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Case Report

Azithromycin Induced Hemophagocytic Lymphohistiocytosis: A Case Report

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Abstract

Introduction: Azithromycin is one of the commonly used antibiotics from the macrolide group. It has become prevalent after covid 19 to such an extent that even the common public is well aware of this drug. This is usually well tolerated and rarely produces severe adverse effects. The most common adverse effect is GI distress which is generally tolerable. This drug has triggered this rare condition called HLH in this patient who was treated for an upper respiratory tract infection.

Reason for Report: Azithromycin is usually not expected to trigger much of life-threatening reactions in patients. This is the drug of choice for people with rheumatic fever who are allergic to penicillin. This rare adverse effect should be considered while treating patients with this drug for common ailments like this case.

Case Summary: The patient was prescribed azithromycin at a dose of 500mg OD for URTI. All the infectious markers in the blood had fallen by day 7, and the fever persisted. With the negative RT-PCR for covid 19 the cause of fever was evaluated. After ruling out other conditions and careful assessment, we diagnosed it as a drug-induced case of Hemophagocytic lymphohistiocytosis.

Keywords: Azithromycin, HLH, COVID-19, URTI

Introduction

Azithromycin belongs to the macrolide class of antibiotics. It is one of the most commonly used antibiotics in India [1]. This is widely used to treat bacterial infections presenting as ailments like upper respiratory tract infection, Pneumonia, sexually transmitted diseases like chlamydia etc… This acts by inhibiting protein synthesis. The most common adverse effect noted is GI distress. The other adverse effects, like cholestatic jaundice, which can be life-threatening is quite rare. Here the patient has prescribed 500mg of azithromycin OD for 7 days due to its concentration-dependent killing property [2]. Usually, symptomatic relief will be seen within 5 days after starting treatment accompanied by defervescence. The patient here had relief from all other symptoms except fever which was still high-grade and showed up at regular intervals. This raised the suspicion that something weird was going on with the patient. This still became complicated when the blood culture turned to be negative. Then all other parameters were assessed, and everything turned out to be normal except for bicytopenia in the

complete blood picture. This was then diagnosed to be a case of hemophagocytic lymphohistiocytosis, which is due to the drug. This dreadful adverse effect which was triggered by a common drug, has to be known by physicians and other healthcare workers.

