Case Report

Acute Cytomegalovirus infection complicated with Haematophagocytic Lymphohistiocytosis in a young male with an inaugural diagnosis of Systemic Lupus Erythematosus: A case report

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Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease due to a diverging immune response resulting in immune-mediated damage to tissues with significant morbidity and mortality. Cytomegalovirus (CMV) is a constantly encountered, widespread herpesvirus with a mild impact on immunocompetent hosts but can lead to significant morbidity and mortality in the immunocompromised host. Hemophagocytic lymphohistiocytosis (HLH) is a rare and potentially fatal clinical condition with a collection of symptoms resulting from exaggerated immune activation, response, and cytokine storm. HLH can be primary which is genetically predisposed, and secondary which is usually preceded by an infection or an inflammatory process which then is referred to as macrophage activation syndrome. Here we report a rare case of a young male with an inaugural diagnosis of SLE complicated with HLH following a recent CMV infection.

Keywords: Cytomegalovirus, Hemophagocytic lymphohistiocytosis, Systemic lupus erythematosus

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare and potentially fatal clinical condition with a collection of symptoms resulting from exaggerated immune activation, response, and cytokine storm resulting in multiorgan failure and tissue damage [1]. CMV is a commonly encountered virus, which can manifest in different ways. In immunocompetent hosts, CMV can remain as a latent infection or persist as asymptomatic with low viremia. But in immunocompromised it acts as an opportunistic infection leading to increased morbidity and mortality [2]. SLE is a common autoimmune disease mainly found in young females [3]. CMV infection and SLE both conditions have been described as potential triggers for HLH [4,5].

Case report

A 15- year-old previously healthy young boy was admitted with a history of fever associated with multiple neck lumps for 2 weeks duration. He complained of daily mild fever spikes of around 100°F. On examination, he had right-sided tender cervical lymphadenopathy and mild to moderate non-tender splenomegaly. On investigations his serum was positive for CMV Ig M. As the fever subsided and the patient was clinically better, he was discharged from the hospital with a diagnosis of acute uncomplicated CMV infection.

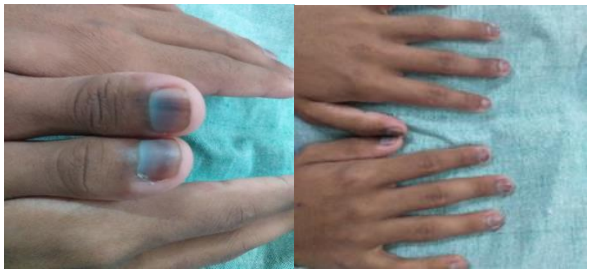
Following six weeks of discharge from the hospital, the patient was readmitted with a high-grade fever for about two weeks duration. Fever was associated with arthralgia, but no significant myalgia. There was no history of cough, wheezing, dysuria, increased frequency, nausea, vomiting, or loose stools. Urine output was normal. Bowel habits were not altered. He did complain of oral ulcers, but there was no history of red eyes, alopecia, skin rashes, photosensitivity, or small joint pain or swelling. He did complain of discoloration of his fingernails in both hands which was recent in onset. He also had one episode of mild epistaxis for one day which had settled on its own and he did give a history of mild gum bleeding while brushing his teeth on the day of admission. There were no other bleeding manifestations. He had a loss of appetite, but no significant loss of weight was observed. He didn't give a history of altered behaviour, visual disturbances, seizures, upper limb or lower limb weakness, or severe headache.

On examination, he was febrile, mildly pale but not icteric. Several oral ulcers involved the soft palate, the buccal mucosa, and the lip. There were a few enlarged posterior cervical lymph nodes on the right side of the neck which were tender, firm, rubbery, and not matted, and the largest of around 2cm in width. There were no peripheral stigmata of infective endocarditis and no finger clubbing. There was bilateral fingernail hyperpigmentation (melanonychia) (Figures 1 and 2). There was no joint swelling or tenderness, and no ankle oedema. The fundal examination was normal. Abdominal examination revealed a non-tender firm moderate splenomegaly and non-tender soft mild hepatomegaly. There was no free fluid. Cardiovascular, Respiratory, Nervous, and Musculoskeletal system examinations were unremarkable. The patient's haematological, biochemical, and other investigations are given in Table 1.

