in reduced red blood cells (RBC) as well as anemia (4). The phenotypes of inherited heterozygous compound beta-thalassemia comprise thalassemia major and thalassemia intermedia (TI). Patients suffering from thalassemia major experience severe anemia in early age, which necessitates lifelong transfusion of blood and iron chelating medications for survival while patient with thalassemia intermedia may not need them (1, 4, 7).

As an adverse effect of regular blood transfusion, vital organs including the heart, kidneys, liver, and tiny endocrines undergo hemosiderosis, which damage the tissues and leads to organ dysfunction. Although iron chelating agents considerably improve the rate of survival depending on blood transfusion, multi-organ hemosiderosis occurs frequently (7- 9).

Deferasirox (DFX) is a newly developed edible iron chelating agent prescribed to be used on a daily basis. The commonly observed complications of Deferasirox include gastrointestinal disorders (15.2%), skin rash (10.8%), as well as a brief rise in serum creatinine and increases in the levels of liver enzyme (38%) (10-13).

Numerous longitudinal research projects have shown the safety and effectiveness of DFX. This medication has been shown to result in maculopapular rash in almost one in ten patients. There have been reports of effective desensitization to DFX in delayed drug hypersensitivity reactions (DHR), including maculopapular rash and erythema multiforme. In these reports, it took many days to determine the desirable dosage. Few studies have reported rapid hypersensitivity reactions (10-14). Thus, we report an instance of immediate dermatopathological drug reactions in a patient suffering from thalassemia after having been prescribed Deferoxamine (DFO) combined with Deferiprone (DFP) without any serious undesirable reactions.

Case report

This case presentation was approved in Ethics Committee of Biomedical Research in Royan Institute IR.ACECR.ROYAN.REC.1401.032. Our case was a 44-year-old female with beta thalassemia, who had received consistent transfusions from the age of five after being diagnosed with the disease. She has been constantly transfused with an interval of 21days. She had been previously prescribed chelating with DFO and DFP. The ferritin level in her body oscillates in the range of 800.0 and 1300 ng/mL (mean 1149ng/mL). Her weight and height are currently 64kg and 164cm, respectively. She has had healthy growth with no adverse effects in the liver or heart . Her latest clinical lab examination results are presented in Table 1.

She has received an Iranian made generic DFX which is an oral iron-chelator as the original DFX has been unavailable. She stopped receiving her usual iron chelating treatment and was started on oral DFX tablets (360 mg), with dosage based on 20 mg/kg/day, two tablets daily, morning and night, and the dosage being increased to three, for the subsequent weeks. Nine days after getting started on the tablets, she complained of deep red-blue partially purpuric itchy skin rashes (maculopapular eruption) and received treatment at (Figure 1). The rashes began in the face and neck, expanding downwards to affect all the body. Based on her history, she had only experi-

Table 1. Patient's clinical data at the time of adverse reaction

Parameters	At referred time	Reference range
Ferritin (ng/mL)	1149	Male: 12 to 300 ng/mL Female: 12 to 150 ng/mL
Cardiac MRI t2* (ms)	39.8– Normal	>20 ms
Hepatic MRI t2* (ms)	10.95– mild Hemosiderosis	>17 ms
LIC (dry weight mg/g)	2.820779	<1.8dry weight mg/g
WBC (10^9/L)	5.6	4.5 to 11.0 × 10^9/L
Hb (g/dL)	9.5	Male: 13.2 to 16.6g/dL Female: 11.6 to 15 g/dL
Platelets (10^3/L)	454	150 to 450 10^3/L
PT (sec)	15.4	
Activated PTT(sec)	36.8	28-44
Glucose (mg/dL)	91	Adult: 74-100mg/dL

ng/mL: nanograms per milliliter
;WBC: white blood cell count
;Hb: hemoglobin
(MRI T2: magnetic resonance imaging (cardiac> 20 ms; normal, Hepatic>17 ms: considered normal
LIC: Liver iron content