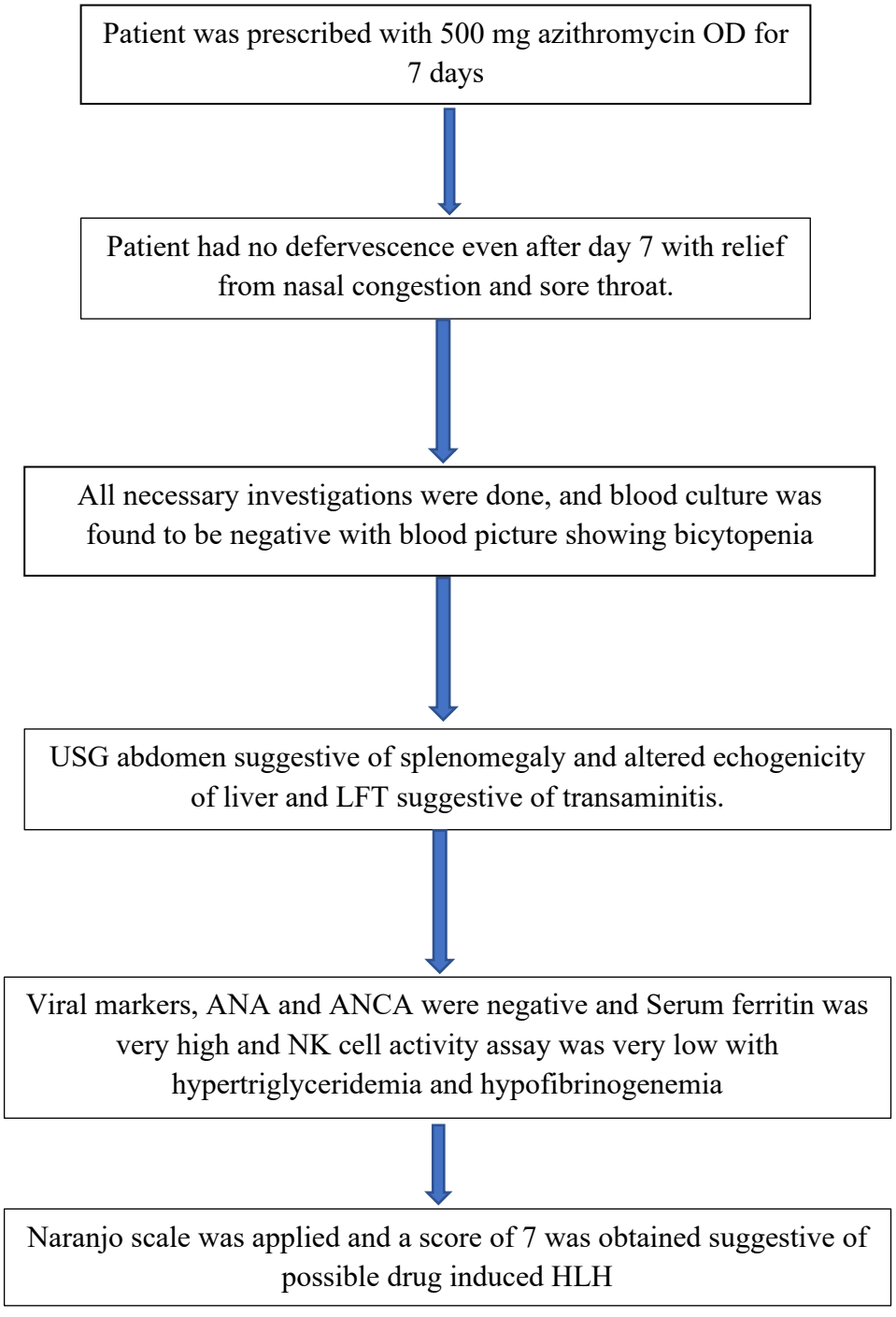
Case description

A 30-year-old male patient who was diagnosed to have an upper respiratory tract infection was started empirically on azithromycin at a dose of 500mg OD. He has been prescribed this antibiotic for seven days. The patient's culture and sensitivity report was awaited. And RT-PCR for covid 19 turned out to be negative. The patient's renal and liver parameters were normal, and the complete blood count was also normal except for leucocytosis, which was suggestive of infection. The patient was assessed on the third day, and still he had a fever but was relieved of nasal congestion and sore throat. His appetite has also improved. Since the fever was persisting, we repeated the blood counts and this revealed bicytopenia. But the blood culture was negative. USG abdomen revealed splenomegaly with mild alteration in echogenicity of the liver. Liver function tests revealed transaminitis. Triglycerides were elevated, and fibrinogen values were reduced. All these pointed towards a non-infectious cause of such a constellation of presentation and made us suspect HLH. So, to confirm the diagnosis and to rule out the other causes of viral markers, ANA and ANCA titers were assessed, and all were within normal limits. There was no family history of HLH. NK cell activity assay was low, and serum ferritin was very high, which pointed toward the diagnosis of HLH. And this presentation subsided after the patient was put on Amoxycillin and clavulanic acid as a replacement for azithromycin, along with supportive care. We applied the Naranjo causality assessment scale, and a score of 7 was obtained, which suggests this reaction is possible due to the drug.

Table 1: Panel of laboratory tests

Tests	Day 0	Day 7	Day 10
Completeblood count	Leukocytosis (12,000 cells/cu.mm)	RBC (98,000 cells/cu.mm) Platelets (60,000 cells/cu.mm)	Normal
Liver Function test	Normal	Transaminitis SGOT (420 IU) SGPT (450 IU)	Normal
Renal Function test	Normal	Normal	Normal
Blood culture	Negative	Negative	Negative
NK cell function assay	-	Reduced	Normal
Serum Ferritin	-	400 mcg/L	300mcg/L
Covid 19 RT-PCR	Negative	-	-
Triglycerides	Normal	190 mg/dl	Normal
ANCA	-	Negative	-
ANA	-	Negative	-
Anti HCV	-	Negative	-
HbsAg	-	Negative	-
HIV	-	Negative	-
Leptospirosis	-	Negative	-
WIDAL	-	Negative	-
VDRL	-	Negative	-
Fibrinogen	-	1.0 g/L	

Note: Since the Patients identity might get revealed original reports couldn't be provided for reference. These are the exact values from Those reports.



Flow Chart 1

Discussion

This case report discusses a rare presentation of drug-induced HLH. HLH, by itself is a rare entity. It is usually never anticipated at all. There is a common practice of predicting anaphylaxis associated with drugs which could lead to death in minutes. This is not as fast as the former one in case of death, but a delay in diagnosis might be fatal. This is associated with genetic mutations in patients who develop this condition.

Unfortunately, we couldn't do genetic testing in our set-up so we have used other criteria to diagnose this. The genetic mutations associated with this include PRF1, RAB27, STX11, STXBP2, UNC13D, and XLP [3]. These genes are associated with familial HLH. A negative family history usually rules out acquired HLH. This condition in adults is still rarer, and it usually affects the paediatric population. The pathogenesis of this condition is still unclear. Some of the pathogenic mechanisms are assumed for this condition.

In immunocompetent individuals, NK cells and CTLs kill infected cells by a non-secretory pathway involving Fas ligand (CD95-L) but, more importantly, by a perforin-dependent pathway. Cytotoxic cells are equipped with cytotoxic granules, also called secretory lysosomes, which contain perforin and granzymes.

Upon activation of NK cells or CTLs, these granules are carried along microtubules toward the immunological synapse between the effector and target cell. In this complex process, granules have to be activated to migrate, dock, and fuse with the cell membrane and to release their contents into the synapse. Together with granzymes, perforin then mediates the apoptotic death of target cells, and the immune response is down-regulated. Patients with FHL-2 have mutations leading to reduced or absent perforin [4]. Mutated genes in FHL3-5 and in GS-2 and CHS are involved in cytotoxic granule processing during various steps of trafficking and exocytosis. Therefore, the pathogenesis of genetic HLH is very likely based on the inability of cytotoxic cells to kill and eliminate the infected antigen-presenting cell [5]. In patients with XLP-1, lymphocyte cytotoxicity is also affected; in patients with XLP-2, IL-2-inducible T-cell kinase (ITK), and CD27 deficiency, the molecular mechanisms are largely unknown [6].

All these mechanisms suggest this condition to be an immunological catastrophe that could be fatal if the diagnosis is delayed. The rare nature of this condition makes it the problematic option to suspect and diagnose it so that it can be appropriately treated. This entity should be considered by treating physicians, as this could make a difference between life and death.

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