Drug-induced Hypersensitivity Syndrome in a Breast Cancer Patient: A Case Report

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Abstract: Drug-induced hypersensitivity syndrome (DIHS) is a life-threatening condition. The diagnosis of DIHS is quite challenging due to highly variable clinical manifestations. This paper was aimed to describe the diagnosis criteria, pathogenesis, and relation of DIHS with cancer. We describe a case of DIHS, probably induced by cefadroxil, in a 50-year-old woman post modified radical mastectomy for her non-specific-type unilateral breast cancer. After four weeks of cefadroxil therapy, the patient started to develop symptoms of drug eruption with elevated liver function tests, direct bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT). The laboratory tests also showed decreased hemoglobin and albumin. The patient's clinical manifestations were highly suggestive of DIHS. Discontinuation of drug consumption and administration of symptomatic therapy did not improve the condition. After four days of postoperative monitoring in the intensive care unit, the patient did not survive the external and internal bleeding due to severe thrombocytopenia. Several hypothetical mechanisms involved in this syndrome include defective detoxifying enzymes, genetic defects related to human leukocyte antigen, viral infections, and concurrent disease processes, such as a neoplasm.

1 INTRODUCTION

Drug-induced hypersensitivity syndrome (DIHS) is one of the adverse drug reactions with systemic manifestation. Approximately 15,1% of adverse drug reaction happens during hospitalization, and 6,7% of them are a severe adverse drug reaction (Demoly *et al.*, 2014). The diagnosis of DIHS is quite challenging due to highly variable clinical manifestations. The DIHS is also recently referred to as DRESS (drug reaction with eosinophilia and systemic symptoms) or DIDMOHS (drug-induced delayed multi-organ hypersensitivity syndrome) (Kumari et al., 2011).

A recent report from a tertiary hospital in Indonesia showed that drug eruption with maculopapular rash was the most common diagnosis (29,82%) in drug hypersensitivity reaction patients, with antibiotics as the most frequent culprit drug (29,8%). Septic shock was the condition that increases the mortality of the patients (Soegiarto and Putra, 2020).

The diagnosis of DIHS/DRESS is sometimes difficult due to its similar characteristics with viral exanthems. Physicians are often more aware of other severe adverse reactions to drugs such as Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (SJS–TEN) Acute Generalized Exanthematous Pustulosis (AGEP) than the DIHS. We want to raise awareness of DIHS, which could happen to any patient, including cancer patients. A better understanding of this condition might improve survival and life expectancy. In this case report, we want to describe the diagnosis criteria and pathogenesis of the DIHS.

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2 CASE PRESENTATION

We describe a case of DIHS, probably induced by cefadroxil, in a 50-year-old woman post modified radical mastectomy for her non-specific-type unilateral breast cancer. The patient previously underwent the first operation on August 16th, 2017, an excisional biopsy for the lump in her right breast. 6 months before the excision, she had felt the tumor but hesitated to see the doctor. The size of the tumor was approximately 5x7 cm. Cefadroxil and mefenamic acid were given two weeks after the excisional biopsy. Histopathology results showed a non-specific type of adenocarcinoma with invasion to local lymph vessels. The patient then underwent the second operation on September 2nd, 2017, unilateral modified mastectomy and axillary lymphadenectomy, thus given another two weeks of cefadroxil and mefenamic acid. The patient started to have a fever, jaundice, and maculopapular rash all around her skin. She also had facial edema, scaling, anorexia, and nausea. The suspected culprit, cefadroxil, was directly stopped. The patient did not have any history of a previous allergic reaction. She was hospitalized on September 17th, 2017, for the next five days. Increased levels of liver function tests, ALP, GGT, and direct bilirubin were observed. The attending physician administered dexamethasone, diphenhydramine, cetirizine, Curcuma, and ursodeoxycholic acid. The patient was hospitalized for the second time on October 11th, 2017, due to severe anemia and hypoalbuminemia. We found the liver function test level was too high, and the rash was reappeared all around her body, despite the discontinuation of the culprit drug consumption.