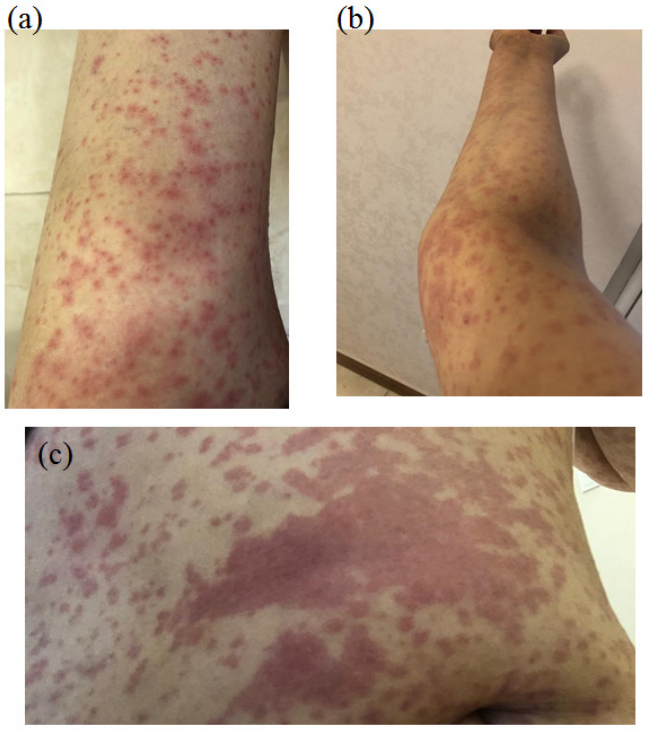

Figure 1. Drug reaction severity (a) leg, (b) arm, and (c) abdomen lesions on the day of referring to the clinic

enced a rise in the number and severity of skin lesions, without any breathlessness, shortness of breath, or losing consciousness.

Further examination revealed that the condition was maculopapular eruption, deep red- blue partially purpuric itchy skin rashes throughout her body. No other organs showed any complications upon physical examination. Laboratory examinations showed a low level of Hb (9.5g/dL), average WBC and platelet count, PT, and activated PTT. The functions of the liver and kidneys were found to be normal. The patient stopped taking oral DFX and, based on the dermatologist's prescription, and was started on oral high dose steroids (one stat Betamethasone LA IM, and 15mg/day for three days and gradual decrease), topical Clobetasol ointment as well as oral antihistamines. The rash started to subside and complete recovery was achieved within two weeks of DFX discontinuation. However, an ecchymotic lesion was seen on the left leg on the healing maculopapular rash (Figure2). To establish the cause of hypersensitivity and its type, skin biopsy was carried out after obtaining the patient's consent upon her first visit. A specimen was taken in formalin which comprised a piece of punch skin biopsy which measured 0.2x0.2cm in terms of surface area and 0.2cm in terms of thickness.

The results are presented as a microscopic description and diagnosis as follows in the next section.

Microscopic Description

A small part of the skin tissue showing mild basket weave keratosis, focal parakeratosis, Irregular mild epidermal acanthosis, slight spongiosis as well as small foci of vacuolar degeneration of basal keratinocytes along with individual cell apoptosis scattered around.

The dermis underneath shows slight RBC extravasation with a mild infiltrate of lymphocytic inflammatory cells and few eosinophils around blood vessels with prominent endothelial cells mostly in the superficial portion of the skin.

Microscopic diagnosis (Skin biopsy of body lesion)

Superficial perivascularor dermatitis with low grade vasculopathy, few eosinophils and mild psoriasiform-spoaglotic-lichenoid epidermal reactions which are associated with Drug Reaction.

After this adverse drug reaction was treated by corticosteroids and the patient returned to a normal and stable situation, she was started on iron chelation therapy again based on DFPO combined with DFP. The drug administrator was informed about the adverse complication.

Since there was a doubt that this might be an adverse reaction to the intrinsic molecule of DF, two months later, the patient accessed the original brand medicine of DFX with a gradual increase of the dose to the prescribed one. The treatment response was accurately monitored