Fever, splenomegaly, pancytopenia, serum ferritin of > 500ng/ml, and high triglycerides of > 265mg/dl were supportive of a diagnosis of hemophagocytic lymph histiocytosis according to the Histiocyte Society Criteria, even though there were no hemophagocytes seen in the bone marrow. Natural Killer cell activity and soluble Inter leukin -2 receptor levels were not accessible. The patient was diagnosed with CMV infection complicated with HLH. He was started on Dexamethasone, a tapering regimen for a total of 8 weeks. The patient's clinical symptoms subsided following the initiation of dexamethasone.

While tapering the dexamethasone on the 3rd week, the patient was again admitted with fever and bilateral ankle joint swelling and pain. This is when his Serum anti-nuclear factor antibodies (ANA) became positive (1:100) and serum double-stranded deoxyribonucleic acid (ds-DNA) was also positive with low Compliment 3(C3) and Compliment 4(C4) levels. ANA positivity of > 1:80 fulfilled the entry criteria for SLE. The presence of fever, leukopenia and thrombocytopenia, oral ulcers, joint involvement, positive ds-DNA, and low C3 and low C4 levels fulfilled the criteria for SLE diagnosis (Total score of 22). A rare diagnosis of acute CMV infection complicated with HLH with underlying SLE in a young male was made.

The patient was started on oral prednisolone, hydroxychloroquine, and Azathioprine for SLE. His fever subsided as well as his joint pains, following the initiation of steroids. Pancytopenia settled, and on discharge, his white blood cell count had risen to 10,400/µL, haemoglobin was 11.3g/dl and platelets were 200,000/µL. Prednisolone was tapered gradually at the clinic level and hydroxychloroquine and Azathioprine were continued. He is being followed up at the medical as well as rheumatology clinic for long-term management of SLE.



Figures 1 and 2: Melanonychia in our patient which was new in onset.

Table 1: Haematological, biochemical, and other investigations of the patient.

Investigation	Results			Normal values
	Day 1	Day 6	On discharge	
White blood cell count(/µL)	4,670 (N-39%, L-55%)	2,940 (N-37%, L- 58%)	3,470 (N-43%, L-51%)	4,000-10,000
Haemoglobin(mg/l)	11	9.0	9.8	11-16
Platelets(/µL)	60,000	50,000	98,000	150,000-450,000
Erythrocyte sedimentation rate (/1st hour)	50mm	56mm	-	<10
C- Reactive protein (mg/l)	1.55mg/l	-	-	<6
Procalcitonin(ng/ml)	0.37 (negative)	-	-	<0.5 -sepsis unlikely
Blood and urine cultures	No growth	-	-	
Aspartate aminotransferase(U/l)	39	43	-	13-31
Alanine aminotransferase (U/l)	33	41	-	7-40
Alkaline phosphatase(U/l)	68	55	-	53-128
Gamma-glutamyl transferase(U/l)	45	48	-	15-30
Total bilirubin(µmol/l)	4.5	4.4	-	3-21
Direct bilirubin(µmol/l)	1.5	2.0	-	1-7
Total protein (g/dl)	6.9	7.1	-	6.4-8.3
Albumin(g/dl)	3.2	3.2	-	3.2-5.4
Serum creatinine(µmol/l)	79.2	77.7	-	80-115
Serum sodium(mmol/l)	143	140	-	135-145
Serum potassium(mmol/l)	4.5	4.6	-	3.5-5. 5
Ultrasound scan of the abdomen	splenomegaly of 14.7cm	-	-	
Ultrasound scan of the neck	sub-centimeter size lymph nodes in the cervical region	-	-	
Urine full report	Normal	-	-	
Chest X-ray	Normal	-	-	
Sputum acid fast bacilli, and Mantoux	Negative	-	-	
Human Immune deficiency virus antibodies	Negative	-	-	
Serum ferritin(ng/ml)	957	-	-	10-300
Serum triglycerides(mg/dl)	395.7	-	-	<150
Serum fibrinogen(mg/dl)	230	-	-	180-450
Lactate dehydrogenase level(U/L)	516	-	-	140-280
Bone marrow aspiration and trephine biopsy	no evidence of hemophagocytes	-	-	
Lymph node biopsy	Reactive features	-	-	
Serum Cytomegalovirus antibodies Ig M	Positive	-	-	
Serum Epstein bar virus antibodies Ig M	Negative	-	-	

Discussion

This case of a young 'male' with underlying SLE which wasn't diagnosed earlier was managed for acute CMV infection and then leading to HLH was indeed challenging. Especially when they have comparable clinical features and are uncommon.

