Case Report

Untangling a case of dapsone-induced acute liver injury

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Abstract

Dapsone hypersensitivity syndrome, although rare, may manifest with fever, rash, and multi-organ failure, mimicking other common diseases. This case study involves a 9-year-old female patient presenting with fever and acute liver injury, in which the intake of dapsone was not revealed until much later. We discuss how the diagnosis was made and the successful outcome following prompt treatment. A high index of suspicion and vigilant history-taking, along with a detailed past treatment history, can provide early clues in reaching a diagnosis. Early intervention with systemic corticosteroids improves the outcome of dapsone hypersensitivity syndrome and can prevent mortality.

Keywords: Dapsone hypersensitivity syndrome, drug-induced liver injury, pediatric drug hypersensitivity

Introduction

Dapsone is a sulfonamide drug commonly used as part of multidrug therapy (MDT) for the treatment of leprosy in India. Its use is rare in the pediatric population. Several medications, such as carbamazepine, phenytoin, phenobarbital, allopurinol, and dapsone, have been associated with hypersensitivity reactions, leading to drug-induced hypersensitivity syndrome (DIHS) or drug rash with eosinophilia and systemic symptoms (DRESS). Dapsone hypersensitivity syndrome (DHS) typically manifests with fever, rash, and multi-organ failure, occurring one to eight weeks after starting dapsone. While the exact pathophysiology is still being unraveled, it is believed that an immune-mediated reaction involving macrophage and T-lymphocyte activation plays a pivotal role. DHS can be life-threatening if not promptly treated. This case emphasizes the importance of thorough history-taking and highlights the societal stigma surrounding leprosy. Additionally, we present a brief review of three similar cases identified in our literature search.

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Clinical description

A previously healthy nine-year-old girl child presented to our hospital with seven days of intermittent fever and a diffuse itchy rash and edema involving her face, limbs, abdomen, and genitals for the past two days. The fever decreased with the intake of oral medications. The rash was first noticed on her limbs and subsequently progressed to the trunk. Edema was observed by her parents for two days, initially affecting the abdomen and now involving her limbs and face. There was no history of sore throat, coryza, decreased urine output, abdominal pain, distension, or dyspnea. The child had been treated at an outside hospital for a cutaneous fungal infection for four months. She was appropriately immunized for her age, and her development was normal. Currently, she is studying in the fourth grade with good scholastic performance. She is the firstborn child from a nonconsanguineous marriage and has a healthy four-year-old sibling, with no similar complaints. On examination, the child was conscious, oriented, and febrile, with a temperature of 102.4°F. Her pulse rate was 108 beats per minute, blood pressure was 100/70 mmHg, and respiratory rate was 18 per minute. The child was icteric. A head-to-toe examination revealed ascites, vulval edema, and tinea corporis and cruris. The anthropometric examination was normal. Systemic examination of the abdomen revealed a maculopapular rash, and palpation

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revealed shifting dullness and hepatomegaly present [Figure 1]. The respiratory, cardiovascular, and central nervous system examinations were within normal limits. A provisional diagnosis of viral exanthematous fever was made based on the history and examination findings.

Upon admission, a complete hemogram showed anemia with thrombocytopenia. A peripheral smear revealed macrocytic RBCs and hyper-segmented neutrophils. Liver function tests indicated direct hyperbilirubinemia with transaminitis. Renal function tests and serum electrolytes were within normal limits [Table 1]. Viral markers for hepatitis were negative. Due to persistent fever spikes and considering infectious and inflammatory pathology, RT-PCR for COVID-19 was performed and returned negative. Serology for leptospirosis, scrub typhus, dengue, and WIDAL tests was also negative. Blood and urine cultures were sterile. An ultrasound of the abdomen demonstrated mild hepatomegaly, an edematous gall bladder wall, and mild ascites. Given the macrocytic anemia, Vitamin B12 and folate levels were measured, showing values of 1101 pg/mL and 9.02 ng/mL, respectively. The direct Coombs' test was negative.

On the second day of hospitalization, the child began experiencing respiratory distress, prompting the initiation of oxygen therapy. We attributed this to moderate hepatomegaly with ascites exerting mechanical pressure on the lungs. A chest X-ray and echocardiogram were performed and returned normal results. On the third day, as the child's condition worsened and a definitive diagnosis remained elusive, further detailed history-taking with the mother revealed that the child had been taking dapsone as part of the MDT for skin lesions [Figure 2]. This has lead us to suspect dapsone-induced hypersensitivity syndrome, given the child's typical presentation. Hence the MDT drug was immediately discontinued, and IV steroids was initiated. A dermatologist was consulted and recommended continuing steroids based on the child's response. Due to worsening hepatitis, as evidenced by LFT monitoring, a hepatologist was also consulted. They advised starting oral rifaximin, N-acetyl cysteine, and ursodeoxycholic acid. A doppler ultrasound of the portal venous system was done to rule out outflow tract obstruction, which returned normal findings. Serum ceruloplasmin levels were tested to rule out Wilson's disease and were found to be within normal limits, thus confirming a diagnosis of dapsone-induced hypersensitivity syndrome. A dose of Vitamin K was administered for the abnormal INR values. Within a couple of days, the child was weaned off oxygen, her fever reduced, and the transaminitis began to resolve. She was discharged on a tapering dose of steroids as her liver function tests and coagulation profile showed a normalizing trend [Table 2]. At follow-up, hepatitis A and B vaccinations and steroids were discontinued.