An abdominal CT scan showed a sign of cholestasis and paraaortic mass. She went to the third operation on October 27th, 2017, a cholecysto-jejunostomy shunt with a planned biopsy for the mass above. During the procedure, we did not found any intraabdominal mass. The liver surface was clean and smooth. Hence, there was possibly no sign of liver metastasis. The patient was monitored thoroughly in the Intensive Care Unit after the operation was done. Day by day, she showed marked deterioration of vital signs. There was also significant bleeding inside her respiratory tract in which the blood clot disturbed her airway. Laboratory tests showed a considerable increase of leukocytes with prolonged hemostasis profile, hypoglycemia, and hypoalbuminemia. We had given human albumin, packed red cells, and thrombocyte concentrate. Endotracheal intubation was done to support the patient's airway. Norepinephrine and dopamine were also administered for her fluid refractory shock. Unfortunately, the patient passed away on October 31st, 2017, due to cardiorespiratory failure. Skin manifestation and macroscopic examination of the breast tumor can be seen in figure 1. The patient's clinical course is described in table 1, and her laboratory results are shown in Table 2.

Table 1: Patient's clinical course.

Timeline (2017)	Description
August 16th	Excisional biopsy for right breast tumor
	Consumption of cefadroxil (two weeks)
September 1st	Histopathology: nonspecific type of adenocarcinoma with invasion to local lymph vessel
September 2nd	Unilateral modified radical mastectomy
	Consumption of cefadroxil (another two weeks)
September 17th	Fever, jaundice, generalized maculopapular rash, facial edema, scaling, anorexia and nausea
	Discontinuation of cefadroxil consumption and hospitalization (5 days)
October 11th	Severe anemia and hypoalbuminemia - rehospitalization
	Abdominal CT scan : cholestasis and paraaortic mass
October 27th	Cholecystic-jejunostomy shunt with planned biopsy
	Postoperative ICU monitoring
October 31st	Patient passed away due to severe hypoalbuminemia, external-internal bleeding, and cardiorespiratory failure

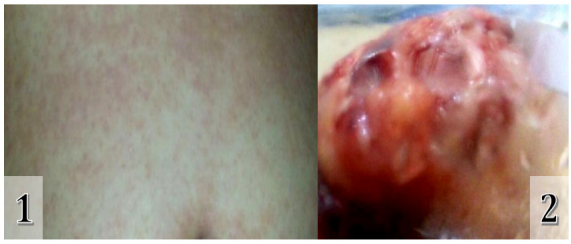

Figure 1: (1) Maculopapular skin rash; (2) The excised breast tumor.

Table 2: Patient's laboratory results.

Parameter	11/10/17 (hospital admission)	14/10/17 (post-transfusion)	28/10/17 (post-operation)
Hemoglobin (g/dL)	7,1 (L)	11,3	
Leukocyte (U/L)	10.870	11.570 (H)	
Haematocrit (%)	21 (L)	33	
Erhythrocyte (cells/µL)	2,8x106 (L)	4,18x106 (L)	
Thrombocyte (cells/µL)	296.000	430.000	
Eosinophil (%)	0,0%	0,0%	
Lymphocyte (%)	14,5% (L)	18,2%	
MCV (fL)	72,7 (L)	80,4	
MCH (pg/cell)	25,2 (L)	27,4	
MCHC (%)	34,6	34	
Serum Iron (µg/dL)	208 (H)		
TIBC (ng/dL)	91 (L)		
CEA (ng/mL)	2,4		
AFP (ng/mL)	1,4		
SGOT (U/L)	202 (H)	184 (H)	102 (H)
SGPT (U/L)	279 (H)	286 (H)	121 (H)
ALP (U/L)	371 (H)	249 (H)	102
GGT (U/L)	434 (H)	282 (H)	105 (H)
Albumin (g/dL)	2,47 (L)	3,05 (L)	1,78 (L)
Total Bilirubin (mg/dL)	8,27 (H)		27,27 (H)
Direct Bilirubin (mg/dL)	6,41 (H)		18,91 (H)
Indirect Bilirubin (mg/dL)	1,86 (H)		8,36 (H)

3 DISCUSSION

Incidence of drug-induced hypersensitivity syndrome ranges from 1:1.000 to 1:10.000 drug exposures. This syndrome can turn into a fatal condition in 10% of patients. It can be related to difficulties in diagnosing the patient. Diagnosis of DIHS is indeed quite challenging. Delay of diagnosis can happen because of variable clinical manifestations and late-onset symptoms (Cacoub *et al.*, 2011). A maculopapular rash can develop three weeks after starting the culprit drug. Discontinuation of the drug consumption did not directly eliminate the symptoms. They may prolong more than 15 days (Shiohara *et al.*, 2009). European Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biological Samples (RegiSCAR) Group Criteria can be used to diagnose DIHS by using a scoring system accurately.