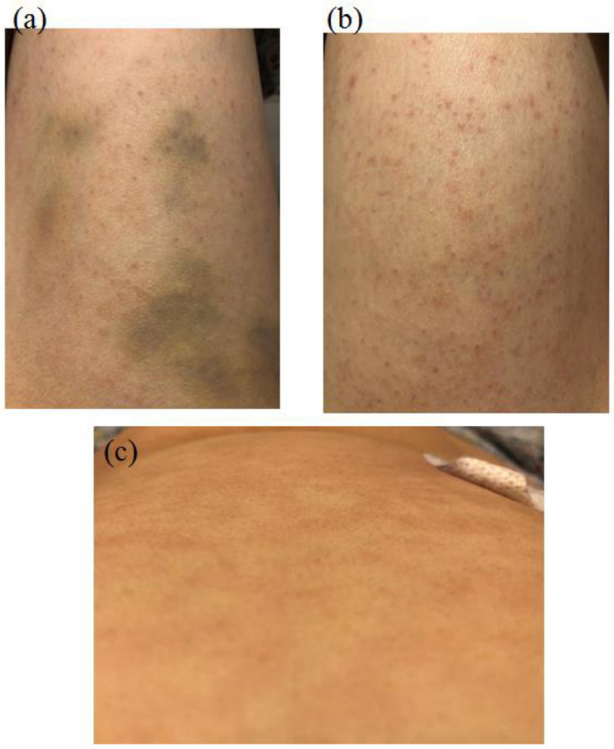

Figure 2. On the fifth day of medical therapy (a) left leg, (b) right leg, and (c) abdomen, oral steroid therapy (to 45mg), note the ecchymotic lesion on the left leg at the site of healing maculopapular rash

under the supervision of dermatologist and hematologist. There was no drug reaction to the intrinsic DFX molecules at the time interval of the appeared drug reaction of generic medicine (Figure 3).

Discussion

Following an extensive review of the literature, several similar case reports of thalassemia patients were found. We observed skin rash occurring in 7-11% of thalassemia patients who re-

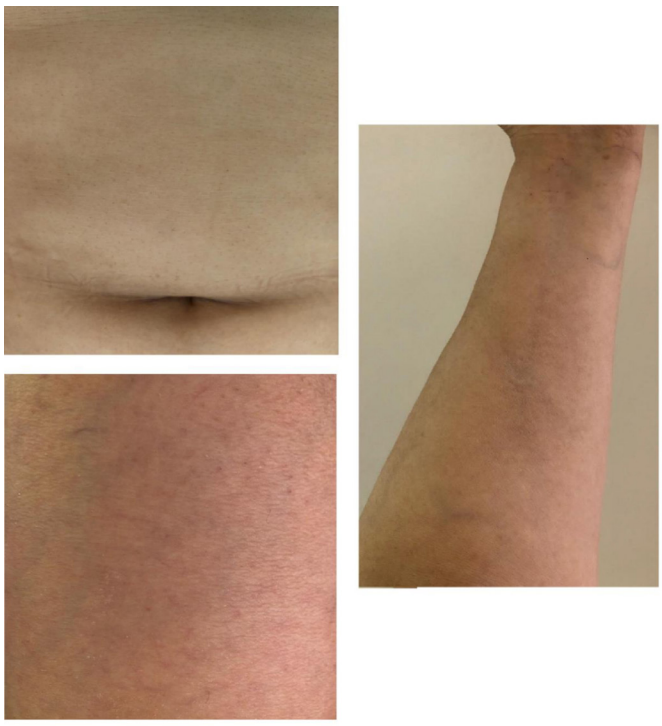

Figure 3. Abdomen, leg, and arm skin 9 days after initiation of original brand tablets DFX, 360 mg

ceived DFX (1).

A case report of challenge-proven immediate adverse drug reaction associated with the use of DFX emerged in 2020 (10). The researchers used graded challenge and treated through the reactions, which included ill-defined erythematous macules and lip angioedema, by administering H1-antihistamine. The patient in the study finally showed increased tolerance to the drug as H1-antihistamine was discontinued (10).

Another case report was related to an Indian patient who showed adverse skin rashes once she was started on DFX. Then, she received DFX at a dose of 750 mg daily. Six days after the therapy, she presented with pruritic skin rashes on the neck which later affected the whole body (14).

In a case report published in 2010, a ten-year-old boy suffering from ß-thalassemia in Turkey was started on 20 mg/kg/day DFX therapy. He showed pruritic skin rashes, starting from the neck and affecting the whole body within seven days of the treatment. His complaints included lesions which were erythematous, and raised skin lesions which became pale after palpation. These lesions were more noticeable on the upper extremities, upper body, and on dorsal areas (15).

Our patient recovered from adverse drug effects and discontinued the generic preparation of DFX. After accessing the brand molecule, original DFX, and initiating the oral chelation again, she was monitored for 10 days and gradually increased the dose to the prescribed one with no dermatopathologic complications.

Last but not least, there is no doubt the reaction to the DFX was not due to the intrinsic characteristic of this medicine. Since there was no recurrence with the original brand, it may be plausible to consider the presence of impurities in active pharmaceutical ingredients (AIP).