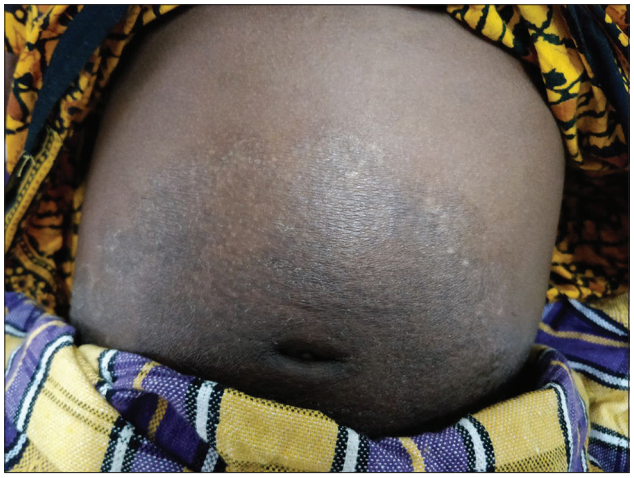

Figure 1: Distended abdomen and alternating hypo- and hyper-pigmented scaly plaques and an exfoliative rash with irregular active margins seen on the abdomen of the child

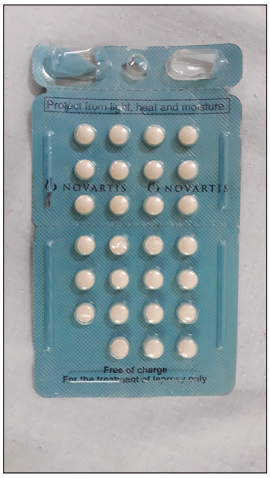

Figure 2: MDT - PB blister pack used by the child

Table 1: Investigations done on admission

CBC	Values	LFT	Values	RFT	Values
Hemoglobin	10 g/dL	T.Bilirubin	2.57 mg/dL	BUN	8 mg/dL
Total count	10890 cu. mm	D.Bilirubin	1.41 mg/dL	Creatinine	0.4 mg/dL
Platelet count	1.86 lakhs/cu.mm	SGOT	652 IU/L	Sodium	135 mmol/L
PCV	32.9%	SGPT	475 IU/L	Potassium	4.2 mmol/L
MCV	97.1 FL	ALP	490 IU/L	Chloride	98 mmol/L
MCH/MCHC	29.5 pg/30.4gm/dl	Total protein	5.7 g/dL	Bicarbonate	27 mmol/L
ESR	2 mm/hr	Albumin	3.6 g/dL	Urine routine	Normal
CRP	1.6 mg%	Globulin	2.1 g/dL		
Peripheral smear	Macrocytic RBC, hyper-segmented neutrophils.	A: G Ratio	1.6		

Table 2: Serial LFT to observe the response to therapy

Investigations/days	Day 1	Day 3	Day 6	Day 7	Day 8	Day 9	Day 10	Day 12
LFT								
Total Bilirubin (mg/dl)	2.57	8.06	14.24	-	12.96	11.21	-	6.47
Direct Bilirubin (mg/dl)	1.41	5.16	8.1	-	7.65	6.49	-	3.32
SGOT (IU/L)	652	830	942	-	508	357	-	129
SGPT (IU/L)	475	499	736	-	659	512	-	251
ALP (IU/L)	490	487	499	-	405	-	-	-
Total Protein (g/dl)	5.7	4.8	5.2	-	6.1	-	-	-
Albumin (g/dl)	3.6	2.8	2.9	-	3	-	-	-
Globulin (g/dl)	2.1	2	2.3	-	3	-	-	-
A: G Ratio	1.6	1.4	1.2	-	1	-	-	-
S. Ammonia (mcg/dL)	-	-	-	74.8	-	-	62.3	-
PT (seconds)	-	-	-	19.0	-	-	13.9	-
PTT (seconds)	-	-	-	Hyper-pigmented	-	-	23.9	-
INR	-	-	-	1.66	-	-	1.20	-

Discussion

Dapsone is an aniline derivative belonging to the group of synthetic sulfones.[1] Owing to its bacteriostatic effect on *Mycobacterium leprae*, it is an FDA-approved drug for the treatment of leprosy.[2] However, dapsone has been associated with a potentially fatal hypersensitivity reaction involving numerous organs. These include hematological effects (such as methemoglobinemia, hemolysis, and agranulocytosis), dermatological reactions, peripheral neuropathy, and gastrointestinal complications. Approximately 0.5%–3.6% of individuals treated with dapsone experience hypersensitivity reactions.[3] DHS is characterized by fever, skin rash, lymphadenopathy, eosinophilia, hepatitis, acute pneumonitis, neurological symptoms, and other systemic signs of multi-organ dysfunction. It can occur within a few weeks of initiating dapsone or may emerge later, even after 6 months.[4] The precise mechanism of DHS remains unclear; however, it is thought to be multifactorial, involving a dysregulated immune response and cytokine release.[5]

Aneseya P. Varghese *et al.*[6] reported a case of DHS in a six-year-old who presented with fever and full-body skin lesions after taking dapsone for 1 month and was successfully treated with steroids. So Yoon Choi *et al.*[7] described a case of a Korean boy who presented an idiosyncratic reaction after 6 weeks of dapsone therapy, resulting in multiorgan failure. The child was successfully managed with supportive care and steroids. Kumar Shambhu Nath *et al.* reported a near-fatal case in an eight-year-old child who succumbed to hypersensitivity reaction in the form of hemolysis and acute liver injury due to dapsone administration.[8]

The primary treatment for DHS is systemic steroids, which have demonstrated significant improvement in the majority of cases. DHS is associated with severe complications, including multiorgan failure and acute respiratory distress syndrome.[9]

Conclusion

Although DHS is rare in pediatric patients, a high index of suspicion is crucial for timely diagnosis, as it can resemble many other diseases. Careful history-taking, including detailed past treatment history, can provide early clues toward identifying DHS. Early intervention with systemic corticosteroids improves outcomes of DHS and can prevent mortality.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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