Table 3: Diagnostic criteria from the RegiSCAR group (Kardaun *et al.*, 207)

Clinical Features	-1	+1	+2
Fever	No or unknown	≥38,5°C	
Lymphadenopathy		≥2 sites, ≥1 cm	
Atypical lymphocytes		Present	
Eosinophilia		10%-19,9%	≥20%
Skin rash			
- Body surface area involved		>50%	
- Edema, infiltration, purpura, scaling	No	Minimum two	
- Biopsy suggesting DIHS	No		
Internal organ involvement		1 organ	≥2 organs
Resolution in more than 15 days	No or unknown	Yes	
More than 3 biological investigations and negative to exclude alternative diagnosis		Yes	

From the scoring system, patients are then classified into definite (>5), probable (4-5), possible (2-3), or no cases (50% (+1), edema and scaling (+1), liver and gallbladder involvement (+2), also the resolution in more than 15 days (+1). Treatment for DIHS includes discontinuation of the culprit drug consumption followed by administration of steroid.

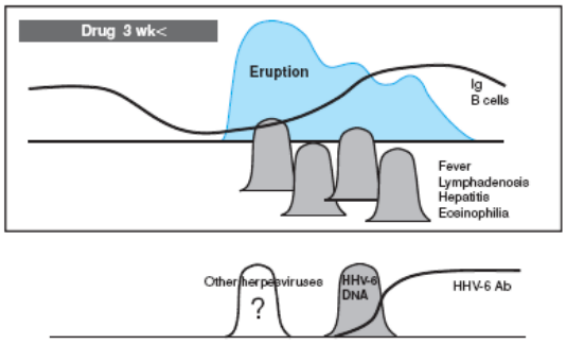

Figure 3: The clinical course of DIHS. Symptoms like maculopapular rash and fever appear three weeks after the culprit drug was initiated (Shiohara *et al.*, 2009).

Two main hypotheses involved in DIHS pathogenesis are the (pro) hapten hypothesis and the pharmacoimmunological (p-i) hypothesis. The drug can act as a hapten or prohapten, covalently bind with larger molecules in vivo - such as protein – forming a brand new antigen. This newly formed antigen will be presented by antigen-presenting cells (APC). Hence, it activates the drug-specific T cells, leading to lymphocyte proliferation. Meanwhile, the p-i hypothesis is proposing a non-covalent interaction between drug and APC. The interaction will activate HLA alleles (probably HLA-B) and T-cell receptors, subsequently trigger an immune response (Choudhary *et al.*, 2013; Schrijvers *et al.*, 2015). Viral infection - such as human herpesvirus 6 (HHV-6), cytomegalovirus (CMV), Epstein Barr virus (EBV), and paramyxovirus – can also induce inflammation and activate the proliferation of drug-specific T cells. Viral infection may lower the threshold for T cell activation. There may be a cross-reaction between activated T cells and the culprit drug. Several individuals can be more susceptible to DIHS due to defects in the detoxification mechanism, resulting in reactive metabolite formation and subsequent immune reaction (Cacoub *et al.*, 2011; Shiohara *et al.*, 2009).

4 CONCLUSIONS

Drug-induced hypersensitivity syndrome is a complicated and fatal condition. The patient presented in this case report is classified into a probable case of DIHS by using the RegiSCAR scoring system. This patient underwent a different path and eventually passed away, despite discontinuing the culprit drug consumption and administration of steroids and other symptomatic drugs. The culprit drugs may act as a (pro) hapten or non covalently interact with APC, resulting in severe immune reaction. The pathogenesis of DIHS may be related to breast cancer via the activity of T helper-2 cells and eosinophils.

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