SLE, a cornerstone of autoimmune conditions is an intricate process involving the interaction of environmental factors, genetic predispositions, and hormonal and immunogenic properties of the body. Loss of immune tolerance to self-antigens, along with proinflammatory and cytokine activity, an autoimmune process plays in place which is triggered by a complicated interaction of impaired lymphocyte biology, neutrophil extracellular traps, nucleic acid sensing, impaired clearance of apoptotic bodies, and immune complexes [3].

Numerous environmental factors have been linked to SLE. The most well-known causes include ultraviolet radiation, medications such as trimethoprim/ sulphamethoxazole, smoking, diseases like Epstein bar virus, silica, mercury, etc. Psychological stress has been associated with a higher risk of lupus [3]. Genetic

susceptibility is also considered to play an important role in the pathogenesis of SLE. There is evidence of disruption of both innate and adaptive immune systems in lupus [3]. Considering the epidemiology of SLE, it's common in females at a ratio of 13:1 and common in women aged 15 to 45 years [3].

Hemophagocytic lymph histiocytosis (HLH) is a rare and potentially fatal clinical condition with a collection of symptoms resulting from exaggerated immune activation, response, and cytokine storm resulting in multiorgan failure and tissue damage. It is a rare disease entity with a high mortality rate of 47% [1]. This condition was first described by Scott and Rhob-smith in the year 1939 [6]. Initially, HLH was considered an atypical form of Hodgkin's lymphoma named "histiocyte medullary reticulosis". The association of viral infections in immunocompromised individual hosts and the dysregulation of the immune system with features of HLH was first proposed in 1979 by Risdall, which was later described as secondary HLH [6].

There is uncertainty regarding the exact molecular and cellular mechanisms in the pathogenesis of HLH. Decades of clinical observations, genetic analysis, and scientific research have described that in HLH, the disease is caused predominantly by an abnormal immunological response, rather than by an underlying trigger, Immune responses in HLH do not appear to self-targeted antigens like in autoimmune diseases and there is uncontrolled activation of T cell activity [6]. Chronic inflammation and immunosuppression are also described as risk factors for HLH. HLH is frequently provoked by infections, most commonly by viruses, but occasionally by other intracellular pathogens. Infections such as Epstein-Barr virus, Cytomegalovirus, *M. tuberculosis*, fungi, and parasites are involved in triggering HLH mainly in an immunocompromised setting [6]. Considering autoimmune diseases, HLH secondary to SLE has a prevalence of around 0.9%-4.6% [4,5].

Defined by the HLH-2004 criteria for the diagnosis of HLH, five of the following eight features are required to be fulfilled [1,4,6,7].

1) Fever
2) Splenomegaly
3) Cytopenia affects 2 of 3 cell lineages (hemoglobin<9g/dl, platelets <100×103/mcL, and neutrophils < 1×10^3/mcL).
4) Hypertriglyceridemia and/or hypofibrinogenemia – fasting triglycerides> 3mmol/L; fibrinogen <1.5g/L
5) Hemophagocytosis,
6) Hyperferritenemia- >500mcg/L
7) High soluble IL-2 receptor levels - >2400U/mL
8) Low/ absent NK cell activity.

However, patients having a molecular diagnosis consistent with HLH are not required to fulfill the diagnostic criteria [7].

NK cell activity and soluble IL-2 receptor levels were not freely accessible in our setting. But fulfilling 5 criteria out of 8, our patient was diagnosed to have HLH according to the 2004 HLH criteria.

Our patient was initially treated for an acute CMV infection. Therefore, the HLH was attributed to being triggered by the CMV infection. Several case reports indicate that CMV infection can be a trigger for SLE [8]. Later on, our patient fulfilled the criteria for SLE as well. Diagnosis of HLH in the background of SLE is complicated as both diseases share some features in common. But unlike SLE, HLH is characterized by hyperferritinemia, hypofibrinogenemia, and hypertriglyceridemia [5]. Fever, and cytopenias both are common features of HLH and SLE, thus it is important to evaluate such patients for the possibility of both diseases by implementing serological tests for SLE like ANA and ds-DNA, and serum ferritin, fibrinogen, and triglycerides for HLH, to avoid a diagnostic delay.

Conclusion

HLH is a rare and potentially fatal disease where early detection and prompt intervention are necessary. SLE, an autoimmune condition common among young females, and viral infections like CMV are described as triggers for both HLH and SLE. This case of a young boy treated initially for CMV infection, then presenting with features of HLH and also fulfilling criteria for SLE is a rare occurrence. This emphasizes how crucial it is to assess patients and rule out other explanations for diseases that share similar clinical symptoms even after a diagnosis has been achieved.

Consent

Informed consent was obtained from the patient and the patient's parents for the publication of the case report.

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