Conclusion

Since there is no transient available data about API analysis used for generic products, we are not able to be fully determined this issue. The noticeable point is that it seems reasonable for the food and drug administration to make available more clear data for AIP of the medicine. Or, it is wiser and more cautious to apply this medicine from low dose, increase it definitely smooth for controllable tolerance. Finally, for moderate to severe reactions, treatment should be stopped under the supervision of medical specialists to be sure there is no threat for the patients about the adverse effects.

Declarations

Ethical Approval

This case presentation was approved by the Ethics Committee of Biomedical Research in Royan Institute IR.ACECR.ROYAN.REC.1401.032.

Conflict of interest

Authors declare that they have no conflicting interests.

Consent for publication

We obtained informed written contest from the patient.

Authors' contributions

Leila Ataie Fashtami contributed to the study by designing and conducting the clinical case report presentation; Afshan Shirkavand was responsible for the literature review and drafting; Azita Azarkeivan and Zohreh Zahedi contributed to this research by reviewing the data and the manuscript; all of the authors collaborated in writing and editing the manuscript, as well as reviewing the manuscript.

Funding

None to declare.

Availability of data and materials

To preserve the patient's privacy, this is not applicable.

Acknowledgements

Thanks are extended to Dr. Sadigh for her precious advice. Thanks also go to Dr. Androulla Eleftheriou, and Dr. Michael Angastiniotis from International Thalassemia Federation for their kind assistance and guidance on editing the manuscript.

References

1. Cappellini MD, Farmakis D, Porter J, Taher A. Guidelines for the clinical management of thalassaemia. 21, 4th edition, Thalassaemia International Federation, 10-72
2. Angastiniotis M, Lobitz S, Thalassaemia: An Overview, International Journal of Neonatal Screening. 2019, 5(16): 2-11
3. Hashemieh M, Azarkeivan A, Akhlaghpoor S, Shirkavand A, Sheibani K. T2-star (T2*) Magnetic Resonance Imaging for Assessment of Kidney Iron Overload in Thalassemic Patients, Archives of Iranian Medicine. 2012, 15(2): 91-94
4. Origa R. Beta-thalassaemiat, Genetics in Medicine. 2017, 19:16
5. Vetsiou E, Mpouras V, Nikolaidou C, Klonizakis P, Mandala E, Vamvakis K, Psarras K, Vlachaki E. Necrobiosis Lipoidica in a Patient with β-ThalassaemiaThalassaemia Major: A Case Report and Review of the Literature, Hemoglobin. 2020, 44(3):221-223
6. Hoffbrand AV, Taher A, Cappellini MD. How I treat transfusional iron overload. Blood. 2012, 120(18):3657–3669.

7. Ziyadeh NF, Musallam KM, Mallat NS, Mallat S, JaberF, Abdulnabi MA, Koussa S, Taher A. Glomerular Hyperfiltration and Proteinuria in Transfusion-Independent Patients with beta - Intermedia, Nephron ClinPract. 2012, 121(3-4): 136-4
8. Koliakos G, Papachristou F, Koussi A, Perifanis V, Tsatra I, Souliou E, Athanasiou M. Urine biochemical markers of early renal dysfunction are associated with iron overload in beta-thalassaemia, Clin. Lab. Haem. 2003, 25: 105–109
9. Rund D, Rachmilewitz E. Medical progress Beta-Thalassaemia, New Eng l J Med. 2005, 353:11-15
10. Sompornrattanaphan M, Krikeerati T, Wongs C, Thongngarm T, Yampayon K. Successful Deferasirox Rechallenge and Treating Through Reaction in a Patient with Challenge-Proven Mild Immediate Reaction: A Case Report. Journal of Asthma and Allergy. 2020,13 557–561
11. Chaudhary P, Pullarkat V. Deferasirox: appraisal of safety and efficacy in long-term therapy. J Blood Med. 2013; 4:101–110.5.
12. Bruner KE, White KM. Deferasirox desensitization. J Allergy Clin Immunol Pract. 2016,4(1):171–172.
13. Davies GI, Davies D, Charles S, Barnes SL, Bowden D. Successful desensitization to deferasirox in a pediatric patient with beta-Thalassaemia major. Pediatr Allergy Immunol. 2017, 28(2): 199–201.
14. Atul Sharma, Ekta Arora, Harmanjit Singh, Hypersensitivity reaction with deferasirox. Journal of Pharmacology and Pharmacotherapeutics, April-June 2015, 6: 2
15. Isik P, Nese Yarli, Bay A, Ozmen S, Tunc B. Type-I Hypersensitivity Reaction Secondary to Deferasirox Intake. UHOD.2010, 20