood pressure, the high dose chemotherapy given, the underground FMF disease and the developed Hodgkin disease. Previous studies describe RPLS in FMF patient [15, 5].

No single chemotherapeutic agent or therapeutic regimen has been identified to date as being consistently associated with RPLS. Implicated drugs have included single-agent cisplatin or cytarabine, as well as combinations of adriamycin, cyclophosphamide, vincristine, corticosteroids [28] and others [4].

One constant feature in the reported cases of RPLS complicating cytotoxic chemotherapy is the presence of systemic hypertension [2]. This happened with our patient who developed systemic hypertension with the onset of neurological signs. Once, the blood pressure of the patient was controlled, the condition resolved with no residual neurological deficit. This is consistent with previous reports [3] that stated that in the majority of cases, RPLS is fully reversible within a period of days to weeks, with removal of the inciting factor and control of the blood pressure. Therapeutic strategy depends on the cause of PRES and clinical picture. Most important are blood pressure regulation, control of epileptic attacks, anti-oedema therapy [29] and correct any electrolytes imbalance [2].

In this child with FMF on colchicine therapy, the progression of amyloidosis was accelerated by the co-development of Hodgkin disease, also known to predispose to amyloidosis [7, 12]. Renal impairment was one of the complications of FMF in this patient, making the use of renotoxic chemotherapy hazardous. The diagnosis can only be confirmed by demonstrating the presence of tissue amyloid deposits. Traditionally this required histology but the recent introduction of labelled serum amyloid P component scintigraphy is a specific alternative that provides a quantitative macroscopic whole body survey of amyloid deposits [30].

Conclusion

RPLS may be an under-appreciated complication of cytotoxic therapy; early diagnosis requires a high clinical index of suspicion, appreciation that initial neurological deficits are variable and often subtle, and timely evaluation of cerebral white matter with neuroimaging. So, meticulous attention is paid to changes in weight and blood pressure in any patient who receives a combination chemotherapy regimen.

References


